2. Studies of Cancer in Humans

The available knowledge on the relationship between tobacco usage and a variety of human cancers is based primarily on epidemiological evidence. An immense amount of such evidence has been obtained, and, of necessity, only a small proportion can be referred to here. The cancers considered to be causally related to tobacco smoking in the previous *IARC Monograph* on tobacco smoking (IARC, 1986) included those of the lung, upper aerodigestive tract (oral cancer and cancer of the oropharynx, hypopharynx, larynx and oesophagus), urinary bladder and renal pelvis and pancreas. Since 1986, there have been numerous additional cohort and case–control studies on the relationship of cigarette smoking and other forms of tobacco use to these and other cancers in many different countries. The most comprehensive evidence, although often not the first or most detailed, has been obtained from several large cohort studies that are referred to repeatedly in this monograph with respect to different cancer sites and types of tobacco product. These cohort studies are described briefly below and in Table 2.1, listed by country. The case–control studies are described in the sections pertaining to particular cancer sites.

Description of cohort studies

(*a*) *Europe*

(i) *United Kingdom*

British Doctors' Study

In 1951, a questionnaire on smoking habits was sent to all British doctors included in the Medical Register; 34 440 men and 6194 women responded, representing 69% and 60%, respectively, of those doctors not known to have died at the time of the inquiry. [The exact number of men and women included in the study varies between publications as a number of women were misclassified as men in early reports.] Further questionnaires about changes in smoking habits were sent in 1957, 1966, 1972, 1978 and 1990 to men and in 1961 and 1973 to women; on each occasion, at least 94% of those alive responded. Reports were published on cause-specific deaths after 10, 20 and 40 years for men and after 10 and 22 years for women; more than 99% of the subjects had been traced. Information on causes of death was obtained principally from the Registrars General of the United Kingdom and, otherwise, from the records of the general Medical Council, the

Bristish Medical Association, relatives or friends. Because the subjects in the study were themselves physicians, they were a reasonably uniform socioeconomic group and the causes of death were certified more accurately than might have been the case among a sample of the general population. For the first 20 years of the study, confirmation of all deaths attributed to lung cancer was obtained from a chest physician who was unaware of the patient's smoking history (Doll & Hill, 1964a,b; Doll & Peto, 1976; Doll *et al.*, 1980, 1994).

Whitehall Study

A total of 19 018 men aged 40–69 years from the British Civil Service were clinically examined between 1967 and 1969, and followed up for vital status until 1987 through the National Health Service Central Registry. Information on exposure was collected only at baseline. The study concentrated on residual risk after smoking cessation as well as comparing risk associated with different tobacco products (Ben-Shlomo *et al.*, 1994).

British United Provident Association (BUPA) Study

Wald and Watt (1997) studied a cohort of 21 520 professional and businessmen with a National Health Service identification number who attended a routine health examination between 1975 and 1982 at a British United Provident Association (BUPA) Medical Centre in London. At this examination, a detailed smoking history was obtained, including self-reported level of inhalation (rated as nil, slight, moderate or deep). In addition, a blood sample was collected and carboxyhaemoglobin saturation and cholesterol levels were measured. Causes of death of cohort members were obtained from records of the National Health Service and the Office of Population Censuses and Surveys records. The risks of mortality from three causes (i.e. ischaemic heart disease, lung cancer and chronic obstructive lung disease) were computed using Cox's proportional hazard analysis.

(ii) *Sweden*

Swedish Twin Registry Study

A cohort of 10 945 twin pairs of the same sex, identified using the Swedish Twin registry, was asked to complete a questionnaire in 1961. Zygosity was based on questions of childhood similarity. Mortality in twins was followed up by record linkage with the central registry of causes of death through 1997. The information from death certificates, hospital records and other data was collected for the period up until 1981 and was reviewed without prior knowledge of smoking status; the underlying cause of death was determined according to the ICD 8th revision. For the period after 1981, the underlying cause of death as stated in the death certificate was used (Floderus *et al.*, 1988; Steineck *et al.*, 1988; Grönberg *et al.*, 1996; Terry *et al.*, 1998, 1999, 2001).

Swedish Census Study

A sample of the Swedish population drawn from the 1960 census was stratified by sex, year of birth and residence (urban or rural). The objective was to determine the smoking habits of the Swedish population by means of postal questionnaires, telephone interviews and home visits. A questionnaire was posted in 1963, and, of 55 074 eligible subjects, 89% responded. Information was collected by telephone or personal interview for another 5.3%. A sub-sample of 20% was sent a second questionnaire in 1969, with the aim of validating the accuracy of the replies and collecting information about changes in smoking patterns. Mortality in the cohort was ascertained through death certificates. In addition, cancer incidence was ascertained through the nationwide Swedish Cancer Registry, which recorded an estimated 95.5% of all cancers. The follow-up period extended from 1964 until 1989. Cancer outcomes were reported after 10 and 26 years for men and women combined (Cederlöf *et al.*, 1975; Nordlund *et al.*, 1999) and after 16 years for men only (Carstensen *et al.*, 1987) and after 26 years for women only (Nordlund *et al.*, 1997). Cox proportional hazards regression models were used to compute odds ratios stratified by age and place of residence.

Swedish Construction Workers' Study

A cohort of male Swedish construction workers was identified in 1971, when workers filled out a questionnaire, the answers to which included a detailed smoking history. The cohort included about 135 000 men recruited between 1971 and 1975 or 350 000 men recruited between 1971 and 1992. Each cohort member contributed person–years of observation from the date of first registration visit until the date of diagnosis, death, migration or end of follow-up (Adami *et al.*, 1996; Nyrén *et al.*, 1996; Adami *et al.*, 1998; Chow *et al.*, 2000). Data on cancer incidence were obtained through linkage with the population-based national cancer registry established in 1958. Each cohort member was identified by his national registration number, a unique personal identifier assigned to all residents in Sweden.

(iii) *Norway*

Norwegian Cohort Study

Heuch *et al.* (1983), Engeland *et al.* (1996a,b) and Kjaerheim *et al.* (1998) reported the cancer incidence of a cohort of 26 000 Norwegians who completed a self-administered questionnaire in 1964–1965. The target population was drawn from three sources: approximately 19 000 persons were randomly drawn from lists of residents of Norway from the 1960 population census, approximately 5200 were drawn from four selected counties, and approximately 13 000 were drawn from a cohort of Norwegians living in Norway who had siblings living in the USA. The final study population comprised 26 126 persons, contributing approximately 540 000 person–years for analysis (230 000 for men and 310 000 for women). At the initial assessment, 17% of the men reported never having been a smoker, whereas 68% of the women had never smoked. Information on cancer incidence was obtained through the population-based Norwegian Cancer Registry, which has been operational through the mandatory reporting of cancer cases by physicians since 1953. All cohort members were followed up from 1966 to the date of the first diagnosis of the cancer being considered, the date of emigration, the date of death, or until 31 December 1993. The only exception was for cancers of the upper aerodigestive tract, where more than one diagnosis per person was allowed. Questionnaire data were not updated during the follow-up period. Analyses were performed using the Cox proportional hazards regression models.

Norwegian Screening Study

The Norwegian Screening study followed the cancer incidence in a random sample of adults from two cities and three counties in Norway who were screened for coronary heart disease between different time periods (see Table 2.1). Participants were followed until death or emigration up to 1988. The officially coded underlying cause of death was used as the end-point. Mortality rates were adjusted for age and area of residence and analysed with Cox proportional hazards models (Vatten & Kvinnsland, 1990; Tverdal *et al.*, 1993; Thune & Lund, 1994; Veierød *et al.*, 1997).

(iv) *Finland*

Finnish Men's Study

A cohort of 4604 Finnish–Norwegian men was interviewed in 1962 about their smoking habits and cardiorespiratory symptoms. The study subjects were selected from three urban areas in western and central Finland, and three rural areas in western and eastern Finland (Pedersen *et al.*, 1969). One hundred and thirty-two men who died or were diagnosed with lung cancer before 1964, and 20 who had not given details of their smoking habits at the interview, were excluded, leaving an effective cohort size of 4452 men. The follow-up period for analysis covered 1964–80. Lung cancer cases were identified through the population-based cancer registry in Finland, by use of the Finnish personal identification number. The effect of smoking and different respiratory symptoms on lung cancer incidence was assessed by a log-linear modelling technique (Tenkanen *et al.*, 1987; Hakulinen *et al.*, 1997).

Finnish Mobile Clinic Health Examination Study

Between 1966 and 1972, the Finnish Mobile Clinic Health Examination Survey performed multiphasic health examinations in rural, semiurban and industrial municipalities in different parts of Finland. A total of 62 440 white adults aged ≥ 15 years were invited to participate, and the participation rate was 83%. All participants completed a questionnaire that had been sent in advance and checked at baseline examination. Participants were followed up until 1991 (Knekt *et al.*, 1998; Heikkilä *et al.*, 1999).

(v) *Iceland*

Reykjavík Study

Tulinius *et al.* (1997) assembled a cohort of 22 946 adult Icelanders in five stages for a study on risk factors for cardiovascular disease. The first stage took place from 1967 to 1969, the second from 1970 to 1972, the third from 1974 to 1979, the fourth from 1979 to 1984 and the fifth from 1985 to 1991. The initial enrolment interview took place at a clinic visit at which the completion of a comprehensive questionnaire concerning various risk factors was followed by a series of anthropometric and biochemical measurements. Although interviews were conducted at each stage, this study used only data from each subject's first interview. Overall, 73% of the initial target population was successfully recruited into the study. The cohort was linked with the Icelandic Cancer Registry, a population-based registry of the entire country that was begun in 1954. Linking to the registry was facilitated by the unique identification number assigned to all residents in Iceland. Cox's regression was used to analyse the predictive power of a number of variables on the incidence of first cancer after enrolment into the study.

(vi) *Netherlands*

Dutch Study

A cohort of 26 697 women from the city of Utrecht in the Netherlands answered a questionnaire and provided a 12-h urine sample at the beginning of the follow-up period. Follow-up continued from entry to the study for up to 15 years. The full cohort was drawn from two previously established screening programmes. The first was a population-based screening programme for the early detection of breast cancer in women aged 40–64 years, called the DOM project. This portion of the cohort had 14 697 women who were enrolled from early 1975 until mid-1977, 72% of whom participated. One year later, 81% of this group participated in a follow-up effort in which a second 12-h urine sample was collected. The second breast cancer screening programme (Lutine study) was undertaken in 1982–83 and included more than 12 000 women 40–49 years of age [exact number not stated by the author]. For this second screening programme, 12-h urine samples were taken on days 21–23 of three consecutive menstrual cycles. Participation in the second screening programme was only 44%, probably because of the demanding study protocol. An all-cause-of-death register was established for this study to which all medical practitioners in the city of Utrecht who saw cohort members in their practices reported. In 1987, a regional cancer register was established, making it possible to follow the entire study cohort for cancer incidence. There were three distinct follow-up periods (Ellard *et al.*, 1995; de Waard *et al.*, 1995; van Wayenburg *et al.*, 2000).

(vii) *Denmark*

Copenhagen City Heart Study

In 1976, a prospective epidemiological study was initiated in which participants were selected from 90 000 persons living in a defined area around the University Hospital of Copenhagen. An age-stratified sample of subjects aged 20 years or more was selected at random. Seventy-four per cent of those invited to participate (14 223 subjects) attended. The subjects were followed up until 1989. Notification of deaths and causes of death were obtained from the Central Death Registry of the National Board of Health (Lange *et al.*, 1992).

(*b*) *North America*

(i) *USA*

Framingham Heart Study

The Framingham Heart Study included 5209 subjects who were first examined between 1948 and 1952, and were aged 45–84 years at baseline examination. Participants were routinely examined every two years for 24 or 34 years. At these examinations, information on smoking status and other risk factors was updated. A tumour registry was set up for this cohort (Williams *et al.*, 1981; Freund *et al.*, 1993).

American Cancer Society (nine-state) Study

In 1952, more than 22 000 volunteers for the American Cancer Society each distributed a questionnaire to 10 white men aged 50–69 years whom the volunteer knew well. Smoking histories were collected from 204 547 men in nine states. After exclusion of unsuitable subjects, a cohort of 187 783 men was followed by the volunteers from 1952 through 1955 (average duration, 44 months). A total of 11 870 deaths (6.2%) and 1.1% losses to follow-up were recorded. Death certificates were obtained for all reported deaths and further information was sought from the physician, hospital or tumour registry whenever cancer was mentioned in the certificate (Hammond & Horn, 1958a,b). The distribution of smoking habits in the study population was in close agreement with that reported in a large survey on smoking habits in a sample of the US population (Haenszel *et al.*, 1956).

US Veterans' Study

Beginning in January 1954, 293 958 holders of US government Life Insurance policies who had served in the armed forces at any time between 1917 and 1940 were sent a questionnaire on smoking habits; 198 834 (68%) responded and 49 361 additional replies were obtained by a subsequent mailing in 1957 (total response rate, 85%). Policy holders were almost exclusively white men of the middle and upper social classes. Subjects were followed up from 1954 until 1980 during which time there were 192 756 deaths. Whenever a claim was filed for payment of a policy, a copy of the death certificate was sent by the Veterans' Administration to the National Institutes of Health study office. 'Terminated' policies were also checked annually to ascertain if termination was due to death or to other reasons. Additional information on policy holders who had died was requested from a certifying physician or hospital. The 26-year follow-up was considered to be almost complete by Chow *et al.* (1995), with 95% of the death certificates of cohort members who had died having been obtained (Kahn, 1966; Rogot & Murray, 1980; Kinlen & Rogot, 1988; McLaughlin *et al.*, 1989; Hsing *et al.*, 1990a; McLaughlin *et al.*, 1990a,b; Hsing *et al.*, 1991; Heineman *et al.*, 1992; Zahm *et al.*, 1992; Chow *et al.*, 1993; Heineman *et al.*, 1994; Chow *et al.*, 1995; McLaughlin *et al.*, 1995; Chow *et al.*, 1996).

Californian Study

Information on occupational exposures and smoking history was collected from self-administered questionnaires in 1954–57 from 68 153 male labour union members, aged 35–64 years, in California. Subjects were followed up for mortality up to December 1962 (average follow-up time, 7.1 years) through California death records. A total of 4706 deaths occurred in the cohort, 936 of which were from cancer (Weir & Dunn, 1970). [The Working Group noted that the data available on smoking habits were less extensive than those obtained in other studies.]

Cancer Prevention Study I (CPS-I)

Between October 1959 and February 1960, volunteers for the American Cancer Society in 25 states recruited more than one million subjects from among their friends, neighbours and acquaintances. Families were enrolled, with the condition that there be at least one person aged over 45 years in the family. All family members over 30 years of age were requested to fill out a detailed four-page questionnaire. Participants were predominantly white (97%), married (82%) and college-educated. For the 1 051 038 subjects enrolled, vital status was monitored by the volunteers, originally to September 1965 (Thun & Heath, 1997). Each subject was traced annually and every 2 years was requested to fill out a brief follow-up questionnaire. Of the subjects originally enrolled, 1% could not be traced in the follow-up, and 2% of the questionnaires were unusable. Death certificates were obtained from state or local authorities and, when cancer was mentioned, further information was sought from physicians. The underlying cause of death was coded according to the ICD 7th revision. During the first 6 years of follow-up, 76 888 subjects died and 14 029 (1.4%) were lost to follow-up; 483 519 white women and 358 422 white men alive at the end of 1966 were further followed up for mortality until 1972 with a success rate for follow-up of 99%. This is the largest of the early cohort studies on tobacco and mortality (Hammond & Garfinkel, 1961; Hammond, 1966; Garfinkel, 1980; Hammond & Seidman, 1980; Garfinkel, 1985; Stellman & Garfinkel, 1986, 1989a,b; Garfinkel & Boffetta, 1990; Thun *et al.*, 1995; Thun & Heath, 1997; Thun *et al.*, 1997a; Shanks & Burns, 1998).

Harvard Alumni Study

A cohort of undergraduates who had entered the University of Harvard between the years of 1916 and 1950 was identified when they responded to a health questionnaire sent out in 1962 or 1966. Updated information was obtained from 13 905 cohort members from periodic surveys that assessed lifestyle habits and medical history. The questions asked for information on daily amount of cigarette smoking, age at start and cessation of cigarette smoking, weight, height and physical activity. In surveys conducted in 1988 and 1993, participants were asked whether a cancer had been diagnosed by a physician. Deaths that occurred up to 1992 were traced using information from the alumni office to obtain death certificates. The authors claimed that mortality follow-up was virtually complete (Paffenbarger *et al.*, 1977, 1978).

Tecumseh Community Health Study

The Tecumseh Community Health Study involved subjects who participated in one or more rounds of physical examinations offered to 9794 persons from a semi-rural community in 1959–60, 1962–65 and 1967–69. Cigarette smoking history was taken at each examination cycle. A retrospective cohort was created from those participants aged 25 years and older and who were free of cancer (except for non-melanoma skin cancer) at baseline or within 1 year of entering the study. These criteria resulted in a fixed cohort of 3956 subjects, for whom complete follow-up data were available. In 1986–87, a comprehensive cancer incidence survey was conducted by means of a questionnaire sent to the participants or their next-of-kin. An estimated completeness of 95% was achieved. The reported cancer cases were verified, with the permission of the participant, by requesting abstracts of hospital records. A Cox proportional hazards model was used to examine lung cancer incidence in relation to smoking habits (Islam & Schottenfeld, 1994).

Kaiser Permanente Medical Care Program Study

The first cohort included approximately 175 000 subjects aged 15–94 years who underwent at least one multi-phasic health check-up between 1964 and 1973 within the Kaiser Permanente Medical Care Program. Cancer incidence was ascertained from the first health examination until 1988 through the San Francisco-Oakland Surveillance, Epidemiology and End Result (SEER) programme and the Northern California Kaiser Permanente Medical Care Program. Approximately 4.4% of the cohort were lost to the study (Hiatt & Bawol, 1984; Hiatt & Fireman, 1986; Friedman, 1993; Friedman & van den Eeden, 1993; Herrinton & Friedman, 1998; Iribarren *et al.*, 2001). Between 1978 and 1985, a similar cohort was established, which included a maximum of 120 000 subjects aged 30–89 years. In one study, the cohort was further followed up until 1987 (Sidney *et al.*, 1993). Cancer cases were ascertained as for the first cohort (Hiatt *et al.*, 1988; Klatsky *et al.*, 1988; Sidney *et al.*, 1993; Hiatt *et al.*, 1994; Herrinton & Friedman, 1998).

American Men of Japanese Ancestry Study

A cohort of 8006 American men of Japanese ancestry, born during the years 1900–19 and who resided on the Hawaiian island of Oahu, were interviewed and examined clinically from 1965 to 1968. Information obtained at the interview included age, smoking history, usual occupation, type of housing, education and religion. A 24-h dietary recall questionnaire was also administered. Newly diagnosed cases of cancer were identified through continuous surveillance of Oahu hospitals and linkage with the Hawaii Tumor Registry (Stemmermann *et al.*, 1988; Severson *et al.*, 1989; Nomura *et al.*, 1990a,b; Chyou *et al.*, 1992, 1993a,b, 1995; Nomura *et al.*, 1995; Chyou *et al.*, 1996).

Lutheran Brotherhood Insurance Study

A cohort of 17 633 white male life insurance policy holders of the Lutheran Brotherhood Insurance Society was identified in 1966. A response rate of 68.5% was achieved and little difference was observed between responders and non-responders to the questionnaire with regard to age, urban or rural residence, policy status and cancer mortality at 11.5 years of follow-up. The questionnaire included questions on tobacco use in the form of cigarettes, cigars, pipes and smokeless tobacco. Other questions asked for details of the longest held occupation, frequency of consumption of 35 food items and the consumption of coffee, beer and spirits. Death certificates were coded for underlying and contributory causes of death. Person–years were accumulated up to death, loss to follow-up or the end of the study in 1986. The age-adjusted relative risks for cancer mortality resulting from exposure to tobacco, occupation and dietary variables were computed using Poisson regression. Statistical interaction between smoking and other risk factors was also examined. About 23% of the cohort members were lost to follow-up (Hsing *et al.*, 1990b; Kneller *et al.*, 1991; Linet *et al.*, 1991; Chow *et al.*, 1992; Linet *et al.*, 1992; Zheng *et al.*, 1993; Hsing *et al.*, 1998).

MRFIT Study

The MRFIT study was conducted on a cohort of 361 662 men who were seen at an initial screening visit at 22 clinical centres throughout the USA and were thereby enrolled into the cohort in 1975. At the initial visit, 37% ($n = 133\ 117$) were current smokers, consuming an average of 26 cigarettes per day. A total of 12 866 participants were selected for an intervention trial based on a high risk score for coronary heart disease assigned at the baseline physical examination. High risk for coronary heart disease was determined by a combination of factors, using a logistic regression function derived from men in the same age group in the Framingham Heart Study, including cigarette smoking habits, diastolic blood pressure and serum cholesterol at the first screening visit (Kuller *et al.*, 1991).

Nurses' Health Study

In 1976, a cohort of 121 700 female registered nurses was assembled in the USA. At enrolment, the nurses completed a mailed questionnaire on risk factors for cancer and heart disease. Responses to food-frequency questionnaires were also collected in 1980, 1984, 1986 and 1990. The response rate to follow-up questionnaires was almost 96% through to 1990. Family members were the main source of vital status information for non-respondents but the National Death Index was also used. Multiple logistic regression models were used to compute odds ratios, after controlling for age, total energy intake and other potentially confounding variables (Willett *et al.*, 1987; Hunter *et al.*, 1990; Chute *et al.*, 1991; Giovannucci *et al.*, 1994a; Grodstein *et al.*, 1995; Kearney *et al.*, 1995; Fuchs *et al.*, 1996; Egan *et al.*, 2002).

Using the same cohort, Speizer *et al.* (1999) collected and updated information on smoking status and health status by means of a follow-up questionnaire distributed every 2 years from baseline until 1992.

Adventists' Health Study

A cohort of 34 198 non-Hispanic white Seventh-day Adventists in California (mean age, 55.4 years) was formed in 1976 when they completed a questionnaire concerning lifestyle. During the period of follow-up from enrolment until December 1982, newly diagnosed cancers were ascertained by various means. First, a record linkage of the cohort members was made with two population-based cancer registries, the Cancer Surveillance Program in Los Angeles and the Resource for Cancer Epidemiology in San Francisco. Second, annual contact was maintained with every member of the cohort by means of a mailed questionnaire in which the study subject was asked to report whether he or she had been hospitalized in the previous 12 months. Study staff reviewed all medical records for evidence of cancer diagnoses. The authors stated that follow-up was 99% complete. Relative risks adjusted for permanent covariates were computed by use of the Cox proportional hazards model (Mills *et al.*, 1988, 1989a,b, 1990, 1991; Singh & Fraser, 1998).

Leisure World Study

A detailed health questionnaire was sent to all residents of a retirement community in California in 1981, and to new residents in 1982, 1983 and 1985. A response rate of 61% was achieved overall. Almost all of the residents were Caucasians of the upper-middle class; about two-thirds were women; and 80% were aged 65–86 years. Histological diagnosis of cancer was obtained from local hospitals. All participants were sent a follow-up questionnaire every 2 years (Wu *et al.*, 1987; Ross *et al.*, 1990; Shibata *et al.*, 1994).

Cancer Prevention Study II (CPS-II)

The Cancer Prevention Study II (CPS-II) is a nationwide prospective mortality cohort study of nearly 1.2 million adults enrolled by volunteers of the American Cancer Society in 1982. As in CPS-I, enrolment was based on families and excluded persons in institutions and military service and others who would be difficult to trace (Garfinkel, 1985). Each participant completed a confidential four-page postal questionnaire on tobacco and alcohol use, diet and other factors potentially related to cancer. Deaths were ascertained from month of enrolment until 31 December 1996 through personal enquiries made by the volunteers in 1984, 1986 and 1988 and later through linkage with the National Death Index. Most of the smoking-related analyses were based on follow-up through 1986, 1988 or 1989 to minimize misclassification of exposure of those smokers who quit during follow-up. By 1988, 1.8% of the cohort were lost to follow-up and 79 802 (6.7%) had died (Thun & Heath, 1997). The ninth revision (ICD-9) of the International Classification of Diseases was used to code the underlying cause of death. Participants in CPS-II were more likely to be white (93%), married (81%) and educated (high school graduates or above, 85.6%) than the general population of the USA. The analyses excluded former cigarette smokers and persons with incomplete or unclassifiable data on smoking status or on the frequency or duration of cigarette smoking; men who ever smoked a pipe or a cigar or for whom pipe or cigar smoking status was unclear, were also excluded (Garfinkel, 1985; Stellman & Garfinkel, 1986; Garfinkel & Stellman, 1988; Stellman & Garfinkel, 1989a; Garfinkel & Boffetta, 1990; Calle *et al.*, 1994; Thun *et al.*, 1995; Heath *et al.*, 1997; Thun & Heath, 1997; Thun *et al.*, 1997a,b; Kahn *et al.*, 1998; Chao *et al.*, 2000; Shapiro *et al.*, 2000; Chao *et al.*, 2002).

Iowa Women's Health Study

The Iowa Women's Health Study was conducted on a cohort of 41 837 women who completed a postal questionnaire (response rate, 42.7%) sent in 1986 to a random sample of women from the Iowa driver's licence list (Potter *et al.*, 1992). The questionnaire covered information on age, smoking history, physical activity, level of education and alcohol consumption. Cigarette consumption was analysed as pack–years for both current and former smokers. Physical activity was ascertained by questionnaire and translated into a three-level physical activity score (low, medium and high). Incident cases of cancer were ascertained by the Health Registry of Iowa, which is a population-based cancer registry in the SEER Program of the National Cancer Institute (Bostick *et al.*, 1994; Harnack *et al.*, 1997; Parker *et al.*, 2000).

Health Professionals' Follow-up Study

In 1986, a cohort of 51 529 male dentists, optometrists, osteopaths, podiatrists, pharmacists and veterinarians in the USA were asked to respond to a postal questionnaire. The questionnaire included questions on age, current and past tobacco use, marital status, height and weight, ancestry, medications, disease history, physical activity and diet. Only men who completed the diet questionnaire adequately at baseline and who reported no cancer other than non-melanoma skin cancer were included in the analysis. After all baseline exclusions, 47 781 men comprised the analysis cohort. Follow-up questionnaires were sent in 1988, 1990, 1992 and 1994 to ascertain new cancer cases and to update smoking status. Family members and the National Death Index were the main source of information on vital status of non-respondents. After repeated mailings, the follow-up response rate was 94% up to 1994 and ascertainment of death was estimated to be 98%. Pooled logistic regression was used in analysis, which accounts for varying time to the outcome event and which is asymptotically equivalent to a Cox regression model with time-dependent covariate, given the short intervals and low probability of outcomes (Giovannuci *et al.*, 1994b; Kearney *et al.*, 1995; Fuchs *et al.*, 1996; van Dam *et al.*, 1999; Giovannuci *et al.*, 1999).

(ii) *Canada*

Canadian War Veterans' Study

After a pilot study to validate the questionnaire in 1955–56, 207 397 war veterans listed by the Canadian Pension Commission were sent a questionnaire on smoking habits, principal occupations and residence history. Approximately 118 000 forms (57%) were returned; after removal of duplicates and unusable forms some 92 000 (44%) (78 000 men and 14 000 women) remained. Follow-up was conducted from 1956 to 1962 through quarterly lists of deaths made available by the Department of Veterans Affairs. There were 9491 deaths among men and 1794 deaths among women; in most cases the cause of death was confirmed by autopsy (Best *et al.*, 1961; Lossing *et al.*, 1966).

National Breast Screening Study

The National Breast Screening Study is a multicentre, randomized controlled trial of mammography screening for breast cancer. Between 1980 and 1985, 89 835 women aged 40–59 years were recruited. In 1982, a second questionnaire was distributed to new attendees and previously enrolled women returning to the screening centres for further screening. A total of 56 837 women returned the questionnaires. Analyses are based mainly on respondents to the second questionnaire (Friedenreich *et al.*, 1993; Terry *et al.*, 2002).

(*c*) *Asia*

(i) *China*

Shanghai Factory Study

Chen *et al.* (1997) studied a cohort of 9351 adults from 11 factories in urban Shanghai. This cohort was identified in two stages: one during 1972–73 and the other during 1977–78, when members completed an interview based on a structured questionnaire. The questionnaire included questions on smoking, alcohol consumption, occupation, medical history and physical exercise. Vital status of the cohort members was monitored using factory records until 1 January 1993, with only 4% of subjects lost to follow-up. Cause of death was ascertained by examination of death certificates and the underlying cause of death was determined by two nosologists blinded to the smoking status of the individual. The Cox proportional hazards model was used for comparing a gradient of smoking categories with nonsmokers, while simultaneously adjusting for relevant covariates. At baseline, 61% of men and 7% of women smoked. Of the men, 46% consumed more than 20 cigarettes per day whereas only 11% of the female smokers consumed this number. Thirty-eight per cent of male smokers had started smoking prior to their twenty-fifth birthday, whereas among women, this figure was 25%.

Xi'an Factory Study

A cohort of 1696 persons was identified for a cross-sectional survey of coronary heart disease among employees of a machinery factory in Xi'an in May 1976. Employees were monitored for cause-specific mortality until 1996. Approximately 7% of the cohort members were subjected to occupationally hazardous exposures according to factory physicians. Vital status was ascertained from personnel and union records and confirmed through interviews of co-workers or relatives. The Cox regression model was used, adjusting for potential confounding factors including age, marital status, occupation, education, diastolic blood pressure and triglycerides and total cholesterol levels. During the 20 years of follow-up, 173 men and 45 women died (Lam *et al.*, 1997).

Shanghai Residential Study

A cohort of 213 800 residents from urban, suburban and surrounding rural areas of Shanghai were surveyed for smoking status. Subjects in urban areas were followed up annually for 12 years (January 1983 to December 1994) and subjects in suburban areas and rural counties for 11 years (January 1984 to December 1994). The cause of deaths during the follow-up period was ascertained by medical professionals. Only data on subjects aged 40 years and over at enrolment were analysed. Because the prevalence of smoking among women aged 40 years and over in suburban and rural areas was very low (3.1% and 1.5%, respectively), data on women in these areas were excluded from the analysis. Person–years observed were calculated by sex, age, smoking status and area of residence. A Poisson regression model was used to estimate age-adjusted relative risks with 95% confidence limits for each cause of death (Gao *et al.*, 1999).

Linxian Intervention Trial Study

In the frame of an intervention trial for micronutrients, approximately 30 000 residents of the Linxian region were interviewed to obtain information on usual dietary intake, tobacco use, alcohol drinking, family history of cancer and other factors. The cohort was followed up from 1986 until 1991, with little loss to follow-up. Information on cause of death and incidence of cancer was collected from local hospitals or a study medical team. Relative risks were adjusted for potential confounders as well as the vitamin/mineral intervention group (Guo *et al.*, 1994).

Shanghai Men's Study

Ross *et al.* (1992) and Yuan *et al*. (1996) studied a cohort of 18 244 male residents of Shanghai, enrolled between 1986 and 1989 (80% of eligible subjects). A structured questionnaire was completed at a face-to-face interview. The information obtained included level of education, history of tobacco and alcohol use, current diet and medical history. At recruitment, 50% of study subjects were current smokers, half of whom smoked 20 or more cigarettes per day. Former smokers represented 7% of the cohort while 43% of cohort members had never smoked cigarettes regularly. Cancer incidence was ascertained through the population-based Shanghai Cancer Registry and vital status was ascertained by inspection of the Shanghai death certificate records. Only 50 subjects were lost to follow-up which continued until 1993.

Taiwanese Study

A cohort of 14 397 residents of metropolitan, urban and rural areas in Taiwan, China were recruited between 1982 and 1986. Information on sociodemographic characteristics, smoking status, alcohol drinking and food habits was collected at interview using a structured questionnaire. The cohort was followed up until 1994 by linkage with the death certification system in Taiwan. Causes of death were classified according to ICD-9. Cox proportional hazards regression models were used to derive relative risks for mortality and to examine dose–responses (Liaw & Chen, 1998).

(ii) *Japan*

Life Span Study

The Life Span Study cohort originally consisted of 100 000 survivors [sex distribution not reported] of the atomic bomb blasts in Hiroshima and Nagasaki. The cohort was expanded in 1968 and 1985 by adding approximately 10 000 survivors each time. The total cohort included approximately 120 000 individuals, of whom approximately 27 000 were non-exposed controls. Information on smoking was obtained from three interview surveys conducted on a subgroup of the entire cohort in 1963–64, 1964–68 and 1968–70, and four postal surveys conducted on various subgroups in 1965, 1969, 1979 and 1980. The cancer incidence in 61 505 survivors for whom smoking data were available was reported. For 42% of this group, information on smoking was available from at least two surveys. Information on cancer incidence and mortality was obtained from the Radiation Effects Research Foundation tumour registry and mortality database. Poisson regression models were used to fit log-linear relative risk and linear excess relative risk models (Akiba, 1994; Land *et al.*, 1994; Goodman *et al.*, 1995).

Japanese Physicians' Study

A survey of smoking and drinking habits among physicians in western Japan was carried out using self-administered questionnaires in 1965. From 6815 male respondents in nine prefectures (51% response rate), a cohort of 5477 male physicians was established. Vital status was followed until 1983 and confirmed by various medical associations. Copies of death certificates were obtained from the District Legal Affairs Bureau and the cause of death coded with the ICD-8. After exclusions, the analysis was done on 5130 men. Statistical analysis was performed using the Cox proportional hazards model (Kono *et al.*, 1987).

Six-prefecture Study

In 1965, 122 261 men and 142 857 women aged ≥ 40 years (95% of the census population) in 29 health centre districts from six prefectures in Japan were interviewed. The six prefectures were selected as being representative of the entire country. The questionnaire included questions on smoking, alcohol consumption and dietary habits, occupation, and marital status. A record linkage system was established for the annual follow-up. During the 16-year follow-up period, 8% of the cohort migrated from the original health districts. Deaths among cohort members were monitored by linkage to vital statistics kept at each public health centre. Cause of death was coded using the 7th revision of the International Classification of Diseases (Hirayama, 1967, 1975a,b, 1977a,b, 1978, 1981, 1982, 1985, 1989a,b,c; Mizuno *et al.*, 1989; Akiba & Hirayama, 1990; Hirayama, 1990; Kinjo *et al.*, 1998).

Regular male smokers who had started smoking between 18 and 22 years of age, and who were, at that time, between the ages of 40 and 79 years, were selected from the cohort for further analysis, resulting in a subcohort of 49 013 men (Mizuno *et al.*, 1989). [This study was large and unique in that it involved a non-Caucasian population and was based on interviews rather than self-completed questionnaires.]

Chiba Center Association Study

The Chiba Center Association Study was a nested case–control study based on a cohort population of 17 200 male participants in a mass screening for gastric cancer by the Chiba Cancer Association in Japan in 1984. Cancer cases in cohort members were detected by record linkage to the Chiba Cancer Registry. The participants were followed from 1984 until 1993. For each cancer case, two controls were selected from the cohort population by matching on sex, birth year and area of residence (Murata *et al.*, 1996).

Fukuoka Study

A baseline survey was conducted from 1986 until 1989 among the general population of Fukuoka, the region with the highest liver cancer mortality in Japan. All inhabitants aged > 30 years were asked to answer a questionnaire, to which the response rate was 84.3%. A follow-up survey was conducted annually to verify the vital status of participants. For study subjects who had died, the cause of death was determined from the health certificate and classified according to ICD-9. The participants were followed up until 1996.

Women were excluded from this survey because of the small numbers of deaths and current smokers. After exclusions, 4050 men were included in the analysis. Cox proportional hazards regression analysis was employed to estimate relative risks and 95% confidence intervals (Mizoue *et al.*, 2000).

(*d*) *Others*

Seven-country Study

Jacobs *et al.* (1999) studied a cohort of 12 763 men in seven countries between 1957 and 1964, after administration of a standardized questionnaire. The questionnaire included questions about daily cigarette consumption at entry, years of smoking cessation for former smokers, age, weight and height. A physical examination at baseline included a comprehensive history of cardiovascular and cerebral vascular health. Information on vital status and cause of death was obtained during the 25 years of follow-up, by examining death certificates, collecting medical records from hospitals and from interviews with physicians and relatives. A Cox proportional hazards model was used to compute relative risk.

Israel Civil Service Centre Study

In 1963, Kark *et al.* (1995) studied a cohort of 9975 male civil servants between the ages of 40 and 69 years living in Haifa, Jerusalem and Tel Aviv, Israel. The initial examination included a physical examination, measurement of blood pressure, weight and height, electrocardiography and venipuncture. A questionnaire, which included questions on sociodemography, health behaviour, diet and psychosocial factors, was administered by a trained interviewer. Further examinations were carried out in 1965 and 1968. The follow-up period ended on 31 December 1986 and included 198 298 person–years of cancer surveillance by linking the cohort list to both the National Cancer Registry and the National Death Registry. A total of 153 cases of lung cancer were identified. The Cox proportional hazards model was used to compute relative risk by including age as a continuous variable, and city of employment, cigarette smoking and body-mass index as dummy variables. The reference categories were never-smokers, resident in Haifa and Tel Aviv, and the upper fifth of the body-mass index frequency distribution.

Table 2.1. Cohort studies of cancer and cigarette smoking

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
United Kingdom								
British Doctors' Study	1951	Doll & Hill (1964a,b); Doll & Peto (1976); Doll *et al.* (1980, 1994)	1951–91	40 634 (34 440 men, 6194 women) British doctors [age not reported]	Postal questionnaire	Deaths	Lung, urinary bladder, kidney, upper aerodigestive tract (oesophagus, mixed), pancreas, stomach, colon, rectum, liver, leukaemia, ovary, non-Hodgkin lymphoma, multiple myelomas	Information on pipe and cigars
Whitehall Study	1967–69	Ben-Shlomo *et al.* (1994)	1967–87	19 018 men from the British Civil Service, clinically examined, aged 40–69 years	Interview	Deaths	Lung	Information on pipe and cigars
British United Provident Association (BUPA) Study	1975–82	Wald & Watt (1997)	1975–93	21 520 professional and businessmen, aged 35–64 years	Interview	Deaths	Lung	Information on pipe and cigars
Sweden								
Swedish Twin Registry Study	1961	Floderus *et al.* (1988); Steineck *et al.* (1988); Grönberg *et al.* (1996); Terry *et al.* (1998, 1999, 2001)	1961–97	10 942 same-sex twin pairs, born 1886–1925	Postal questionnaire	Deaths	Lung, urinary bladder, stomach, colon, rectum, endometrium, prostate	Information on pipe and cigars Floderus *et al.* mentioned 10 945 pairs.

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Swedish Census Study	1963	I: Cederlöf *et al.* (1975); Carstensen *et al.* (1987)	1963–72	Adults selected from the 1960 census population, aged 18–69 years I: 51 911 (25 444 men, 26 467 women)	Postal questionnaire (94%), telephone, interview	Deaths	Lung, urinary bladder, pancreas, colon, rectum, liver, endometrium, cervix	Information on pipe and cigars Stratified by urban-rural residence
		II: Nordlund *et al.* (1997, 1999)	1964–89	II: 41 710 (15 881 men, 25 829 women)	Postal questionnaire (87%), telephone, home visits	Cases	Lung, urinary bladder, kidney, upper aerodigestive tract (oral cavity, pharynx, oesophagus, mixed), pancreas, stomach, colon/ rectum, liver, breast, endometrium, cervix, leukaemia	Stratified by place of residence
Swedish Construction Workers' Study	1971–75 (I) 1971–91 (II) 1971–92 (III)	I: Adami *et al.* (1996); Nyrén *et al.* (1996) II: Adami *et al.* (1998) III: Chow *et al.* (2000)	1971–92	Male construction workers, aged ≥ 35 years I: 143 998 II: 334 957 III: 363 992	Self-administered questionnaire/ interview	Cases	Kidney, colon, rectum, prostate, leukaemia, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myelomas	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Norway								
Norwegian Cohort Study	1964–65	Heuch *et al.* (1983); Engeland *et al.* (1996a,b); Kjaerheim *et al.* (1998)	1966–93	26 132 subjects (11 863 men, 14 269 women) including a sample of the 1960 census population, a random sample from 4 selected counties and a sample of siblings living in Norway with a sibling living in the USA, aged 33–72 years	Postal questionnaire	Cases	Lung, urinary bladder, kidney, upper aerodigestive tract (mixed), pancreas, stomach, colon, rectum, breast, endometrium, cervix, prostate, leukaemia, ovary	
Norwegian Screening Study	1974–78 (I) 1972–78 (II) 1977–83 (III)	I: Vatten & Kvinnsland (1990) II: Tverdal *et al.* (1993); Thune & Lund (1994) III: Veierød *et al.* (1997)	1972–88	Participants in a health screening programme, aged 35–49 years I: 24 329 women II: 44 290 men, 24 535 women; 53 242 men III: 26 119 men	Interview	Deaths	Lung, pancreas, stomach, colon, rectum, breast, cervix, prostate	Information on pipe and cigars
Finland								
Finnish Men's Study	1962	Pedersen *et al.* (1969); Tenkanen *et al.* (1987); Hakulinen *et al.* (1997)	1964–80	4452 men from 3 urban and 3 rural areas, born 1898–1917	Interview	Cases	Lung, prostate	Hakulinen *et al.* (1997) also included subjects from another survey in 1972–77

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Finnish Mobile Clinic Health Examination Study	1966–72	Knekt *et al.* (1998); Heikkilä *et al.* (1999)	1966–91	56 973 subjects having received multiphasic health examination from the Mobile Clinic [sex distribution not reported]	Postal questionnaire, checked by interview	Cases	Colon, rectum, prostate	
Iceland								
Reykjavík Study	1967–91	Tulinius *et al.* (1997)	1968–95	22 946 (11 366 men, 11 580 women) residents of Reykjavík, born 1907–1954, aged 31–61 years	Self-administered questionnaire	Cases	Lung, urinary bladder, oesophagus, pancreas, stomach, colon, endometrium, cervix, prostate, leukaemia	
The Netherlands								
Dutch Study	1975–77, 1982–83	Ellard *et al.* (1995); de Waard *et al.* (1995); van Wayenburg *et al.* (2000)	1975–90	26 697 women from 2 breast cancer screening programmes (DOM project and Lutine Study) in Utrecht, aged 40–64 years	Self-administered questionnaire	Cases	Lung, colon/rectum	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Denmark								
Copenhagen City Heart Study	1976–78, 1981–83	Lange *et al.* (1992); Prescott *et al.* (1999)	1976–89	14 223 subjects (6511 men, 7703 women) randomly selected among 90 000 persons living in a defined area of Copenhagen, aged ≥ 20 years	Self-administered questionnaire	Deaths	Lung	The study by Prescott *et al.* (1999) was based on data from three cohorts, including the Copenhagen City Heart Study, the Centre of Preventive Medicine and the Copenhagen Male Study.
USA								
Framingham Heart Study	1948–52	Williams *et al.* (1981); Freund *et al.* (1993)	1948–82	5209 subjects receiving routine examinations at the Framingham Heart Study Clinic, MA	Interview	Cases	Lung, colon	
American Cancer Society (nine-state) Study	1952	Hammond & Horn (1958a,b)	1952–55	187 783 men from 9 states, aged 50–69 years	Self-administered questionnaire	Deaths	Lung, urinary bladder, upper aerodigestive tract (mixed), pancreas, colon, rectum	Information on pipe and cigars

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
US Veterans' Study	1954, 1957	Kahn (1966); Rogot & Murray (1980); Kinlen & Rogot (1988); McLaughlin *et al.* (1989); Hsing *et al.* (1990a); McLaughlin *et al.* (1990a,b); Hsing *et al.* (1991); Heineman *et al.* (1992); Zahm *et al.* (1992); Chow *et al.* (1993); Heineman *et al.* (1994); Chow *et al.* (1995); Heineman *et al.* (1995); McLaughlin *et al.* (1995); Chow *et al.* (1996)	1954–80	293 958 male holders of a US Government Life Insurance, aged 31–84 years	Postal questionnaire	Deaths	Lung, urinary bladder, kidney, upper aerodigestive tract (oral cavity, nasopharynx, larynx, pharynx, oesophagus), pancreas, stomach, colon, rectum, liver, leukaemia, soft-tissue sarcoma, brain, biliary ducts, adrenals, non-Hodgkin lymphoma, Hodgkin's lymphoma, multiple myelomas	Information on pipe and cigars
Californian Study	1954–57	Weir & Dunn (1970)	1954–62	68 153 male labour union members, aged 35–64 years	Postal questionnaire	Deaths	Lung, urinary bladder, upper aerodigestive tract (oral cavity, larynx, pharynx, oesophagus), pancreas	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Cancer Prevention Study I (CPS-I)	1959–60	Hammond & Garfinkel (1961); Hammond (1966); Garfinkel (1980); Hammond & Seidman (1980); Garfinkel (1985); Stellman & Garfinkel (1986, 1989a,b); Garfinkel & Boffetta (1990); Thun *et al.* (1995); Thun & Heath (1997); Thun *et al.* (1997a); Shanks & Burns (1998)	1959–72	1 051 038 adults from 25 states, aged > 30 years	Postal questionnaire	Deaths	Lung, urinary bladder, upper aerodigestive tract (oesophagus, mixed), pancreas, stomach, colon/rectum, liver, endometrium, cervix, leukaemia, biliary ducts	Information on pipe and cigars For women, all sites of the aerodigestive tract and all cancers of the haematopoietic system were grouped.
Harvard Alumni Study	1962, 1966	Paffenbarger *et al.* (1977, 1978)	1962–92	13 905 male Harvard alumni; mean age, 58.3 years	Postal questionnaire	Cases/ deaths	Leukaemia, Hodgkin lymphoma	
Tecumseh Community Health Study (I/II/III)	1962–69	Islam & Schottenfeld, 1994	1962–87	3956 residents (1857 men, 2099 women) of Tecumseh, MI, aged > 25 years	Interview	Cases	Lung	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Kaiser Permanente Medical Care Program Study	1964–73 (I) 1978–85 (II) 1964–91 (I+II)	I: Hiatt & Bawol (1984); Hiatt & Fireman (1986); Friedman (1993); Friedman & van den Eeden (1993); Iribarren *et al.* (1999, 2001) II: Hiatt *et al.* (1988); Klatsky *et al.* (1988); Sidney *et al.* (1993); Hiatt *et al.* (1994) I+II: Herrinton & Friedman (1998)	I: 1964–97 II: 1978–87 I + II: 1973–93	Members of the Kaiser Permanente Medical Care Program I: approx. 175 000 members aged 15–94 years II: approx. 80 000 members aged 30–89 years I+II: 252 836 members aged 16–84 years	Interview	Cases	Lung, pancreas, colon, rectum, breast, prostate, leukaemia, thyroid, non-Hodgkin lymphoma, multiple myelomas	Information on pipe and cigars Period of collection and age range of participants at baseline vary slightly between studies, leading to different cohort sizes
American Men of Japanese Ancestry Study	1965–68	Stemmermann *et al.* (1988); Severson *et al.* (1989); Nomura *et al.* (1990a,b); Chyou *et al.* (1992, 1993a,b, 1995); Nomura *et al.* (1995); Chyou *et al.* (1996)	1965–95	8 006 American men of Japanese ancestry residing in Hawaii, born 1900–19	Interview	Cases	Lung, urinary bladder, upper aerodigestive tract (mixed), stomach, colon, rectum, colorectal polyps, prostate	
Lutheran Brotherhood Insurance Study	1966	Hsing *et al.* (1990b); Kneller *et al.* (1991); Linet *et al.* (1991); Chow *et al.* (1992); Linet *et al.* (1992); Zheng *et al.* (1993); Hsing *et al.* (1998)	1966–86	17 633 male holders of a Lutheran Brotherhood Insurance policy, largely of Swedish, Norwegian or German descent, aged ≥ 35 years	Postal questionnaire	Deaths	Lung, pancreas, stomach, colon/rectum, leukaemia, non-Hodgkin lymphoma, multiple myelomas	Information on pipe and cigars
MRFIT Study	1975	Kuller *et al.* (1991)	1975–85	12 866 randomized participants initially selected for the MRFIT, aged 35–57 years	Interview	Deaths	Lung, urinary bladder, kidney, upper aerodigestive tract (oesophagus, mixed), pancreas	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Nurses' Health Study	1976	Willett *et al.* (1987); Hunter *et al.* (1990); Chute *et al.* (1991); Giovannucci *et al.* (1994a); Kearney *et al.* (1995); Grodstein *et al.* (1995); Fuchs *et al.* (1996); Speizer *et al.* (1999); Egan *et al.* (2002)	1976–92	121 700 female nurses from 11 states, aged 30–55 years	Postal questionnaire	Cases	Lung, colon, rectum, colorectal polyps, pancreas, breast, skin	
Adventists' Health Study	1976	Mills *et al.* (1988, 1989a,b, 1990, 1991); Singh & Fraser (1998)	1976–82	34 198 male and female Adventists, aged > 25 years	Postal questionnaire	Cases	Urinary bladder, breast, pancreas, colon, prostate, leukaemia, multiple myeloma	
Leisure World Study	1981–82 (I) 1981–85 (II)	I: Wu *et al.* (1987) II: Ross *et al.* (1990); Shibata *et al.* (1994)	1981–85	Retirees living in a retirement community I: 11888 II: 13 976 [sex distribution not reported]	Postal questionnaire	Cases	Pancreas, colon/rectum, prostate	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Cancer Prevention Study II (CPS-II)	1982	Garfinkel (1985); Stellman & Garfinkel (1986); Garfinkel & Stellman (1988); Stellman & Garfinkel (1989a); Garfinkel & Boffetta (1990); Calle *et al.* (1994); Thun *et al.* (1995); Heath *et al.* (1997); Thun & Heath (1997); Thun *et al.* (1997a,b); Kahn *et al.* (1998); Chao *et al.* (2000); Shapiro *et al.* (2000); Chao *et al.* (2002)	1982–96	1 185 106 adults from 25 states, aged > 30 years	Postal questionnaire	Deaths	Lung, kidney, stomach, colon/rectum, colorectal polyps, breast, leukaemia	Information on pipe and cigars
Iowa Women's Health Study	1986	Potter *et al.* (1992); Gapstur *et al.* (1992); Bostick *et al.* (1994); Harnack *et al.* (1997); Parker *et al.* (2000)	1986–98	41 837 women randomly selected from the Iowa driver's licence list, aged 55–69 years	Postal questionnaire	Cases	Lung, pancreas, colon, breast, non-Hodgkin lymphoma	
Health Professionals' Follow-up Study	1986	Giovannucci *et al.* (1994b); Kearney *et al.* (1995); Fuchs *et al.* (1996); van Dam *et al.* (1999); Giovannucci *et al.* (1999)	1986–94	47 781 male health professionals, aged 40–75 years	Postal questionnaire	Cases	Pancreas, colon/rectum, colorectal polyps, prostate, skin	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Canada								
Canadian War Veterans' Study	1956	Best *et al.* (1961); Lossing *et al.* (1966)	1956–62	92 000 war veterans (78 000 men, 14 000 women), aged 55–79 years	Postal questionnaire	Deaths	Lung, urinary bladder, pancreas	
National Breast Screening Study (NBSS)	1980–85	Friedenreich *et al.* (1993); Terry *et al.* (2002)	1980–93	Multicentre randomized controlled trial of mammography screening for breast cancer in almost 90 000 women, aged 40–59 years	Self-administered questionnaire	Cases	Breast, endometrium	Friedenreich *et al.* (1993) conducted a nested case–control study.
China								
Shanghai Factory Study	1972–73, 1977–78	Chen *et al.* (1997)	1972–93	9351 factory employees (6494 men, 2857 women) aged 35–64 years	Interview	Deaths	Lung, upper aerodigestive tract (oesophagus), stomach, colon/rectum, liver	Site-specific analyses conducted for men only
Xi'an Factory Study	1976	Lam *et al.* (1997	1976–96	1696 factory employees (1124 men, 572 women) aged ≥ 35 years	Interview	Deaths	Lung, upper aerodigestive tract (oesophagus), liver	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Shanghai Residential Study	1983–84	Gao *et al.* (1999)	1983–94	213 800 residents of urban, suburban and rural areas of Shanghai, aged > 20 years [sex distribution not reported]	Interview	Deaths	Lung, upper aerodigestive tract (oesophagus), stomach, liver	
Linxian Intervention Trial Study	1985	Guo *et al.* (1994)	1985–91	Approx. 30 000 residents of 4 communes in Linxian, aged 40–69 years [sex distribution not reported]	Interview	Cases	Upper aerodigestive tract (oesophagus), stomach	Nested case–control study
Shanghai Men's Study	1986–89	Ross *et al.* (1992); Yuan *et al.* (1996)	1986–93	18 244 male residents of 4 communities in Shanghai, aged 45–64 years	Interview	Cases	Lung, urinary bladder, upper aerodigestive tract (oesophagus, mixed), pancreas, stomach, colon, rectum, liver	Ross *et al.* (1992) conducted a nested case–control study on smoking and risk of colorectal adenomatous polyps.
China, Province of Taiwan								
Taiwanese Study	1982–86	Liaw & Chen (1998)	1982–94	14 397 residents (11 096 men, 3301 women) of Taiwan, aged > 41 years	Interview	Deaths	Lung, urinary bladder, upper aerodigestive tract (nasopharynx, oesophagus, mixed), stomach, colon/rectum, liver, pancreas, cervix	

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ deaths	Neoplasms analysed	Comments
Japan								
Life Span Study	1963, 1968, 1985	Akiba (1994); Land *et al.* (1994); Goodman *et al.* (1995)	1963–87	93 000 exposed survivors of the atomic blasts and 27 000 non-exposed controls [sex distribution not reported]	Postal questionnaire, interview	Cases	Lung, upper aerodigestive tract (nasal cavity and sinuses, larynx, oesophagus, mixed), colon, rectum, liver, breast	
Japanese Physicians' Study	1965	Kono *et al.* (1987	1965–83	5477 male physicians, aged 27–89 years	Self-administered questionnaire	Deaths	Lung, upper aerodigestive tract (oesophagus, mixed), stomach, colon/rectum, liver	
Six-prefecture Study	1965	Hirayama (1967, 1975a,b, 1977a,b, 1978, 1981, 1982, 1985, 1989a,b,c); Mizuno *et al.* (1989); Akiba & Hirayama (1990); Hirayama (1990); Kinjo *et al.* (1998)	1965–81	265 118 subjects (122 261 men, 142 857 women) covering > 90% of the census population from 29 districts, aged > 40 years	Interview	Deaths	Lung, urinary bladder, upper aerodigestive tract (larynx, oesophagus, mixed), pancreas, stomach, colon, rectum, liver, cervix	
Chiba Center Association Study	1984	Murata *et al.* (1996)	1984–93	17 200 male participants in a mass screening for gastric cancer	Self-administered questionnaire	Cases	Lung, urinary bladder, upper aerodigestive tract (mixed), pancreas, stomach, colon, rectum, liver	
Fukuoka Study	1986–89	Mizoue *et al.* (2000)	1986–96	13 270 residents of 4 towns in Fukuoka, aged ≥ 30 years [sex distribution not reported]	Self-administered questionnaire	Deaths	Stomach, liver	Results reported include only men because of the low prevalence of site-specific cancer deaths in women.

Table 2.1 (contd)

Country Name of study	Date of cohort sampling	References	Maximum years of follow-up	Cohort sample and age at beginning of follow-up	Collection of information	Cases/ Deaths	Neoplasms analysed	Comments
Others								
Seven-Country Study	1957–64	Jacobs *et al.* (1999)	25 years	12 763 men from 16 cohorts in Croatia, Finland, Greece, Italy, Japan, the Netherlands, Serbia and the USA, aged 40–59 years	Self-administered questionnaire	Deaths	Lung	
Israel Civil Service Centre Study	1963	Kark *et al.* (1995)	1963–86	9975 male civil servants in Israel, aged 40–69 years	Interview	Cases	Lung	

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2.1 Cigarette smoking

2.1.1 *Lung cancer*

Lung cancer is now the most common type of cancer in the world, and the total number of cases that occur annually is estimated to be 1.2 million (Parkin *et al.*, 2000).

The causal relationship between tobacco smoking and lung cancer was established during the 1950s (Medical Research Council, 1957; Doll, 1998).

Tobacco smoking was considered to be causally related to cancer of the lung in the *IARC Monograph* on tobacco smoking based on the findings of the studies available at that time (IARC, 1986). Since 1986, much further evidence has accumulated on the magnitude of the increase in lung cancer risk associated with prolonged smoking, the progressive increase in smoking rates in women as well as in men, the decrease in risk that occurs among smokers after cessation compared with smokers who continue smoking, and the increase in the risk for adenocarcinoma of the lung in smokers in recent years. The current epidemiological evidence comes from many more countries and geographical regions than were considered in 1986. The following section summarizes the epidemiological evidence on how the relationship between smoking and lung cancer varies with duration and intensity of smoking, cessation of smoking, type of cigarette, histological type of lung cancer and population characteristics. The main characteristics and the results of the cohort studies are presented in Tables 2.1 and Tables 2.1.1.1–2.1.1.3, respectively. For the case–control studies, the study designs are summarized in Table 2.1.1.4 while results are presented in Tables 2.1.1.5–2.1.1.13.

(*a*) *Factors affecting risk*

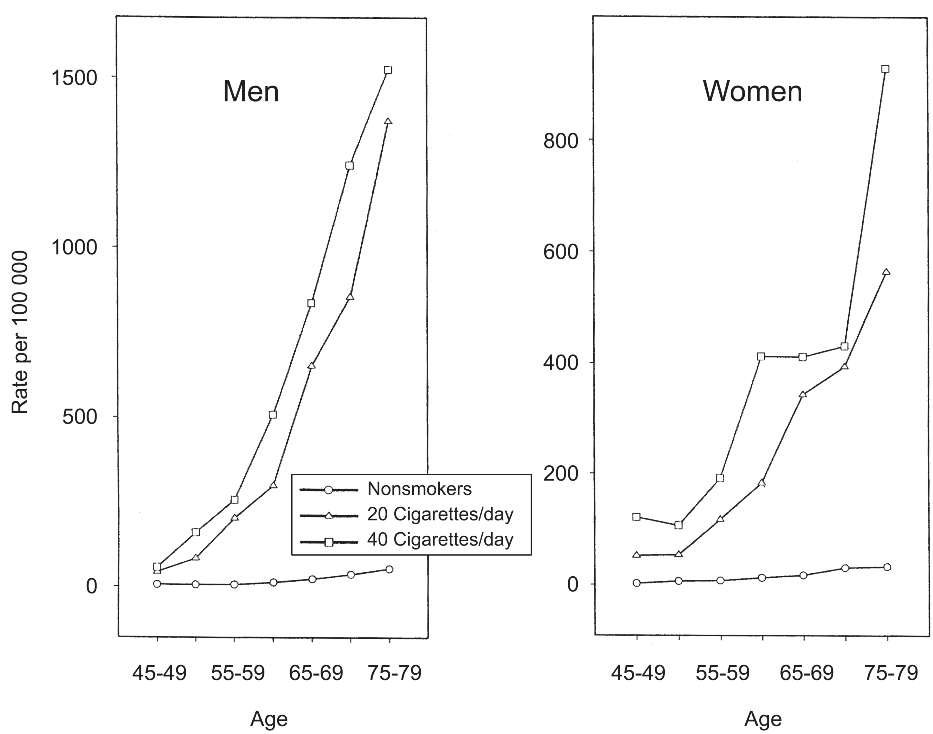
(i) *Duration and intensity of smoking*

The results of cohort and case–control studies that reported on duration and intensity of smoking in association with lung cancer risk are presented in Tables 2.1.1.1 and Tables 2.1.1.5–2.1.1.7, respectively. In smokers, the most important parameter of smoking that affects lung cancer risk is the duration of regular smoking, although risk also increases with the number of cigarettes smoked per day. The stronger association of lung cancer risk with the duration than with the intensity of smoking may in part reflect the accuracy with which these two parameters are measured. Duration is determined by the age at initiation and attained age in current smokers or by age at smoking cessation. These parameters can be estimated reasonably accurately in epidemiological studies. The intensity of smoking is influenced not only by the number of cigarettes smoked per day, which can be estimated from self-reporting, but also by depth of inhalation, number of puffs taken per cigarette and retention time in the lung. Misclassification of smoking intensity may occur because of the necessity for a smoker to maintain his or her accustomed level of nicotine intake. Smokers therefore compensate for reductions in the number of cigarettes smoked per day by smoking each cigarette more intensively. The studies that are most informative about the relative importance of duration of smoking versus number of cigarettes smoked per day are large cohort studies where age-specific lung cancer rates can be compared across a broad range of ages and durations of smoking within narrow strata of numbers of cigarettes smoked per day.

For example, Figure 2.1.1.1 presents the annual death rate from lung cancer (per 100 000) among men and women enrolled in the American Cancer Society cohort (CPS-II) during the first 6 years of follow-up (1982–88) (see Table 2.1 for cohort description). Age-specific death rates are presented for lifelong nonsmokers and for participants who reported that they smoked 20 cigarettes per day or 40 cigarettes per day at the time of enrolment in the study. For men and women, the death rate from lung cancer increased approximately 30-fold from age 45–49 years to age 75–79 years among those who reported currently smoking either 20 cigarettes per day or 40 cigarettes per day at enrolment. This age interval corresponds to an average increase in the duration of smoking from 22–26 years to 62–66 years among current smokers in this population. There is a much smaller increase in the age-specific death rates between participants who smoked 40 cigarettes per day and those who smoked 20 cigarettes per day.

The critical relationship between the duration of smoking and risk for lung cancer was demonstrated by Peto and Doll (1984) based on a 20-year follow-up of the British Doctors' Study (Doll & Peto, 1976). Using a statistical model fitted to data from the men

Figure 2.1.1.1. Lung cancer mortality rates by age and amount currently smoked

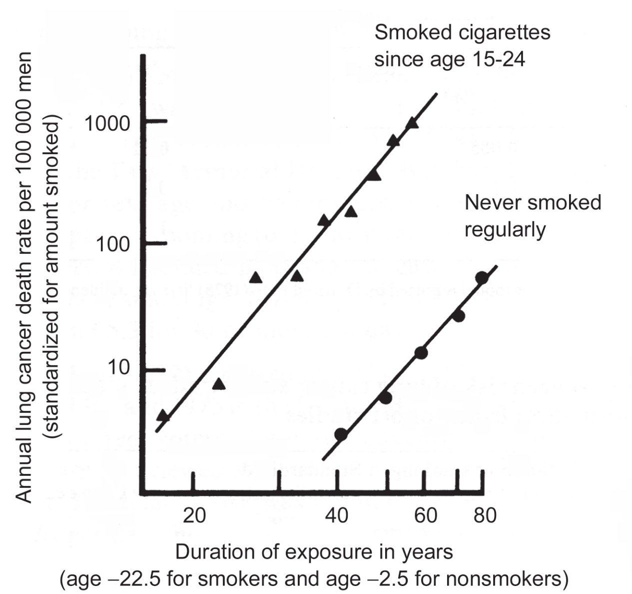


in the British Doctors' Study, Doll and Peto (1978) estimated that the annual excess incidence of lung cancer increased approximately 100-fold when men who had smoked for 45 years were compared with those who had smoked for 15 years (see Table 2.1.1.14). This 100-fold increase with duration of smoking is seen for both moderate and heavy smokers. Case–control studies that have examined risk in relation to both duration of smoking and number of cigarettes smoked per day have demonstrated a stronger association with duration (see Table 2.1.1.7).

The effects of duration of smoking are so strong, and so closely correlated with age, that it is difficult to determine whether ageing itself has any independent effect on excess lung cancer rates among people of different ages who have similar smoking histories. Lung cancer risk was found to increase exponentially with age among male current smokers in both the British Doctors' Study (Figure 2.1.1.2) and in CPS-II (Figure 2.1.1.3). Death rates from lung cancer also increased exponentially with age among female current smokers in CPS-II during the 1982–88 follow-up, except in women aged ≥ 80, who represented birth cohorts of women who started smoking 4–15 years later than the average age of starting smoking among women aged 40 in 1982 (Thun *et al.*, 1997a).

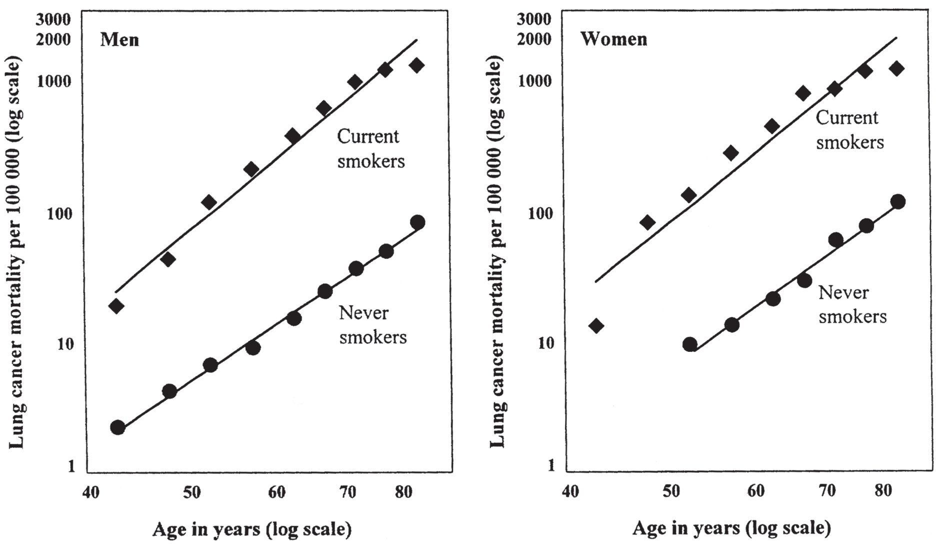
The close correspondence between the age of starting smoking and the duration of cigarette smoking among current smokers results in higher age-specific cancer death rates in smokers who began smoking at earlier ages. This is illustrated in Figure 2.1.1.4, based on 8.5 years of follow-up of the US Veterans cohort (Kahn, 1966). In both 'moderate'

Figure 2.1.1.2. Lung cancer mortality rates among male nonsmokers and regular cigarette smokers



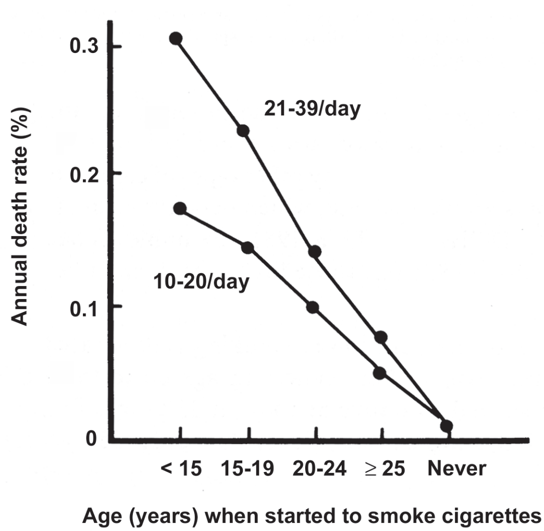
From Doll (1971) and Peto and Doll (1984)

Figure 2.1.1.3. Lung cancer mortality rates by cigarette smoking status and age in men and women from the CPS-II cohort, 1982–88



Adapted from Thun *et al.* (1997a)

Figure 2.1.1.4. Relationship between age at starting regular cigarette smoking and lung cancer death rates at age 55–64 years in US men



From Doll and Peto (1981)

smokers (10–20 cigarettes per day) and 'heavy' smokers (21–39 cigarettes per day), the annual death rate from lung cancer at age 55–64 was higher the younger the age at which the men had started to smoke. Age at starting smoking cannot be separated from the duration of smoking in analyses of current smoking by attained age.

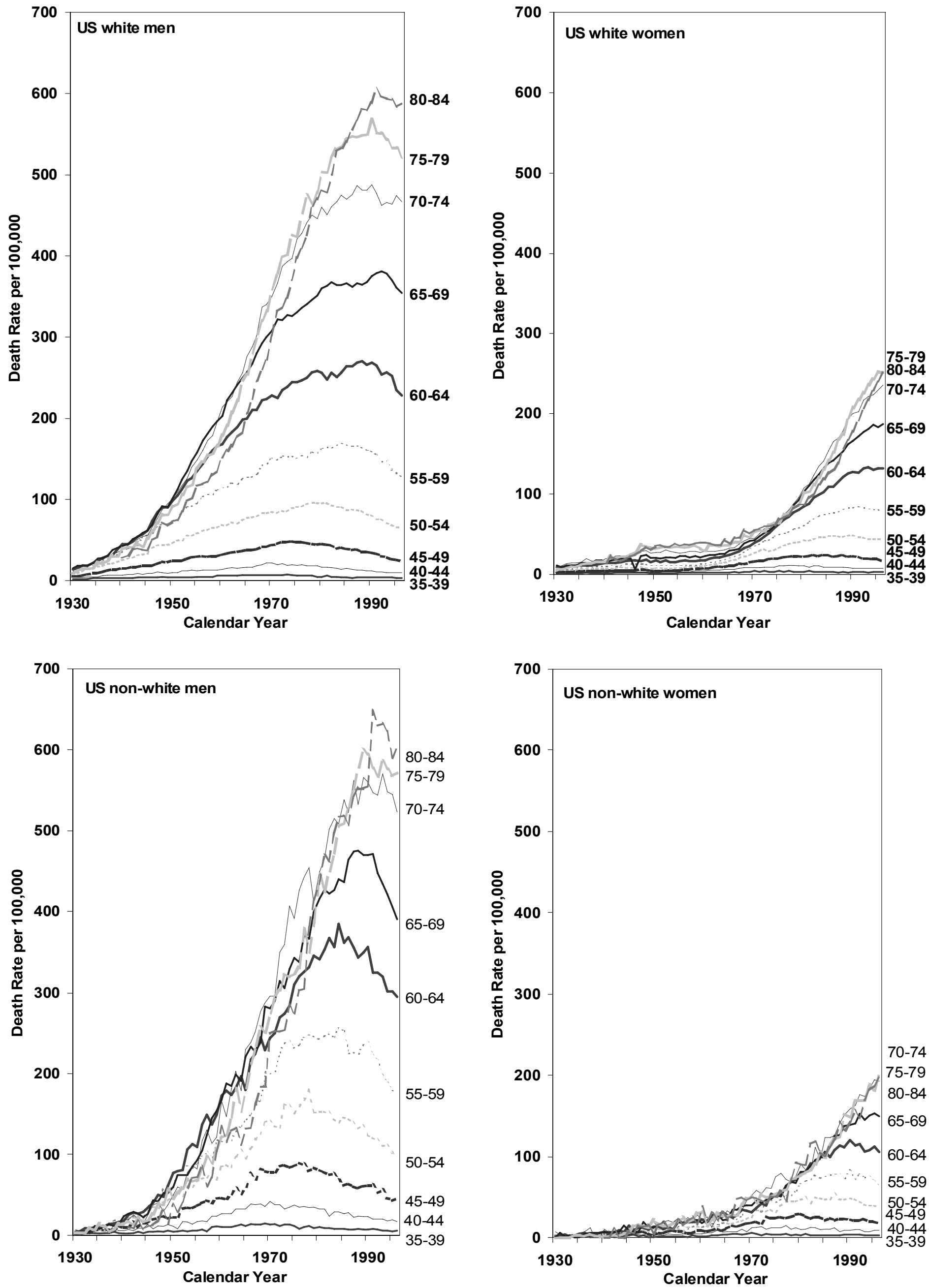
A consequence of the strong relationship between prolonged smoking and lung cancer risk is that the full effect of smoking in a population is not seen in national rates of lung cancer until regular smoking has been entrenched in that population for at least 50 years. The consequences of smoking on lung cancer may also be underestimated in epidemiological studies that do not include long-term smokers. Differences in the distribution of the age groups of the smokers being studied and in the duration of regular heavy smoking contribute to the quantitative variations in the age-specific absolute lung cancer rates and in the relative risks associated with current smoking. The maturation of the smoking epidemic is evident in temporal changes in age-specific death rates for lung cancer in countries where cigarette smoking has been common for many decades. The age-specific lung cancer rates reflect the ageing of successive birth cohorts of smokers. For example, Figure 2.1.1.5 depicts the changes in age-specific death rates from lung cancer in white and non-white men and women in the USA from 1930 to 1996. Within each age group, the death rate from lung cancer has first increased and then decreased, with the downturn in the age-specific death rate from lung cancer beginning earlier at younger than at older ages. These temporal patterns in lung cancer reflect historical patterns in cigarette smoking over the previous 10–60 years. Successive birth cohorts (generations) of men and women smoked progressively more than the previous generation over the first half of the twentieth century, and then progressively less until intensified marketing to adolescents began in the 1990s.

(ii) *Smoking cessation*

The effect of smoking cessation on relative risk for lung cancer has been evaluated by a large number of analytical studies. In many case–control studies (Table 2.1.1.8) and in cohort studies (Table 2.1.1.2) that examined the lung cancer risk among people who quit smoking cigarettes, a significant reduction in the relative risk of lung cancer was observed. This reduction in relative risk was observed in both men and women, among light (i.e. < 20 cigarettes/day) and moderate to heavy cigarette smokers (i.e. ≥ 20 cigarettes/day), and among those who typically smoked manufactured cigarettes as well as who rolled their own cigarettes. The reduction in risk was observed within 1–4 years of smoking cessation, and the magnitude of the reduction in relative risk increased with increased time since cessation.

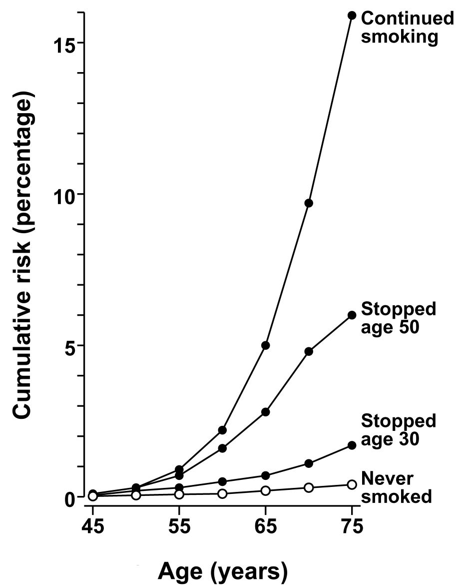
However, comparisons between smokers and former smokers in particular populations were often made when the hazards among the continuing smokers in those populations were still far from maximal; therefore, the comparisons seriously underestimated the magnitude of the long-term benefits of stopping. The most accurate estimate of the benefit of smoking cessation comes from studies conducted in populations, like the United Kingdom, where the full hazards of continued smoking were already apparent and

Figure 2.1.1.5. Lung cancer mortality rates in US white and non-white men and women, 1930–1996



Source: US Vital Statistics

Figure 2.1.1.6. Cumulative lung cancer risk by smoking status and age at quitting smoking in men in the United Kingdom



From Peto *et al.* (2000)

where there were many long-term former smokers. For men in the United Kingdom, where the worst affected generation of smokers was that born around 1900, a study conducted in 1990 (and published 10 years later — Peto *et al.*, 2000) found a high lifelong risk of lung cancer among continuing smokers and substantially lower lifelong risks among those who stopped at 50 or, particularly, at 30 years of age (see Figure 2.1.1.6). Former smokers had significantly higher risks than men who had never smoked, but they also had very substantially lower lifelong risks than those who continued, with most of the benefit accruing not in the first decade after stopping, but in subsequent decades (see Figure 2.1.1.6).

(iii) *Type of cigarette and inhalation*

The *IARC Monograph* on tobacco smoking (IARC, 1986) concluded that case–control and cohort studies available at that time suggested that prolonged use of 'high-tar' and untipped cigarettes is associated with greater risks than prolonged use of filter-tipped and 'low-tar' cigarettes. The results of cohort and case–control studies on the type of cigarette, tar level in cigarettes, type of tobacco and inhalation are summarized in Table 2.1.1.3 and Tables 2.1.1.9, 2.1.1.10, 2.1.1.11 and 2.1.1.12, respectively.

As discussed in Section 1.1, cigarette composition changed substantially during the second half of the twentieth century with the introduction of blended tobacco, filter-tipped cigarettes and other changes intended to modify the nicotine and tar yield of these cigarettes as measured by machine smoking. The actual impact of these changes on the exposure of an individual smoker to carcinogens is difficult to assesss because of the large increase in tobacco-specific nitrosamines from the introduction of blended tobacco, variability in curing processes over time and in different countries, and compensatory changes in smoking behaviour by smokers to maintain their accustomed level of nicotine intake. Most importantly, the majority of smokers have used several different products at different stages of their life as a smoker.

In the absence of large populations of smokers who have consumed a single tobacco product for many decades, epidemiologists have relied on three lines of evidence to examine the relationship between cigarette design and cancer risk. The first involves analytical studies that compare smoking histories (particularly the switch from unfiltered, high-tar cigarettes to filter-tipped medium-tar cigarettes) in relation to lung cancer; the second involves comparisons of different time periods of the epidemic in cohort studies of long duration; the third examines trends in age-specific death rates from lung cancer in different countries in relation to the types of cigarettes being smoked. Each of these approaches has its strengths and limitations, as discussed below.

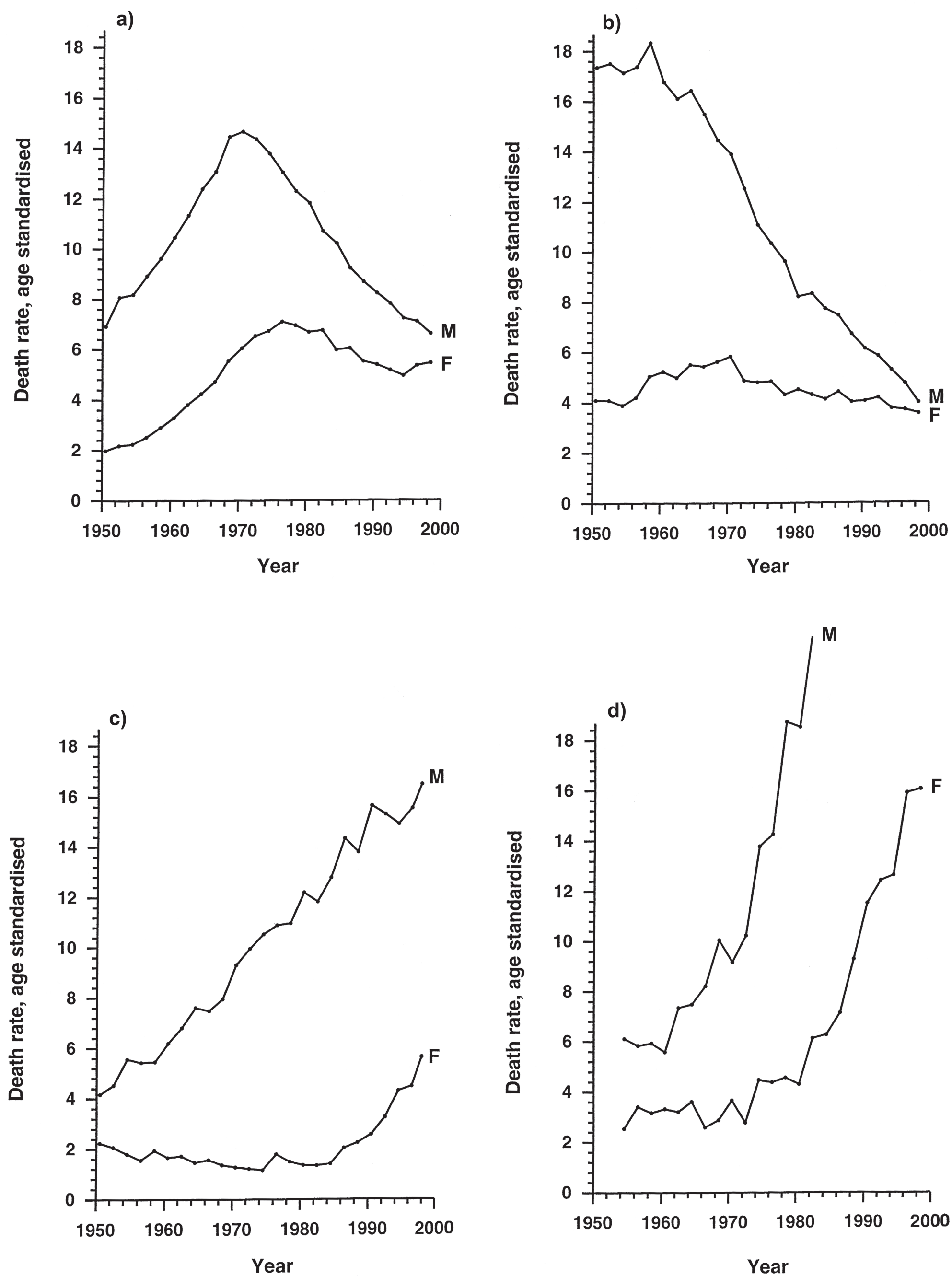
Many case–control studies conducted since the 1960s have reported a somewhat lower risk for lung cancer among smokers of filter-tipped 'reduced yield' cigarettes than in smokers of untipped 'high-yield' cigarettes. These studies are summarized in Tables 2.1.1.3 and 2.1.1.9–2.1.1.10. A similar observation was made in an analysis of the CPS-I cohort by Hammond *et al*. (1976). The majority of case–control studies (Kaufman *et al*., 1989; Zang & Wynder, 1992; Harris *et al*., 1993; Benhamou *et al*., 1994; Kabat, 1996; Zang & Wynder, 1996) show a dose–response relationship between the tar content of the cigarette smoked and the relative risk for lung cancer. The greater risk associated with higher tar level has been shown in both sexes in both Kreyberg I and Kreyberg II histological types and in both squamous-cell carcinoma and in adenocarcinoma.

In cohort studies, the reported magnitude of the risk reduction associated with low-tar cigarettes ranged from 25–50% in the CPS-I cohort (Hammond *et al*., 1976; Stellman & Garfinkel, 1989b) to 14% in the MRFIT cohort (Kuller *et al*., 1991) and to no reduction in the Kaiser Permanente cohort (Sidney *et al*., 1993). The studies comparing 'high-yield' and 'reduced yield' cigarettes have had limited ability to control for all the factors that affect smoking behaviour, compensatory changes or selection of type of cigarettes. Furthermore, since the quantification of the tar content of cigarettes varied somewhat from study to study, the measures of the magnitude of risk reduction are not directly comparable. In all of these studies, the risk for lung cancer in smokers greatly exceeded that in never-smokers and former smokers irrespective of the type of cigarette.

Several cohort studies have examined changes in risk for lung cancer among cigarette smokers in the United Kingdom and the USA during the mid-twentieth century, when most of the cigarettes smoked were untipped, high-tar types, and during the late twentieth century, when the majority of smokers used filter-tipped, intermediate yield cigarettes. These cohort studies have indicated that the relative and absolute risks for lung cancer associated with smoking continued to increase among older smokers, despite a dramatic decrease in machine-measured tar delivery over the same time period. The increase in risk associated with smoking has been interpreted as evidence against the efficacy of lower yield products in reducing risk for lung cancer (Burns *et al.*, 2001). However, the interpretation of the trend in risk from CPS-I to CPS-II is difficult because these cohorts represent time intervals in which there were major increases in the intensity of smoking by young people (Peto & Doll, 1984; IARC, 1986). A similar comparison was made for male smokers in the British Doctors' Study in which the first 20 years of follow-up (1951–70) were compared with the second 20 years (1971–90). Although the age-specific comparisons are based on a much smaller number of deaths in the British Doctors' Study than in the American Cancer Society cohorts, this study also showed higher age-standardized death rates from lung cancer during the second than during the first follow-up interval. A strength of these cohort studies is that they indicate that the introduction of filter-tipped cigarettes did not result in the expected rapid reduction in risk for lung cancer, especially among older smokers, for whom risk actually continued to increase. The principal limitation of these studies is that they cannot distinguish between potential changes in the pathogenicity of cigarettes and unmeasured differences in lifetime smoking, particularly differences in the intensity of smoking by young people.

Another line of evidence involves ecological comparisons of changes in age- and sex-specific death rates from lung cancer in various countries in relation to the type of cigarette being smoked. These national trends highlight major differences in lung cancer rates between men and women and across countries. In the United Kingdom, the lung cancer death rate in men aged 35–44 years decreased by more than 75% between the early 1960s and 2000, whereas the rate in women remained approximately stable. The decrease in lung cancer mortality among men in this age group exceeded the 48% decrease in smoking prevalence in British men aged 25–34 years over the same interval. In contrast, the decrease in death rates from lung cancer among men aged 35–44 years in the USA (Figure 2.1.1.7a) began later and has been smaller than that in the United Kingdom (Figure 2.1.1.7b), consistent with the later uptake of widespread cigarette smoking in the USA. The 54% decrease in death rates from lung cancer in this age range in the USA roughly equals the 51% decrease in age-specific smoking prevalence (Thun & Burns, 2001). Among men in France (Figure 2.1.1.7c), death rates from lung cancer have increased precipitously in men aged 35–44 years since 1950 and in women since 1985. It is plausible that the continued use of high-tar cigarettes may have influenced these patterns, but it is not possible to separate the effects of changing cigarette consumption from the effects of changing cigarette composition. A final example is that of Hungary, where death rates from lung cancer increased precipitously from 1960 to 1980 to levels exceeding the highest rates reported in the USA, and have subsequently declined (Figure 2.1.1.7d). A strength of the ecological data is that they suggest that the shift from very high-tar cigarettes to medium yield products may attenuate the lung cancer risk, as can be seen, for example, in men in the United Kingdom where this trend is not obscured by rapidly increasing lung cancer rates from increasing cigarette consumption. Limitations

Figure 2.1.1.7. Trends in lung cancer mortality rates in men and women, 35–44 years in a) USA, b) United Kingdom, c) France and d) Hungary



of the ecological studies are that such analyses lack data on individual exposure and outcomes and cannot control for potentially relevant covariates such as diet and air pollution.

The Working Group considered each of the lines of observational evidence that contribute to the assessment of the consequences of changes in cigarettes. Each has serious limitations that reflect the inherent difficulties of tracking the consequences of a single aspect of smoking that has varied over time concomitantly with other aspects of smoking, including intensity of smoking, particularly at younger ages. Successive birth cohorts have had differing profiles of exposure to cigarettes of differing characteristics. These patterns have varied between countries.

Nevertheless, after considering the limitations of the evidence, the Working Group concluded that changes in cigarettes since the 1950s have probably tended to reduce the risk for lung cancer associated with the smoking of particular numbers of cigarettes at particular ages. Supporting evidence for this conclusion came from the limited data from case–control and cohort studies on cigarette type and from the patterns of declining mortality rates from lung cancer among men in early middle age, particularly in the United Kingdom. However, the introduction of cigarettes that can be misperceived as 'safe' may well have adversely affected smoking uptake rates, cessation rates and consumption per smoker. Hence, the Working Group could not estimate the net impact of changes in cigarettes on national mortality rates. Moreover, there are still massive epidemics of lung cancer and other diseases caused by cigarette smoking in the United Kingdom, the USA and many other countries.

Differences in risk associated with type of tobacco, i.e. blond versus black, have been examined in case–control studies as summarized in Table 2.1.1.11. Relative risks are consistently higher among smokers of black tobacco than smokers of blond or mixed types.

(iv) *Histological type*

The major histological types of lung cancer are squamous-cell carcinoma, adenocarcinoma (including bronchioloalveolar), large-cell carcinoma and small-cell undifferentiated carcinoma. In the 1950s and 1960s, Doll *et al.* (1957) and Kreyberg (1962) found little or no relationship between tobacco smoking and adenocarcinoma. Similarly, early studies of bronchioloalveolar carcinoma reported no relation between tobacco smoking and this subtype of adenocarcinoma. Since that time a number of studies have examined this issue and are summarized in Table 2.1.1.13. In general, these more recent studies have demonstrated a statistically significant association and exposure–response relationship between tobacco smoke and all histological types of lung cancer. However, the association has been weaker historically for adenocarcinoma than for the other histological types of lung cancer.

There have been notable shifts over time in the incidence rates of lung cancer by histological type. In the initial decades of the smoking-related epidemic of lung cancer, squamous-cell carcinoma was the most common type of lung cancer observed among smokers and small-cell carcinoma was the next most common. In the USA, incidence rates of adenocarcinoma increased steadily between 1973 and 1987, when adenocarcinoma supplanted squamous-cell carcinoma as the most frequent form of lung cancer (Travis *et al.*, 1995). Similar increases in adenocarcinoma have been observed in Asia (Lam *et al.*, 1987; Choi *et al.*, 1994; Sobue *et al.*, 1999) and in Europe (Levi *et al.*, 1997; Russo *et al.*, 1997).

A comparison of two large prospective cohort studies initiated by the American Cancer Society (CPS-I and CPS-II) in 1960 and 1980, respectively, indicates that the association between smoking and adenocarcinoma has strengthened in the most recent follow-up of these cohorts (Thun & Heath, 1997). The relative risk for adenocarcinoma increased for men from 4.6 (95% CI, 1.7–12.6) to 19.0 (95% CI, 8.3–47.7), and for women from 1.5 (95% CI, 0.3–7.7) to 8.1 (95% CI, 4.5–14.6) in CPS-I and CPS-II, respectively. The age-standardized rates for adenocarcinoma (44.2 for men and 18.1 for women per 100 000 person–years) were only slightly lower than the rates for squamous-cell carcinoma (60.2 for men and 21.7 for women) in the more recent study (CPS-II).

An association between cigarette smoking and bronchioloalveolar carcinoma has also been found (Morabia & Wynder, 1992; Falk *et al.*, 1992; Morabia & Wynder, 1993).

The reasons for the increase in the incidence rate of adenocarcinoma in the general population and among smokers are unclear. One possible contributory factor may be related to advances in methods to detect tumours in the distal airways. Since the late 1960s, there have been a number of innovations that have probably improved the diagnosis of adenocarcinoma, such as flexible bronchoscopy, fine-needle aspiration and computerized scans. The histological classification of lung cancer has also improved. [The Working Group noted that these diagnostic advances would contribute to the rise in adenocarcinoma, but seem inadequate to explain the full increase and cannot explain the increased association with smoking.] There are no known risk factors other than smoking for adenocarcinoma of the lung that might explain the increase in incidence.

The other explanation that has been proposed is that changes in the formulation of cigarettes could have led to a the shift in histological type. The introduction of filter cigarettes in the 1950s may have resulted in deeper inhalation of smoke, and thus higher doses to the distal airways from which adenocarcinomas most commonly arise. In addition, blended reconstituted tobacco, introduced in the 1950s, releases higher concentrations of nitrosamines, which are known to induce adenocarcinomas in rodents (Hoffman & Hoffmann, 1997). Thun *et al.* (1997b) observed in an analysis of the Connecticut cancer registry data that there was a relationship between adenocarcinoma rates and birth cohort that peaked among people born between 1930 and 1939, which might be consistent with changes that occurred in filter usage and tobacco composition in the 1950s.

(*b*) *Population characteristics*

(i) *Lung cancer risk in women versus men*

There is currently inconsistent and inadequate epidemiological evidence to support the proposal that women are more susceptible than men to developing lung cancer as a result of smoking. Several case–control (see Tables 2.1.1.5, 2.1.1.6, 2.1.1.8, 2.1.1.9, 2.1.1.10, 2.1.1.13) and cohort studies (Tables 2.1.1.1–2.1.1.3) have failed to show a greater relative risk in women (case–control studies: Higgins & Wynder, 1988; Lei *et al.*, 1996; Xu *et al.*, 1996; Yu & Zhao, 1996; Hu *et al.*, 1997; Muscat *et al.*, 1997; Jöckel *et al.*, 1998; Wunsch-Filho *et al.*, 1998; Kreuzer *et al.*, 2000; Mao *et al.*, 2001; Simonato *et al.*, 2001; Stellman *et al.*, 2001; cohort studies: Freund *et al.*, 1993; Sidney *et al.*, 1993; Islam *et al.*, 1994; Nordlund *et al.*, 1999), whereas several others have shown a greater relative risk among women (case–control studies: Gao *et al.*, 1988; Hebert & Kabat, 1991; Risch *et al.*, 1993; Yu & Zhao, 1996; Zang & Wynder, 1996; Pacella-Norman *et al.*, 2002; cohort studies: Engeland *et al.*, 1996a; Tulinius *et al.*, 1997). What is most relevant is the absolute risk rather than the relative risk. All of the studies that postulate greater risk in women than men are cohort or case–control studies that have estimated relative risk, but not absolute risk (Risch *et al.*, 1993; Hoover, 1994; McDuffie, 1994; Wilcox, 1994). In a large prospective study, women have been shown to have lower death rates from lung cancer than do men within equivalent strata of age and smoking (Thun *et al.*, 2000). Despite similar smoking characteristics among women and men up to and including early middle age in some countries in northern Europe, the lung cancer rates were the same in men and women (Nordlund *et al.*, 1999). Incidence rates for lung cancer in nonsmokers have generally been shown to be lower in women than men. This can result in large relative risks from an equivalent or even lower increase in absolute risk for lung cancer.

(ii) *Ethnicity*

It has been postulated that susceptibility to lung cancer from tobacco smoking may differ by race and ethnicity. The best comparative data available are on risk in African Americans compared with risk in whites, and in Asian Americans compared with whites. Even for these groups, differences in nutritional and other factors between racial and ethnic groups complicate such comparisons.

African Americans versus Caucasians

Compared with white men, black men have a higher incidence of and death rate from lung cancer, younger age at diagnosis and shorter survival (Stewart, 2001). Furthermore, the racial and ethnic differences in smoking vary considerably depending on the parameter being measured. Black men and women begin smoking at a later age and consistently report smoking fewer cigarettes per day (Novotny *et al.*, 1988). However, smoking prevalence has been higher in black than white men since 1950 (Burns *et al.*, 1997) and the brands preferred by black smokers are more likely to be mentholated or to have higher machine-measured levels of nicotine and tar (King & Brunetta, 1999; Stellman *et al.*, 2003). However, studies that have compared the risk associated with mentholated and non-mentholated cigarettes have not found any difference (Carpenter *et al.*, 1999). Black smokers have higher blood levels of cotinine, the main metabolite of nicotine, than do whites who smoke a similar number of cigarettes per day (Caraballo *et al.*, 1998; King & Brunetta, 1999).

Several case–control studies have compared relative risks in whites with those in African Americans, especially in men (Harris *et al.*, 1993; Schwartz & Swanson, 1997; Stellman *et al.*, 2003). In a study that compared smokers of less than 41 pack–years with nonsmokers, African Americans had a higher relative risk than did whites aged 40–54 years (Schwartz & Swanson, 1997). In another study (Harris *et al.*, 1993), black smokers were at a higher risk only for Kreyberg II cancers. In the most recent study (Stellman *et al.*, 2003), similar risks for blacks and whites with similar smoking habits were reported.

Asians versus Caucasians

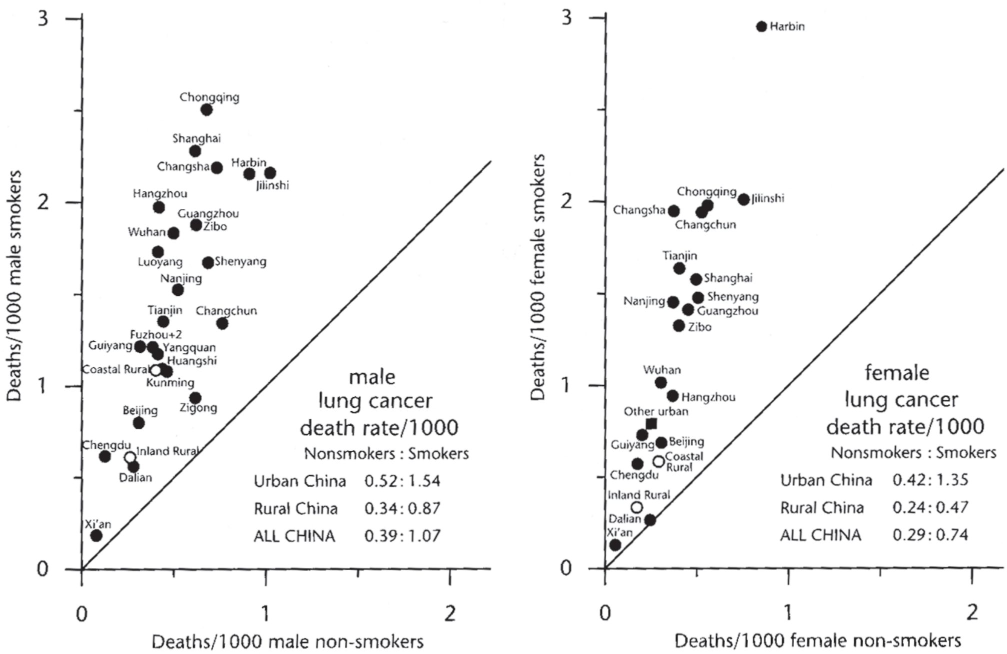
Comparisons of lung cancer risk in Caucasians with that in Chinese and Japanese populations are also perplexing. Absolute lung cancer rates were found to be high among nonsmoking women in certain areas of China, perhaps as a result of indoor cooking with poorly vented coal-fuelled stoves (Fraumeni & Mason, 1974; Law *et al.*, 1976; Gao *et al.*, 1988; Wu-Williams *et al.*, 1990). Because of the high background rate, the absolute increase in risk for lung cancer among women who smoke in some areas of China is actually larger than the absolute increase in lung cancer risk among women who smoke in the USA. Peto *et al.* (1999) have demonstrated that the absolute death rate from lung cancer among female smokers in these areas in China is substantially higher than the average death rates from lung cancer among women in the USA (Figure 2.1.1.8; Thun *et al.*, 1997c), despite a relative risk of approximately 2 associated with smoking in rural areas and a relative risk of 3 in urban areas.

The situation is substantially different in Japan, where lung cancer rates among men in the general population and among male smokers in large cohort studies (Wakai *et al.*, 2001) remain lower than in North America (Stellman *et al.*, 2001). Peto and others attribute this difference to the more recent initiation of regular heavy smoking, because consumption of cigarettes in Japan did not increase markedly until the 1970s, and the main increase in cigarette smoking prevalence occurred 40 years later in China than in the USA (Liu *et al.*, 1998; Niu *et al.*, 1998). However, the relative risk for lung cancer ranges between 3 and 5 among middle-aged women and men in the largely (95%) Chinese population of Hong Kong SAR, where cigarette smoking prevalence reached its peak about 20 years earlier than in mainland China (Lam *et al.*, 2001). There is some evidence that differences in nicotine metabolism may contribute to differences in intensity of smoking between Caucasians and Chinese and Japanese. Benowitz *et al.* (2002) reported slower clearance and reduced intake of nicotine from cigarette smoking in Chinese-Americans than whites; they postulated that this may cause Asian smokers to smoke fewer cigarettes per day. This issue has yet to be resolved.

(*c*) *Lifetime probability that a smoker will develop lung cancer*

The lifetime probability that a smoker will develop lung cancer is conditional on lifetime smoking practices and competing causes of death. The frequently quoted axiom that ‘only 10%’ of cigarette smokers develop lung cancer (Mabry *et al.*, 1998) underestimated

Figure 2.1.1.8. Lung cancer mortality rates in male and female smokers and non-smokers aged 35–69 years in different parts of China, 1986–88



From Peto *et al.* (1999)
In comparison, the nationwide US lung cancer death rates in 1990, similarly standardized for age, were 1.4 per 1000 men and 0.6 per 1000 women, and 0.1 per 1000 male or female US nonsmokers.

the actual lifetime probability among smokers in the late twentieth century in countries such as the USA, where cigarette smoking has been entrenched for many decades and the death rates from competing conditions such as cardiovascular diseases have declined (Thun *et al.*, 2002).

Mattson *et al.* (1987) estimated the probability that a male smoker, aged 35 years, would develop lung cancer by the age of 85 years if he continued smoking. In analyses of over 293 000 US Veterans followed from 1954 to 1962 (Kahn, 1966), it was estimated that 9.3% of men who smoked < 25 cigarettes per day and 17.9% of those who smoked ≥ 25 cigarettes per day at age 35 would develop lung cancer by the age of 85 years. This led to the estimate that 'only 10%' of smokers develop lung cancer (Mabry *et al.*, 1998).

More recent studies indicate that the lifetime probability of a continuing cigarette smoker developing lung cancer has increased over time. Analyses of the American Cancer Society Cohort (CPS-II) have shown that the cumulative probability of death from lung cancer in male and female smokers aged ≥ 85 years, not conditioned on surviving other causes of death, reached 14.6% and 8.3%, respectively, compared with 1.1% among male and 0.9% among female lifelong nonsmokers of this age (Thun *et al.*, 2002). If the impact of competing causes of death were excluded from the calculation, the lifetime probabilities would be 24.1% and 11.0% in male and female smokers, respectively, and 1.6% and 1.1% in male and female never-smokers, respectively. The latter estimates are probably more relevant for estimating the fraction of genetically susceptible persons in the population than are the unconditional percentages, because they are independent of other causes of death. These estimates reflect only the risk of developing lung cancer from smoking; the estimates would be approximately 50% if they considered all of the conditions through which smoking causes premature death.

Table 2.1.1.1. Cohort studies on tobacco smoking and lung cancer

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Hammond & Horn (1958a,b) USA, 1952–55	American Cancer Society (9-State) Study 187 783 men	8	Occasional smoker	1.5		
		249	Current smoker	9.9		
			Cigarettes/day			
		24	1–9	7.4		
		84	10–20	8.4		
		90	21–40	17.9		
		27	≥ 41	20.6		
Lossing *et al.* (1966) Canada 1956–62	Canadian War Veterans' study 78 000 men	18	Former smoker	6.1		
		325	Current smoker	14.9		
			Cigarettes/day			
		57	1–9	10.0		
		204	10–20	16.4		
		63	> 21	17.3		
Weir & Dunn (1970) USA 1954–62	Californian Study 68 153 men	368	Ever smoker			
			Cigarettes/day			
			1–14	3.7		
			15–24	9.1		
			≥ 25	9.6		
			Duration (years)			
			1–9	1.1		
			10–19	6.5		
			≥ 20	8.7		
Cederlöf *et al.* (1975) Sweden 1963–72	Swedish Census Study 25 444 men	12	Former smoker	6.1		
		28	Current smoker	7.0		
			Cigarettes/day			
		4	1–7	2.3		
		11	8–15	8.8		
		13	≥ 16	13.9		
			Duration (years)			
		5	1–29	1.8		
		23	≥ 30	7.4		

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
			Age at start (years)			
		11	≥ 19	6.5		
		10	17–18	9.8		
		7	≤ 16	6.4		
Doll *et al.* (1980) United Kingdom 1951–73 (see also Doll *et al.*, 1994)	British Doctors' Study 6194 women	27		Mortality rate		Annual mortality rate per 100 000 women; adjusted for age and calendar period
			Nonsmoker	7		
			Former smoker	23		
			Cigarettes/day			
			1–14	9		
			15–24	45		
			≥ 25	208		*p* for trend < 0.001
Kono *et al.* (1987) Japan 1965–83	Japanese Physicians Study 5130 men	74	Cigarettes/day			Adjusted for age and alcohol consumption
			1–19	3.2	1.6–6.5	
			≥ 20	8.2	4.1–16.1	
Tenkanen *et al.* (1987) Finland 1963–80	Finnish Men's Study 4604 men		Tobacco/day (g)	Mortality rate		Annual incidence rate per 100 000 persons for the period 1972–80
			Cohort born 1908–17			
		1	Non/former smoker	22		
		15	< 15	599		
		22	≥ 15	708		
			Cohort born 1898–1907			
		15	Non/former smoker	178		
		42	< 15	997		
		30	≥ 15	1094		
Floderus *et al.* (1988) Sweden 1961–97	Swedish Twin Registry Study 10 942 same-sex twin pairs	Men			90% CI	
		14	Former smoker	5.4	2.3–12.9	
		78	Current smoker	19.7	9.1–42.7	
			Cigarettes/day			
		33	≤ 10	12.4	5.5–27.7	
		45	> 10	33.3	15.2–72.7	

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
		Women				
		19	Current smoker	5.1	3.0–8.7	
			Cigarettes/day			
		12	≤ 10	4.1	2.3–7.6	
		7	> 10	8.6	4.1–18.1	
Garfinkel & Stellman (1988); Stellman & Garfinkel (1989a) USA 1982–86	Cancer Prevention Study II 619 925 women	1006		SMR		Standardized mortality ratios based on age-specific rates in nonsmokers within cohort; analysis by years of smoking restricted to women without history of chronic illness
		262	Former smoker	4.8		
		570	Current smoker	12.7		
			Cigarettes/day			
			for 21–30 years of smoking			
		3	1–10	2.9		
		3	11–19	6.7		
		16	20	13.6		
		9	21–30	18.4		
		7	≥ 31	18.9		
			for 31–40 years of smoking			
		18	1–10	7.9		
		22	11–19	19.2		
		59	20	19.2		
		36	21–30	26.5		
		27	≥ 31	25.3		
			for 41–70 years of smoking			
		29	1–10	10.0		
		23	11–19	17.0		
		83	20	25.1		
		36	21–30	34.3		
		30	≥ 31	38.8		

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Stellman & Garfinkel (1989b) USA 1959–72	Cancer Prevention Study I 222 830 men	969		SMR		Standardized mortality ratios based on age-specific rates in nonsmokers within cohort
		51	Never-smoker	1.0		
		94	Former smoker	2.7		
			Cigarettes/day			
			Low tar			
		20	1–19	5.2		
		32	20	9.2		
		25	21–39	10.9		
		16	≥ 40	11.0		
			Medium tar			
		87	1–19	7.7		
		131	20	10.5		
		95	21–39	14.1		
		66	≥ 40	18.2		
			High tar			
		62	1–19	7.2		
		140	20	12.8		
		88	21–39	15.6		
		60	≥ 40	19.3		
Akiba & Hirayama (1990) Japan 1965–81	Six-prefecture Study 122 261 men, 142 857 women	Men				
		1120	Current smoker	4.5	3.6–5.7	
			Cigarettes/day			
		14	1–4	2.5	1.4–4.3	
		361	5–14	3.3	2.6–4.3	
		629	15–24	5.4	4.3–6.9	
		76	25–34	7.1	5.1–9.7	
		40	≥ 35	8.4	5.7–12.3	*p* for trend < 0.001

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
		Women				
		91	Current smoker	2.5	2.0–3.2	
			Cigarettes/day			
		11	1–4	1.9	1.0–3.2	
		65	5–14	2.5	1.9–3.3	
		15	≥ 15	3.1	1.8–5.1	p for trend < 0.001
Kuller *et al.*	MRFIT Study		Current smoker	6.7	$p < 0.0001$	
(1991)	12 866 men			Mortality rate		Annual mortality rate per 10 000
USA		456	Nonsmoker	19.2		persons; adjusted for age
1975–85			Cigarettes/day			
		130	1–15	49.5		
		479	16–25	111.8		
		371	26–35	140.4		
		411	36–45	189.0		
		157	≥ 46	205.1		
Chow *et al.*	Lutheran Brotherhood	63	Former + occasional smoker	6.3	2.5–15.6	Non-significant protective effect
(1992)	Insurance Study		Cigarettes/day			observed for higher dietary intake of
USA	17 818 men	38	1–19	15.1	5.9–38.4	vitamin A and β-carotene
1966–86		60	20–29	23.8	9.5–59.5	
		40	≥ 30	48.4	19.0–123.7	
Chyou *et al*.	American Men of		Pack–years			
(1992)	Japanese Ancestry	33	< 31	6.3	3.3–12.3	
USA	Study	44	31–45	9.0	4.8–17.1	
1965–95	8006 men	92	≥ 46	23.3	12.8–42.6	p for trend < 0.0001
Potter *et al.*	Iowa Women's Health	126				Adjusted for alcohol consumption,
(1992)	Study		Pack–years			education and physical activity
USA	41 843 women		< 20	2.9	1.2–7.0	
1986–88			20–39	9.4	4.8–18.4	
			≥ 40	17.6	9.5–32.3	

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Chyou *et al.*	American men of		Pack–years			Adjusted for age
(1993)	Japanese Ancestry		Current smoker†			†Relative risk of 16.0 for squamous/
USA	Study	16	< 25	4.3	2.1–9.0	small-cell carcinoma and 6.8 for
1965–90	7961 men	83	25–49.9	9.8	5.5–17.6	adenocarcinoma
		82	≥ 50	23.3	12.9–41.8	*p* for trend < 0.001
Freund *et al.*	Framingham Heart		Men	Incidence rate		Annual incidence rate per 1000
(1993)	Study	31	45–64 years old			persons; adjusted for age
USA	1916 men, 2587		Nonsmoker	0.0		The authors also reported relative
1948–82	women		Cigarettes/day			risks for current smokers for each age
			1–10	0.0		group.
			11–20	1.6		
			21–30	2.1		
			> 30	4.3		
		40	65–84 years old			
			Nonsmoker	0.5		
			Cigarettes/day			
			1–10	4.2		
			11–20	4.7		
			21–30	4.7		
			> 30	13.1		

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
			Women			
		10	45–64 years old			
			Nonsmoker	0.2		
			Cigarettes/day			
			1–10	0.0		
			11–20	0.3		
			21–30	1.3		
			> 30	1.6		
		13	65–84 years old			
			Nonsmoker	0.4		
			Cigarettes/day			
			1–10	0.9		
			11–20	2.7		
			21–30	2.8		
Tverdal *et al.* (1993) Norway 1972–88	Norwegian Screening Study 44 290 men, 24 535 women	Men		Mortality rate		Annual mortality rate per 100 000 persons; adjusted for age and study area
		4	Nonsmoker	3.6		
		11	Former smoker	7.5		
		144	Current smoker	58.5		
			Cigarettes/day			
		18	1–9	32.4		
		68	10–19	50.3		
		57	≥ 20	99.4		
		Women				
		3	Nonsmoker	1.9		
		24	Current smoker	21.0		
			Cigarettes/day			
		5	1–9	8.6		
		19	≥ 10	34.2		

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Akiba (1994)	Life Span Study	411	Men			†Upper 95% limit could not be
Japan	61 505 men and women	48	Former smoker	2.5	1.5–4.3	obtained.
1968–87		345	Current smoker	5.1	3.3–?†	
			Cigarettes/day			
			1–14	3.5	2.2–6.0	
			15–24	6.1	3.9–?†	
			≥ 25	9.1	5.4–15.9	
		199	Women			
		9	Former smoker	1.4	0.7–2.6	
		74	Current smoker	3.9	2.9–5.3	
			Cigarettes/day			
			1–14	3.6	2.6–5.0	
			15–24	5.8	3.3–9.5	
Ben-Shlomo *et al.*	Whitehall Study			Mortality rate		Annual mortality rate per 1000
(1994)	19 018 men		Nonsmoker	0.3		persons; adjusted for age
United Kingdom		58	Former smoker	0.7		
1967–87		365	Current smoker	3.0		
Doll *et al.* (1994)	British Doctor's Study	893		Mortality rate		Annual mortality rate per 100 000
United Kingdom	34 439 men		Nonsmoker	14		men; adjusted for age and calendar
1957–91			Former smoker	58		period
			Current smoker	209		
			Cigarettes/day			
			1–14	105		
			15–24	208		
			≥ 25	355		p for trend < 0.001
Islam &	Tecumseh Community	60	Men	Incidence rate		Annual incidence rate per 1000
Schottenfeld	Health Study		Nonsmoker	0.6		persons; adjusted for age
(1994)	1857 men, 2099 women		Current smoker	2.3		
USA			Cigarettes/day			
1962–87			1–19	1.3		
			20–39	2.0		

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
		17	Women			
			Nonsmoker	0.2		
			Current smoker	0.9		
			Cigarettes/day			
			1–19	0.4		
			20–39	1.3		
			> 40	2.0		
			Current smoker	Relative risk		
			Men	4.1	1.6–10.3	
			Women	5.3	1.7–16.4	
Ellard *et al.* (1995) The Netherlands 1974–88	Dutch Study over 26 000 women	47	Current smoker	6.3	3.5–11.4	
			Cigarettes/day			
		4	< 10	1.3	0.4–4.2	
		29	10–20	9.7	4.9–19.5	
		14	> 20	9.4	3.9–22.5	
Kark *et al.* (1995) Israel 1963–86	Israel Civil Service Centre Study 9975 men	153				Adjusted for age, city of employment and body mass index
			Former smoker	1.5	0.7–3.2	
			Cigarettes/day			
			1–10	1.6	0.8–3.4	
			11–20	5.1	2.8–9.3	
			> 20	10.0	5.7–17.5	
McLaughlin *et al.* (1995) USA 1954–80	US Veterans' Study 293 958 men	5097				
			Former smoker	3.6	3.1–4.1	
			Ever smoker	8.4	7.5–9.4	
			Current smoker	11.6	10.4–13.0	
			Cigarettes/day			
			1–9	3.7	3.1–4.5	
			10–20	9.9	8.8–11.2	
			31–39 [sic]	16.9	15.0–19.0	
			≥ 40	22.9	19.8–26.6	*p* for trend < 0.01

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Engeland *et al.* (1996a) Norway 1966–93	Norwegian Cohort Study 11 857 men, 14 269 women	Men				Adjusted for age at start, cigarette type, pipe smoking and urban/rural status
		48	Former smoker	1.3	0.8–2.2	
			Cigarettes/day			
		28	1–4	1.4	0.6–3.7	
		49	5–9	4.1	1.7–10	
		97	10–14	7.0	2.9–17	
		27	15–19	11.0	4.2–28	
		57	≥ 20	15.0	6.1–37	
			Age at start (years)			
		173	< 20	1.0	–	
		50	20–29	0.5	0.4–0.7	
		17	≥ 30	0.6	0.3–0.9	
		Women	Cigarettes/day			
		12	1–4	12	4.5–32	
		20	5–9	12	4.4–30	
		24	10–14	24	9.5–59	
		9	≥ 15	26	9.2–73	
			Age at start (years)			Adjusted for daily number of cigarettes
		18	< 20	1.0	–	
		36	20–29	0.6	0.1–0.3	
		10	≥ 30	0.1	0.0–0.3	
Murata *et al.* (1996) Japan 1984–93	Chiba Centre Association Study 17 200 men		Cigarettes/day			Adjusted for age and county
		9	1–10	1.4		
		47	11–20	3.6	$p < 0.01$	
		20	≥ 21	4.6	$p < 0.01$	p for trend < 0.01
Yuan *et al.* (1996) China 1986–93	Shanghai Men's Study 18 244 men	142				Adjusted for age
			Ever smoker	6.5		
			Cigarettes/day			
			< 20	3.6		
			≥ 20	9.4		

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Chen *et al.* (1997) China 1972–93	Shanghai Factory Study 9351 persons	97	Current smoker	3.8	$p < 0.001$	Adjusted for age, systolic blood pressure, serum cholesterol, alcohol drinking (yes/no) and factory
			Cigarettes/day			
			1–19	2.8	$p < 0.01$	
			≥ 20	5.4	$p < 0.001$	p for trend < 0.001
Lam *et al.* (1997) China 1976–96	Xi'an Factory Study 1124 men, 572 women	5	Women			Analysis for women only since none of the male cases were nonsmokers.
			Ever smoker	1.8	0.1–18.1	
Liaw & Chen (1998) China, Province of Taiwan 1982–94	Taiwanese Study 11 096 men, 3301 women		Current smoker			Ajusted for age and sex
		105	Men	3.7	2.1–6.6	
		22	Women	3.6	1.0-12.2	
Tulinius *et al.* (1997) Iceland 1968–95	Reykjavík Study 11 366 men, 11 580 women	273	Men			Adjusted for age
			Former smoker	2.9	1.5–5.7	
			Cigarettes/day			
			1–14	6.5	3.3–13.0	
			15–24	13.5	7.8–25.6	
			≥ 25	28.7	14.9–55.1	
		199	Women			
			Former smoker	3.7	1.7–8.1	
			Cigarettes/day			
			1–14	9.4	5.0–17.7	
			15–24	30.7	16.8–56.0	
			≥ 25	44.1	21.1–91.8	
Wald & Watt (1997) United Kingdom 1975–93	British United Provident Association (BUPA) Study 21 520 men	77	Current smoker	16.4	7.55–44.2	Adjusted for age at entry

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Gao *et al.* (1999) China 1983–94	Shanghai Residential Study 213 800 men and women		Men		†CI does not include 1.0	p for trend < 0.05 for intensity of smoking and age at start for men and women
			Urban	5.6†		
			Suburban	2.9†		
			Rural	3.3†		
			Women (urban)	4.8†		
Jacobs *et al.* (1999) 25 years	Seven-Country Study 12 763 men			Mortality rate		25-year mortality rate per 1000 men; adjusted for age and cohort
		24	Nonsmoker	1.1		
			Current smoker			
			Cigarettes/day			
		8	1–4	0.7		
		29	5–9	2.6	$p < 0.05$	
		168	10–19	4.8	$p < 0.001$	
		142	20–29	6.0	$p < 0.001$	
		22	≥ 30	6.1	$p < 0.001$	
Nordlund *et al.* (1999) Sweden 1963–89	Swedish Census Study 15 881 men, 25 829 women	Men				
		16	Former smoker	1.3	0.7–2.3	
		18	Occasional smoker	1.6	0.8–2.9	
		135	Current smoker	8.4	5.5–12.9	
			Pack–years			
		5	≤ 5	1.6	0.6–4.3	
		25	6–15	4.4	2.5–7.7	
		33	16–25	14.2	8.3–24.3	
		72	≥ 26	17.9	11.1–28.8	p for trend < 0.001
			Age at start (years)			
		4	> 24	1.0	–	
		29	20–23	2.2	0.7–6.3	
		102	< 19	3.1	1.1–8.7	p for trend = 0.005

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
		Women				
		3	Former smoker	1.1	0.3–3.4	
		5	Occasional smoker	0.6	0.3–1.6	
		59	Current smoker	4.7	3.3–6.8	
			Pack–years			
		15	≤ 5	2.1	1.2–3.8	
		27	6–15	6.3	4.0–10.0	
		11	16–25	10.3	5.3–19.8	
		6	≥ 26	16.5	7.0–38.5	*p* for trend < 0.001
			Age at start (years)			
		22	> 24	1.0	–	
		15	20–23	1.6	0.8–3.2	
		22	< 19	2.3	1.2–4.4	*p* for trend = 0.013
Prescott *et al.* (1999) Denmark 1964–94	Copenhagen City Heart Study 17 699 men, 13 525 women	480	Men			Adjusted for age
			Former smoker	5.4	2.4–12.3	
			Non-inhaling smoker	7.6	3.3–17.3	
			Tobacco/day (g)			
			1–14	12.1	5.3–27.4	
			15–24	20.9	9.3–47.0	
			> 24	25.9	11.4–59.0	
		194	Women			
			Former smoker	2.9	1.5–5.7	
			Non-inhaling smoker	3.3	1.8–6.3	
			Tobacco/day (g)			
			1–14	10.2	5.7–18.3	
			15–24	13.7	7.5–24.8	
			> 24	18.8	8.7–40.5	

Table 2.1.1.1 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Speizer *et al.* (1999) USA 1976–92	Nurses' Health Study 121 700 women		Age at start (years)			Adjusted for age and number of cigarettes per day
			> 21	0.8	0.6–1.1	
			18–19	1.0	–	p for trend < 0.0001 for number of cigarettes smoked per day (1–4, 5–14, 15–24, 25–34, ≥ 35 cigarettes/day)
			< 18	1.1	0.9–1.5	[categories for age at start are not comprehensive]

Table 2.1.1.2. Cohort studies on tobacco smoking and lung cancer: smoking cessation

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Cederlöf *et al.*	Swedish Census Study	7	Nonsmoker	1.0		
(1975)	25 444 men		Years since quitting			
Sweden		12	< 10	6.1		
1963–72		3	> 10	1.1		
Rogot & Murray	US Veterans' Study		Years since quitting	SMR		Standardized mortality ratio, using
(1980)	293 958 men	2609	Current smoker	11.3		nonsmokers as the reference group
USA, 1954–69		47	< 5	18.8		†Values estimated from graph
		86	5–9	~7.5†		
		100	10–14	~5.0†		
		115	15–19	~5.0†		
		123	≥ 20	2.1		
Garfinkel &	Cancer Prevention		Years since quitting	SMR		Standardized mortality ratios based
Stellman (1988)	Study II		Former smokers of			on age-specific rates in nonsmokers
USA	619 925 women		1–20 cigarettes/day			within cohort; analysis for women
1982–86		335	Current smoker	10.3		stratified by history of heart disease,
		52	< 2	13.6		stroke or cancer
		33	3–5	8.4		
		20	6–10	3.3		
		21	11–15	3.0		
		41	≥ 16	1.6		
			Former smokers of			
			≥ 21 cigarettes/day			
		195	Current smoker	21.2		
		39	< 2	32.4		
		23	3–5	20.3		
		17	6–10	11.4		
		6	11–15	4.1		
		9	≥ 16	4.0		

Table 2.1.1.2 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Chyou *et al.*	American Men of		Former smoker (pack–years)			Adjusted for age
(1993)	Japanese Ancestry	14	< 25	2.2	1.1–4.8	
USA	Study	10	25–49.9	3.1	1.4–7.1	
1965–90	7961 men	8	≥ 50	6.3	2.6–15.3	p for trend = 0.0002
Tverdal *et al.*	Norwegian Screening	Men	Years since quitting			Annual mortality rate per 100 000
(1993)	Study	1	< 3 months	11.9		persons; adjusted for age and area
Norway	44 290 men, 24 535	1	3–12 months	8.2		
1972–88	women	5	1–5 years	9.9		
		4	> 5 years	4.7		
Ben-Shlomo *et al.*	Whitehall Study		Years since quitting			Rate ratios adjusted for age and civil
(1994)	19 018 men	14	1–9	8.7	4.0–18.9	service employment grade
United Kingdom		23	10–19	4.1	2.0–8.2	
1967–87		15	20–29	2.6	1.2–5.5	
		6	≥ 30	1.0	0.3–3.1	
			per 10 years	0.5	0.4–0.7	
			Cigarettes/day			
		3	1–9	0.8	0.2–2.8	
		10	10–19	1.5	0.6–3.6	
		26	20–29	4.6	2.2–9.5	
		19	≥ 30	6.7	3.1–14.4	
			per 10 cigarettes	1.4	1.2–1.6	
			Duration (years)			
		2	0–9	0.8	0.2–3.4	
		5	10–19	1.3	0.7–2.2	
		18	20–29	3.1	1.5–6.8	
		33	≥ 30	5.1	2.5–10.3	
			per 10 years	1.7	1.3–2.1	

Table 2.1.1.2 (contd)

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Jacobs *et al.*	Seven-Country Study		Years since quitting			25-year mortality rate per 1000 men;
(1999)	12 763 men	11	< 1	3.4		adjusted for age and cohort
25 years		19	1–9	1.6		
		5	> 10	0.2	$p < 0.05$	
Speizer *et al.*	Nurses' Health Study		Years since quitting			Adjusted for age, 2-year follow-up
(1999)	121 700 women	391	Current smoker	1.0	–	interval and age at start
USA		24	< 2	0.4	0.2–0.7	
1976–92		34	2–4.9	0.6	0.4–1.0	
		41	5–9.9	0.6	0.4–0.9	
		17	10–14.9	0.1	0.1–0.3	
		28	≥ 15	0.1	0.1–0.2	

Table 2.1.1.3. Cohort studies on tobacco smoking and lung cancer: tobacco type

Reference Country and years of follow-up	Subjects	Number of cases	Smoking categories	Relative risk	95% CI	Comments
Garfinkel & Stellman (1988) USA 1982–86	Cancer Prevention Study II 619 925 women		Inhalation	SMR		Standardized mortality ratios based on age-specific rates in nonsmokers within cohort; analysis restricted to women with no history of chronic illness
		25	Non-inhaler	6.9		
		72	Slight	15.2		
		252	Moderate	18.5		
		84	Deep	31.9		
Sidney *et al.* (1993) USA 1979–87	Kaiser Permanente Medical Care Program Study II 34 975 men, 44 971 women	Men	Tar content (mg/cigarette)			Adjusted for age, race, education, cigarettes/day and duration of smoking
		14	< 11	1.0	–	
		39	11–18	1.3	0.7–2.4	
		29	> 18	1.3	0.7–2.4	
		Women				
		29	< 11	1.0	–	
		34	11–18	0.9	0.6–1.6	
		13	> 18	0.7	0.3–1.3	
Nordlund *et al.* (1999) Sweden 1963–89	Swedish Census Study 15 881 men, 25 829 women	Men	Inhalation			
		4	None/slight	1.0	–	
		131	Moderate/deep	1.6	0.6–4.4	
		Women	Inhalation			
		4	None/slight	1.0	–	
		55	Moderate/deep	2.1	0.7–5.9	

Table 2.1.1.4. Case–control studies on tobacco smoking and lung cancer: main characteristics of study design

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Damber & Larsson (1986)	Sweden	1972–77	Men: 579 deceased/ 572 deceased/447 alive	42/208/171	Cases: P (deaths) Control 1: P (deaths) Control 2: P (alive)	Matched on sex, age, municipality, year of death or year of birth for living controls
Pathak *et al.* (1986)	USA, New Mexico	Jan. 1980– Aug. 1983	Men: 311/493 Women: 158/271	9/125 19/160	Cases: P Controls: P	Frequency-matched for sex, age and ethnicity
Benhamou *et al.* (1987)	France	1976–80	Women: 96/192	50/159	Cases: H Controls: H	Matched on age, sex, hospital and interviewer
Gao *et al.* (1988)	China, Shanghai	Feb. 1984– Feb. 1986	Men: 733/760 Women: 672/735	62/202 435/605	Cases: P Controls: P	Frequency-matched on age to the Cancer Registry distribution of lung cancer cases
Higgins & Wynder (1988)	USA, 6 cities	1977–84	Men: 2085/3948 Women: 1012/1891	64/918 125/991	Cases: H Controls: H	Crude odds ratios
Wilcox *et al.* (1988)	USA, New Jersey	1980–81	Men: 763/900	13/142	Cases: P Controls: P	Analysis includes 373 cases and 247 controls who smoked during 1973–80
Benhamou *et al.* (1989)	France	1976–80	Men: 1057/1503	Smokers only	Cases: H Controls: H	Further analysis of data already included in IARC (1986)
Kaufman *et al.* (1989)	USA, Canada	Nov. 1981– June 1986	Men: 534/998 Women: 347/1572	Sexes combined 35/925	Cases: H Controls: H	
Schoenberg *et al.* (1989)	USA, New Jersey	Aug. 1982– Sept. 1983	Women: 994/995	119/497	Cases: P Controls: P	Matched on race, age for living cases and date of death for deceased cases
Svensson *et al.* (1989)	Sweden, Stockholm	1983–86	Women: 210/209	38/120	Cases: multicentric H Controls: P	Matched on day of birth
Xu *et al.* (1989)	China, Shenyang, Liaoning	Sept. 1985– Sept. 1987	Men: 729/788 Women: 520/557	102/355 156/362	Cases: H Controls: P	Frequency-matched to expected age and sex distribution of cases

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Jedrychowski *et al.* (1990)	Poland, Cracow	Jan. 1980–Dec. 1985	Men: 901/875 Women: 198/198	49/219 78/166	Cases: P Controls: P (death certificates)	Matched on age, date of death; controls excluding respiratory diseases
Wu-Williams *et al.* (1990)	China, Harbin and Shenyang	1985–87	Women: 964/959	415/601	Cases: 70 H Controls: P	Frequency-matched to the expected age distribution of the cases
Becher *et al.* (1991)	Germany	1985–86	Men: 146/146/146 Women: 48/48/48	3/32/22 10/31/21	Cases: H Control 1: H/ control 2: P	Matched on sex and age
Hebert & Kabat (1991)	USA	Not stated	Men: 812/1719 Women: 568/1238	88/853 97/868	Cases: H Controls: H	Matched on sex, age, hospital and time of interview
Holowaty *et al.* (1991)	Canada, Ontario, Niagara	Jan. 1983–March 1985	Women: 51/45	5/27	Cases: H Controls: P	Matched on age and municipality
Kabat & Hebert (1991)	USA, 4 cities	1985–90	Men: 588/914 Women: 456/410	Current smokers only	Cases: H Controls: H	Matched on age, sex, race, hospital and date of interview
Katsouyanni *et al.* (1991)	Greece, Athens	18 mo. 1987–89	Women: 101/89	48/67	Cases: H Controls: H	
Liu *et al.* (1991)	China, Xuanwei	Nov. 1985–Dec. 1986	Men: 56/224 Women: 54/202	Both sexes combined: 4/52	Cases: H Controls: P	Restricted to farmers Matched on age, sex, occupation and residence
Morabia & Wynder (1991)	USA	1985–90	Men: 851/888 Women: 507/608	Not given	Cases: H Controls: H	Matched by age, hospital and date of admission
Osann (1991)	USA, California	1969–77	Women: 217/203	33/109	Cases: H Controls: H	Nested case–control study Matched on year of birth, race and date of first check-up

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Alavanja *et al.* (1992)	USA, Missouri	June 1986–April 1991	Women: Never smoked 432/1169; Former smokers 186/234	Not applicable	Cases: P Controls: P	Excludes current smokers
Falk *et al.* (1992)	USA, Louisiana	1979–82	Both sexes combined: 21/101	3/31	Cases: H Controls: H	Only bronchioloalveolar carcinomas. Matched by hospital, race, sex and age (5:1)
Jedrychowski *et al.* (1992)	Poland, Cracow	Jan. 1980–Dec. 1987	Men: 627/1343	16/289	Cases: P Controls: P (death certificates)	Interviews with next-of-kin; matched on sex, age and date of death
Jöckel *et al.* (1992)	Germany, 5 cities, 7 hospitals	Not stated	Men: 146/146/146 Women: 48/48/48	3/32/22 10/31/21	Cases: H Controls: H/P	Matched by sex and age
Liu (1992)	China: Beijing, Shenyang, Harbin, Shanghai, Nanjing, Shengzou, Taiyuan, Nanchang	1984–89	Both sexes combined: 4081/4338	1151/1979	Cases: P (7 studies)/H (1 study) Controls: P (7 studies)/H (1 study)	Combined analysis of 8 studies; matched on age and sex
Lubin *et al.* (1992)	China, Yunnan, Gejiu	1984–88	Men: 427/1011	9/72	Cases: P Controls: P	Matched on age; city residents and Yunnan Tin Corporation workers
Morabia & Wynder (1992)	USA	1977–89	Both sexes combined: 87/286 non-cancer/297 cancer	15/97 non-cancer/122 cancer	Cases: H Controls: H	Only bronchioloalveolar carcinomas. Matched on sex, race, age, hospital, date of interview
Zang & Wynder (1992)	USA	1981–88	Men: 1380/2828 Women: 916/1839	51/820 83 /899	Cases: H Controls: H	Matched by age, sex, race and time of admission

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Gao *et al*. (1993)	Japan, Nagoya	Jan. 1988–June 1991	Men: 282/282	13/56	Cases: H Controls: H	Matched by sex, age and date of first visit to the hospital
Ger *et al*. (1993)	China, Province of Taiwan	May 1990–July 1991	Men: 92/184/184 Women: 39/78/78	Both sexes combined: 48/111/118	Cases: H Controls: H/ neighbourhood	Matched on age, sex, date of interview and insurance status (H); age, sex and residence (neighbourhood)
Harris *et al*. (1993)	USA	1980–90	Men: white 2678/2445 black 238/169 Women: white 1394/1418 black 113/139	 83/581 4/36 145/776 14/80	Cases: H Controls: H	Controls matched by sex, race, age and year of interview
Hegmann *et al*. (1993)	USA, Utah	Oct. 1989–May 1991	Men: 182/2195 Women: 100/1087	Both sexes combined: 27/2080	Cases: P (cancer registry) Controls: P	Frequency-matched on age and sex
Liu *et al*. (1993)	China	June 1983–June 1984	Men: 224/224 Women: 92/96	12/44 38/69	Cases: H Controls: H	Individually matched on age, sex, residence and date of diagnosis/hospital admission
Osann *et al*. (1993)	USA, Orange County	Jan. 1984–Dec. 1986	Men: 1153/1851 Women: 833/1656	45/833 96/1093	Cases: H Controls: H	Data extracted from medical records
Pezzotto *et al*. (1993)	Argentina, Rosario	1987–91	Men: 215/433	4/116	Cases: H Controls: H	Matched on age
Risch *et al*. (1993)	Canada	Jan. 1981–March 1985	Men: 403/362 Women : 442 /410	12/85 52/214	Cases: H Controls: P	Male cases matched to female cases; controls matched on sex, residence and age
Agudo *et al*. (1994)	Spain	1989–92	Women: 103/206	80/183	Cases: H Controls: H	Matched for age at diagnosis, hospital and interviewer

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Benhamou & Benhamou (1994)	France	1976–80	Men: 1334/2409 Women: 96/192	36/650 50/159	Cases: H Controls: H	Matched on age, sex, hospital and interviewer
Benhamou *et al.* (1994)	France	1976–80	Men: 1114/1466	Only lifelong smokers	Cases: H Controls: H	
De Stefani *et al.* (1994)	Uruguay, Montevideo	Jan. 1989–Dec. 1992	Men: 476/561	Only former and current smokers	Cases: H Controls: H	
Miller *et al.* (1994)	USA, Erie County, PA	1972–76, 1979–84	Women: 168/5235	28/3638	Cases: P Controls: P (deaths)	Nested in a retrospective population study
Sankanarayanan *et al.* (1994)	India, Trivandrum	1990	Men: 281/1207	28/767	Cases: H Controls: visitors and patients' bystanders	
Shimizu *et al.* (1994)	Japan, Tokyo	1973–91	Men: 413/82 Women: 192/101	37/65 43/21	Cases: H Controls: H	Information from hospital records; controls were patients with metastatic lung cancer
Sobue *et al.* (1994)	Japan, Osaka	Jan. 1986–Dec. 1988	Men: 1082/1141 Women: 294/1089	34/128 167/857	Cases: H Controls: H	Methods for selection of controls not stated
Suzuki *et al.* (1994)	Rio de Janeiro, Brazil	Aug. 1991–Feb. 1992	Men: 99/99 Women: 24/24	Both sexes combined: 11/55	Cases: H Controls: H	Matched on age, sex and race
Alavanja *et al.* (1995)	USA, Missouri	1986–92	Women: lifetime nonsmokers, 432/1168 long-term former smokers, 186/234	Not applicable	Cases: P Controls: P	Excludes current smokers A cancer group was also used as control, but data are not shown in tables
Siemiatycki *et al.* (1995)	Canada	Sept. 1979–June 1985	Men: 857/533	13/105	Cases: H Controls: P	Age-stratified, matched to age distribution of cases
De Stefani *et al.* (1996a)	Uruguay, Montevideo	May 1994–Dec. 1995	Men: 307/307 Women: 13/13	Both sexes combined: 20/108	Cases: H Controls: H	Frequency-matched on age and residence (urban/rural)

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
De Stefani *et al.* (1996b)	Uruguay, Montevideo	Jan. 1988–Dec. 1994	Men: 497/497	27/163	Cases: H Controls: H	Matched on sex, age and residence
Du *et al.* (1996)	China, Guangzhou	1985	Men: 566/566 Women: 283/283	Not given	Cases and controls: death registry	Review of published studies, with some updated data Matched on age, sex, race, hospital and date of admission
Kabat (1996)	USA	1969–91	Both sexes combined: 7553/17 992	Men: 2085/3951 Women: 1012/1891	Cases: H Controls: H	Matched on age, sex, race, hospital and date of admission
Lei *et al.* (1996)	China, Guangzhou	1986	Men: 563/563 Women: 229/229	41/123 85/147	Cases: P Controls: P	Matched on sex and closest birth date
Luo *et al.* (1996)	China, Fuzhou	1990–91 (1.5 years)	Both sexes combined: 102/306	37/160	Cases: H Controls: P	Frequency-matched by age and sex
Rylander *et al.* (1996)	Sweden	Jan. 1989–June 1993	Men: 308/644	16/160	Cases: H Controls: P	Matched by closest birth date, sex and residence
Shen *et al.* (1996)	China, Nanjing	1986–93	Both sexes combined: 163/163	No data	Cases: H Controls: P	Matched on age, sex, nationality and street of residence
Wang *et al.* (1996)	China, Guangzhou, Guangdong	1990–93	Men: 291/291 Women: 99/99	29/no data 82/no data	Cases: H Controls: H	Matched on sex, residence, education and age
Xu *et al.* (1996)	China, Shenyang, Liaoning	Sept. 1985–Sept. 1987	Men: 729/788 Women: 520/577	No data	Cases: P Controls: P	‘Age and sex distribution of controls closely matched those of cases’
Yu & Zhao (1996)	China	1981–90	Both sexes combined: 5703/5669	1766/2644	Meta-analysis 15 studies	Matched on age, sex and residence

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Zang & Wynder (1996)	USA	1981–94	Men: 1108/1122 Women: 781/948	*Men* SCC [2.3%[†]] AC [10.0%[†]] SCLC [0.0%[†]] Controls [52.6%[†]] *Women* SCC [7.3%[†]] AC [15.1%[†]] SCLC [2.1%[†]] Controls [71.0%[†]]	Cases: H Controls: H	Individually matched by age, sex, hospital and time of admission [†]% of nonsmokers for each histological type of lung cancer and % of nonsmoking controls
Barbone *et al*. (1997)	Italy, Trieste	1979–81; 1985–86	Men: 755/755	22/188	Cases and controls: autopsies	Matched on age and period of death
Dosemeci *et al*. (1997)	Turkey, Istanbul	1979–84	Men: 1210/829	142/293	Cases: H Controls: H	Matched by sex, age (within 5 years) and area of residence
Hu *et al*. (1997)	China, Heilongjiang	May 1985–April 1987	Men: 161/161 Women: 66/66	41/40 67/48	Cases: H Controls: H	Only large-cell cancer
Muscat *et al.* (1997)	USA	1980–95	Men: 228/2545 Women: 154/1715	7/650 13/936	Cases: H Controls: H	Only large-cell carcinoma Frequency-matched by age, sex, hospital and date of interview
Pawlega *et al*. (1997)	Poland, Cracow	Jan. 1992–Dec. 1994	Men: 176/341	4/92	Cases: P Controls: P	Matched by age
Pohlabeln *et al*. (1997)	Germany, Bremen, Frankfurt	1988–93	Men: 839/839	18/138	Cases: H Controls: P	Matched for age, sex and region
Rachtan & Sokolowski (1997)	Poland, Cracow	March 1991–June 1994	Women: 118/141	33/98	Cases: H Controls: H	Controls were next of kin of patients with diseases unrelated to smoking

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Schwartz & Swanson (1997)	USA, Detroit, Michigan	Nov. 1984– June 1987	Men: white: 2767/1395 African American: 913/379 Women: white 1533/1492 African American: 375/426	 119/376 50/104 182/855 40/247	Cases: P Controls: P	African Americans compared with whites
Stellman *et al*. (1997a)	USA	1997–95	Men: 1442/876 Women: 850/467	Only current smokers	Cases: H Controls: H	Frequency-matched on age, sex, hospital and date of admission
Stellman *et al*. (1997b)	USA	1997–95	Men: 1366 SCC/ 1332 AC/3442 controls Women: 431 SCC/982 AC/ 2190 controls	Men: SCC 2%[†] AC 5.4%[†] Women SCC 6%[†] AC 15% [†] Controls: No data	Cases: H Controls: H	Frequency-matched on age, sex, hospital and date of admission [†]% of nonsmokers for each histological type of lung cancer
Wakai *et al*. (1997)	Japan, Okinawa	Jan. 1998– Nov. 1991	Men: 245/490 Women: 88/176	10/65 50/145	Cases: H Controls: P	Matched by sex, region and age; nonsmokers included occasional smokers
Jöckel *et al*. (1998)	Germany, Bremen, Frankfurt	1989–93	Men: 839/839 Women: 165/165	18/138 53/98	Cases: H Controls: P	Adjusted for age, region and exposure to asbestos
Khuder *et al*. (1998)	USA, Philadelphia	1985–87	Men: 482/1094	23/309	Cases: H Controls: P	Matched by race and age
Kreuzer *et al*. (1998)	Germany	1990–96	Men: young: 183/200 older: 1709/1761 Women: young: 68/80 older: 300/278	 6/54 22/403 7/38 95/177	Cases: H Controls: P	Cancer in young adults Frequency-matched on sex, age and region

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Liu *et al*. (1998)	China, 24 urban, 74 rural areas	1989–91	Men, urban 16 317/30 709 Men, rural 38 82/22 046 Women, urban 7300/21 171 Women, rural 1530/13 389	13440/18544 3219/14208 3080/3124 325/1191	Cases: P Controls: P (deaths)	Proportional mortality study
Matos *et al*. (1998)	Argentina, Buenos Aires	March 1994–March 1996	Men: 200/397	11/110	Cases: H Controls: H	Matched for age, sex and hospital
Wunsch-Filho *et al*. (1998)	Brazil, São Paolo	July 1990–June 1991	Men: 307/546 Women: 91/314	14/99 29/208	Cases: H Controls: H	Matched on age, hospital and sex
Armadans-Gil *et al*. (1999)	Spain	1986–90	Men: 325/325	4/64	Cases: H Controls: H	Matched on age
Carpenter *et al*. (1999)	USA, Los Angeles County	Sept. 1990–Jan. 1994	Men: 202/349 Women: 135/129	Smokers only	Cases: H Controls: P	
Mzileni *et al*. (1999)	South Africa	1993–95	Men: 288/183 Women: 60/197	34/103 32/190	Cases: H Controls: H	Only 61% of the lung cancers diagnoses were confirmed
Tousey *et al*. (1999)	USA, Florida	1993–96	Men: 301/567 Women: 206/440	4/130 13/226	Cases: P Controls: P	Frequency-matched on age, race and sex distribution
Agudo *et al*. (2000)	Germany, France, Italy, Spain, United Kingdom	1988–94	Women: 1556/2450	441/1337	Cases: H Controls: P or H, according to centre	Data included in the study (multicentric) by Simonato *et al*. (2001)
Dikshit & Kanhere (2000)	India, Bhopal	Cases: 1986–92 Controls: 1989–92	Men: 163/260	17/146	Cases: P Controls: P	Selected randomly according to age distribution of cases
Kreuzer *et al*. (2000)	Germany, Italy	1988–94	Men: 3723/4075 Women: 900/1094	81/1043 286/715	Cases: H Controls: P or H (1 centre)	Frequency-matched on sex, age and area of residence or individually (1 centre)

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Osann *et al*. (2000)	USA, Orange County, California	July 1990–June 1993	Women: 98/204	1/107	Cases: 28 H Controls: P	Only small-cell carcinoma Frequency-matched on age
Rauscher *et al*. (2000)	USA, New York	July 1982–Dec. 1984	Men: 206/206 Women: 206/206	Current smokers excluded	Cases: P Controls: P	Individually matched on smoking
Simonato *et al*. (2000)	Italy, Venice	Feb. 1992–Feb. 1994	Men: 178/277 Women: 41/52	Sexes combined: 20/135	Cases: H Controls: P	Stratified by Venice Islands and inland; frequency-matched by age and sex
Boffetta *et al*. (2001)	Germany, Spain, France	1991–94	Women < 45 years: 116/174	18/98	Cases: H Controls: H, Spain, France; P, Germany	Matched on age
Goldoni *et al*. (2001)	Italy, Ferrara	1988–93	Men: 249/500	4/77	Cases: P (deaths) Controls: P (alive)	Matched by age
Lam *et al*. (2001)	Hong Kong, SAR	Dec. 1997–Jan. 1999	Men 35–69 years 917/1480 ≥ 70 years 994/2425 Women 35–69 years 314/4930 ≥ 70 years 670/4183	 789/841 887/1502 72/457 303/692	Cases: P (deaths) Controls: P (alive)	Living persons aged at least 60 years identified by the informant
Lee *et al*. (2001)	China, Province of Taiwan	1993–99	Men: 236/[†] Women: 291/[†]	42 cases of SCC, SCLC and AC, and 119 controls	Cases: H Controls: H	[†]Cases matched to 1 or 2 controls on age and sex; 805 controls in total. Data are presented separately for SCC + SCLC and AC.
Mao *et al*. (2001)	Canada, 8 provinces	1994–97	Men: 1722/2542 Women: 1558/2531	45/680 161/1271	Cases: P Controls: P	Frequency-matched to the age/sex distribution of all cancer cases

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Simonato *et al*. (2001)	France, Germany, Italy, Spain, Sweden, United Kingdom	1988–94	Men: 6035/7967 Women: 1574/2464	120/1953 467/1601	Cases: H Controls: P or H, according to centre	Frequency-matched to the age and sex distribution of the cases
Stellman *et al*. (2001)	Japan, USA	USA: March 1992–Feb. 1997 Japan: June 1993–May 1998	Men: USA: 371/373 Japan: 410/252/411	USA: 16/153 Japan: 19/29/70	USA: Cases: H Controls: H Japan: Cases: H Controls: H/P	Hospital controls frequency-matched on age, hospital and date of interview; population controls matched on age, date of interview and residence
Bhurgri *et al*. (2002)	Karachi, Pakistan	Not given	Men: 282/561[†] Women: 38/79[†]	Men and women, 45/418	Cases: H Controls: 320 H; 320 V	[†]Men, 279 HC + 282 VC; women, 41 HC + 38 VC matched on age and sex
Kubik *et al*. (2001, 2002)	Prague, Czech Republic	1998–2000	Women: 269/1079	51/603	Cases: H Controls: H	Controls within the same age group and catchment area
Pacella-Norman *et al*. (2002)	Johannesburg, South Africa	March 1995–April 1999	Men: 105/804 Women: 41/1370	8/317 16/1143	Cases: H Controls: H	Only blacks; cancer controls
Petrauskaite *et al*. (2002)	Kedainiai, Lithuania	1981–91	Men: 226/886	4/80	Death certificates and cancer registry	Matched by age, year of death
Rachtan (2002)	Cracow, Poland	March 1991–Dec. 1997	Women: 242/352	54/251	Cases: H Controls: H	

Table 2.1.1.4 (contd)

Reference	Country	Study years	No. of cases/controls	No. of nonsmokers (cases/controls)	Source of cases and controls	Comments
Sasco *et al*. (2002)	Casablanca, Morocco	Jan. 1996– Jan. 1998	Men: 114/227 Women: 4/8	Both sexes: 5/94	Cases: H Controls: H	Matched on age, sex and residence
Stellman *et al*. (2003)	USA	1984–98	Men: white, 1710/4491 black, 254/440 Women: white, 1321/2862 black, 163/358	 3.5%/29.8% 2.4%/25.5% 9.2%/50.5% 6.8%/49.7%	Cases: H Controls: H	Frequency-matched for sex, hospital and year of interview
Wang *et al*. (2002)	China, Gansu	Jan. 1994– April 1998	Men: 563/1232 Women: 205/427	28/110 181/385	Cases: P Controls: P	Matched on age, stratified on sex and prefecture

H, hospital; P, population; V, visitor; SCC, squamous-cell carcinoma; AC, adenocarcinoma; SCLC, small-cell carcinoma

Table 2.1.1.5. Case–control studies on tobacco smoking and lung cancer: intensity and cumulative amount

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio				95% CI	Adjustments, comments
Damber & Larsson (1986)	Men/C1	1–7	2.3				Numbers not stated [figure]	Reference level not stated; smoking includes any tobacco. C1 deceased, C2 alive; adjustment variables not stated
		8–15	7.3					
		≥ 16	10.2					
	Men/C2	1–7	2.3					
		8–15	7.0					
		≥ 16	18.2					
Pathak *et al.* (1986)	Men < 65 years	1–15	16.2					Reference level, never-smoker; adjusted for sex and ethnicity
		16–20	27.6					
		21–30	47.1					
		≥ 31	89.3					$p < 0.001$ for linear trend
	Men ≥ 65 years	1–15	8.6					
		16–20	12.3					
		21–30	22.9					
		≥ 31	24.3					$p < 0.001$ for linear trend
Benhamou *et al.* (1987)	Women	< 10	0.6				0.1–2.6	Reference level, nonsmoker; matched analysis, adjusted for filter, duration, inhalation, age at starting smoking and type of tobacco
		10–19	0.9				0.2–4.4	
		≥ 20	4.8				0.7–35.6	
Gao *et al.* (1988)	Men		Duration (years)	1–29	30–39	≥ 40	CI not provided	Reference level, lifelong nonsmoker; adjusted for age and education
		1–19		0.9	3.2	3.8		
		20–29		2.1	7.1	7.2		
		≥ 30		3.0	10.8	15.4		
	Women			< 30	≥ 30			
		< 10		1.4	2.4			
		10–19		2.6	3.2			
		≥ 20		8.9	14.2			
Benhamou *et al.* (1989)	Men	1–9	1.0					Adjusted for age and duration of smoking
		10–19	2.4				1.6–3.6	
		≥ 20	5.2				3.5–7.6	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio				95% CI	Adjustments, comments
Kaufman *et al*. (1989)	Men and women	< 15	8.0				5–13	Adjusted for age, sex, ethnicity, region, education and date of interview
		15–24	15.0				10–23	
		25–34	28.0				17–44	
		35–44	43.0				27–68	
		≥ 45	60.0				35–102	
Schoenberg *et al*. (1989)	Women	< 20/day < 35 years	3.2				2.3–4.4	Adjusted for age, race and respondent
		≥ 20/day < 35 years	6.5				4.5–9.4	
		< 20/day ≥ 35 years	8.4				6.2–11.2	
		≥ 20 day ≥ 35 years	16.0				11.9–21.7	
Svensson *et al*. (1989)	Women	Former smoker	2.6				1.4–5.1	Reference level, never-smoker; ?, not given
		1–10	4.6				2.5–9.3	
		11–20	12.6				6.5–25.2	
		≥ 21	59.0				7.6–?	
Xu *et al*. (1989)			Duration (years)	1–29	30–39	≥ 40		Reference level, nonsmoker; adjusted for age and education
	Men	1–19		1.8*	2.1	3.3*		
		20–29		1.5*	2.7*	6.0*		
		≥ 30		5.3*	4.9*	17.1*		
	Women	1–19		1.4	3.1	3.4*		
		≥ 20		2.1	3.4*	9.4*		
Jedrychowski *et al*. (1990)	Men	1–19	3.5				2.3–5.2	Reference level, never-smoker; adjusted for age
		20–29	6.2				4.2–8.9	
		≥ 30	7.7				5.1–11.5	
		Unknown	2.4				1.2–4.7	
	Women	1–19	6.4				2.7–15.2	
		20–29	2.4				1.2–6.9	
		≥ 30	7.4				2.2–24.7	
		Unknown	2.9				0.5–18.6	
Wu-Williams *et al*. (1990)	Women		Duration (years)	1–29	30–39	≥ 40		[†]Only 9% of the cases and 4% of the controls in this category
		1–19		1.3	2.6*	3.2*		
		≥ 20[†]		1.8	3.3*	5.7*		

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Hebert & Kabat (1991)	Men	1–19	3.8	2.7–5.5	Reference level, never-smoker; adjustment not stated
		20–29	8.3	6.3–11.1	
		≥ 30	10.9	8.4–14.1	
	Women	1–19	4.9	3.4–7.1	
		20–29	12.9	9.6–17.5	
		≥ 30	19.7	14.9–26.1	
Katsouyanni *et al*. (1991)	Women	Nonsmoker	1.0		Adjusted for age
		≤ 20	2.3	1.1–4.8	
		≥ 21	7.5	2.4–23.2	
Liu *et al*. (1991)	Men	Never-smoker	1.0		Only 56 cases, restricted to farmers; adjusted on 'other risk factors'
		≤ 0.5 kg/month[†]	1.4	0.3–6.1	
		0.6–1 kg/month	1.1	0.2–4.8	
		> 1 kg/month	1.9	0.3–11.4	[†]kg/month of tobacco smoked
		Smoking index[‡]			[‡]Amount × years of smoking
		< 2	1.0		
		2–19	2.6	0.7–9.8	
		20–34	2.2	0.5–8.6	
		≥ 35	4.7	1.03–21.4	
Osann (1991)	Women	< 1 pack/day	2.5	1.2–5.2	Adjusted on age
		≥ 1 pack/day	12.6	6.2–25.6	
Jöckel *et al*. (1992)	Men	> 0–20 pack–years	7.3	2.4–22.3	Reference level, nonsmoker; hospital and population controls combined
		> 20–40 pack–years	8.3	2.8–25.0	
		≥ 41 pack–years	16.2	5.1–51.3	
	Women	> 0–20 pack–years	5.7	1.3–24.7	
		≥ 21 pack–years	20.0	5.0–80.2	
Liu (1992)	Men and women	< 10	1.0	0.8–1.3	Reference level, nonsmoker; combined analysis of 5 studies; Mantel-Haenzel summary odds ratios (each city = one stratum)
		10–19	2.0	1.7–2.5	
		≥ 20	3.3	2.7–4.2	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio		95% CI	Adjustments, comments
Lubin *et al.* (1992)	Men	1–6	0.7			Reference level, nonsmoker; adjusted for age, source of subject, type of respondent and years of work underground p for trend < 0.01
		7–14	1.2			
		15–19	6.5			
		≥ 20	8.0			
Morabia & Wynder (1992)	Men and women		Non-cancer control	Cancer control		Only bronchioalveolar carcinoma; reference level, never-smoker; adjusted for age and sex
		1–19	1.5	1.9		
		20–29	3.3*	4.6*		
		30–39	4.1*	6.7*		
		40–80	5.0*	7.6*		
Gao *et al.* (1993)	Men	1–19	3.5		1.6–7.2	Reference level, nonsmoker; adjusted for age
		20–29	7.5		3.7–15.3	
		≥ 30	10.6		5.1–22.2	
Liu *et al.* (1993)	Men	Never-smoker	1.0			Adjusted for education, occupation and living area; present and former smokers combined
		1–19	1.2		0.4–3.5	
		20–29	7.1		2.6–19.5	
		≥ 30	21.4		7.1–64.0	
	Women	Never-smoker	1.0			
		1–9	1.8		0.6–5.9	
		10–19	3.5		1.2–9.8	
		≥ 20	17.9		4.0–80.6	
Pezzotto *et al.* (1993)	Men	< 21	1.0			Adjusted for age, hospital and duration of smoking
		21–40	8.2		$p < 0.0001$	
		> 40	11.6		$p < 0.0001$	
Risch *et al.* (1993)	Men	1–29 pack–years	5.2		2.4–11.5	Reference level, never-smoker; adjusted for sex, age, residence and years since cessation
		30–59 pack–years	11.0		5.4–22.3	
		≥ 60 pack–years	22.6		10.0–51.2	
	Women	1–29 pack–years	7.3		4.1–13.0	
		30–59 pack–years	26.7		14.0–50.6	
		≥ 60 pack–years	81.9		25.3–267	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Benhamou *et al*. (1994)	Men	1–14	1.0		Adjusted for age and other smoking variables
		15–20	1.7	1.4–2.1	
		> 20	3.2	2.5–4.0	
De Stefani *et al*. (1994)	Men	*Manufactured*			Smokers only; adjusted for age, residence, education and duration
		1–14	1.0		
		15–20	3.3	1.4–7.7	
		21–40	4.4	1.8–10.6	
		≥ 41	11.9	3.7–38.6	
		Hand rolled			
		1–14	1.0		
		15–20	1.9	1.2–3.0	
		21–40	2.4	1.5–3.9	
		≥ 41	4.1	2.4–6.8	
Sankanarayanan *et al*. (1994)	Men	*Pack–years*			Reference level, never-smoker; crude odds ratios
		1–5	1.7	0.8–3.8	
		6–10	3.7	1.8–7.5	
		11–15	7.7	3.9–15.2	
		16–20	9.3	4.8–17.9	
		21–25	21.7	11.0–42.8	
		26–30	35.8	16.8–76.2	
		31–40	44.2	23.9–81.8	
		41–50	57.5	25.2–131.0	
		51–60	71.6	29.3–174.5	
		≥ 61	113.6	35.2–303.3	
Sobue *et al*. (1994)	Men	1–19	1.0		Adjusted for duration, fraction smoked per cigarette, filter and inhalation
		20–29	1.3	1.0–1.8	
		≥ 30	1.7	1.2–2.3	
Suzuki *et al*. (1994)	Men and women	1–30[†]	1.0		Adjusted for age, sex and race, in a multivariate analysis excluding nonsmokers [†]overlapping intervals
		30–50[†]	2.2	0.9–5.0	
		> 50	7.4	3.1–17	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio					95% CI	Adjustments, comments
Siemiatycki *et al.* (1995)	Men	Nonsmoker	1.0						Adjusted by age, ethnic group, socioeconomic status, coffee consumption, and composite scores for consumption of alcohol and β-carotene
		1–500 cig–years	4.4					2.2–8.6	
		501–1000 cig–years	9.9					5.3–18.7	
		1001–1500 cig–years	16.1					8.5–30.8	
		≥ 1501 cig–years	28.0					14.5–54.0	
De Stefani *et al.* (1996a)	Men	1–10	2.9					1.6–5.0	Reference level, never-smoker; adjusted for age, residence, urban/rural status and education
		11–20	8.4					5.2–13.6	
		21–40	10.4					6.4–16.9	
		≥ 41	23.7					13.4–42.1	
		1–29 pack–years	3.8					2.3–6.3	
		30–50 pack–years	7.6					4.6–12.6	
		51–85 pack–years	12.7					7.7–21.1	
		≥ 86 pack–years	14.9					8.9–24.8	
De Stefani *et al.* (1996b)	Men and women	1–33 pack–years	1.9					1.0–3.8	Reference level, nonsmoker; adjusted for age, sex, residence, urban/rural, education, family history of cancer and body-mass index
		34–54 pack–years	6.5					3.5–12.1	
		55–84 pack–years	14.5					7.7–27.2	
		≥ 85 pack–years	16.1					8.6–30.4	
Lei *et al.* (1996)	Men	< 400 cig–years	1.8					1.2–3.3	[Adjustment not stated]
		400–799 cig–years	3.3					2.7–5.6	
		≥ 800 cig–years	5.4					3.6–7.9	
	Women	< 400 cig–years	1.9					1.7–3.0	
		400–799 cig–years	3.6					2.4–5.1	
		≥ 800 cig–years	5.5					3.2–7.2	
Rylander *et al.* (1996)	Men		Duration (years)					*p* trend	Reference level, nonsmoker; adjusted for age, marital status, job classification, 'other fruits and berries' and milk consumption.
			< 20	20–29	30–39	40–49	≥ 50		
		< 10	0.9	1.4	4.3*	5.7*	17.6*	0.008	
		10–19	2.6	2.3	6.0*	16.2*	22.6*	0.001	
		≥ 20	1.3	2.8*	10.9*	12.6*	41.0*	0.001	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio				95% CI	Adjustments, comments
Xu *et al*. (1996)			Duration (years)	1–29	30–39	≥ 40		Reference level, nonsmoker; adjusted for age and education
	Men	1–19		1.8*	2.1*	3.3*		
		20–29		1.5*	2.7*	6.0*		
		≥ 30		5.3*	4.9*	17.1*		
	Women	1–19		1.4	3.1*	3.4*		
		≥ 20		2.1	3.4*	9.4*		
Yu & Zhao (1996)	Men and women	< 10	1.2				0.9–1.8	Meta-analysis of 15 studies
		10–19	2.2				1.4–2.8	
		≥ 20	4.5				2.8–7.2	
	Women	< 10	2.2				1.7–2.9	Meta-analysis of 12 studies
		10–19	6.1				4.6–8.1	
		≥ 20	12.2				8.8–16.8	
Barbone *et al*. (1997)	Men	1–9	2.7				1.5–5.1	Reference level, nonsmoker; adjusted for age
		10–19	9.8				5.9–16.3	
		20–29	10.9				6.7–17.8	
		30–39	13.6				8.1–23.0	
		≥ 40	17.7				10.7–29.2	
Dosemeci *et al*. (1997)	Men	1–10	2.2				1.4–3.3	Adjusted for age and alcohol consumption
		11–20	3.1				2.3–4.1	
		≥ 21	6.6				4.4–10.2	
Hu *et al*. (1997)	Men	Nonsmoker	1.0					Adjustment not stated
		1–14[†]	1.6				0.8–3.0	[†][Overlapping intervals]
		14–24[†]	2.1				1.2–3.8	
		≥ 25	3.7				1.6–8.4	
	Women	Nonsmoker	1.0					[‡]Only 6 cases and 6 controls for 14–24 cigarettes/day and 1 case and 2 controls for ≥ 25 cigarettes/day
		1–14[†]	2.3				0.9–6.0	
		14–24[†]	1.2[‡]				0.3–4.6	
		≥ 25	0.6[‡]				0.3–9.7	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio				95% CI	Adjustments, comments
Muscat *et al.* (1997)			Cig/day	1–19	20–39	≥ 40		Analysis of large-cell carcinomas only; adjusted for age and education all *p* for trend < 0.01
	Men	Current smoker		8.3*	14.6*	37.0*		
		Former smoker		4.8*	7.4*	11.1*		
	Women	Current smoker		6.0*	21.0*	72.9*		
		Former smoker		4.2*	9.9*	10.5*		
Pawlega *et al.* (1997)	Men	1–20 pack–years	2.9				0.8–10.4	Adjusted for age, residence, education, years of occupational exposure and frequency of fruit and vegetable consumption
		21–40 pack–years	15.2				4.8–47.5	
		> 40 pack–years	18.7				6.0–58.2	
Rachtan & Sokolowski (1997)	Women	< 10	3.6				1.1–12.3	Reference level, never-smoker; adjusted for age
		10–19	3.5				1.7–7.2	
		≥ 20	13.8				6.5–29.2	
Schwartz & Swanson (1997)	Men	*40–54 years*						Risk for African Americans compared with whites in each category of smokers within each age group, for men and women separately; adjusted for age, education and number of years since cessation
		Nonsmoker	8.0				2–32.8	
		1–40 pack–years	3.1				1.9–5.4	
		≥ 41 pack–years	1.8				0.7–4.7	
		55–84 years						
		Nonsmoker	1.0				0.6–1.5	
		1–40 pack–years	0.8				0.6–1.1	
		≥ 41 pack–years	0.9				0.7–1.2	
	Women	*40–54 years*						
		Nonsmoker	0.8				0.2–3.4	
		1–40 pack–years	1.2				0.7–2.1	
		≥ 41 pack–years	–				–	
		55–84 years						
		Nonsmoker	0.8				0.5–1.1	
		1–40 pack–years	1.1				0.8–1.6	
		≥ 41 pack–years	0.8				0.5–1.2	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Wakai *et al*. (1997)	Men	1–19	1.8	0.8–4.0	Current smokers; reference level, nonsmoker; adjusted for age
		20–29	4.0	1.9–8.4	
		≥ 30	9.2	4.2–20.1	
Jöckel *et al*. (1998)	Men	Nonsmoker	1.0		Nonsmoker includes occasional smokers; matched for age, sex and region; no further adjustments
		0–20 pack–years	3.8	2.2–6.5	
		> 20–40 pack–years	9.7	5.7–16.5	
		> 40 pack–years	14.0	8.1–24.4	
	Women	Nonsmoker	1.0		
		0–20 pack–years	1.8	1.0–3.3	
		> 20–40 pack–years	5.2	2.6–10.4	
		> 40 pack–years	11.3	3.1–41.2	
Khuder *et al*. (1998)	Men	1–19	2.5	1.5–4.1	Reference level, nonsmoker Crude odds ratios
		20–39	10.4	6.6–16.5	
		≥ 40	32.8	19.6–55.0	
Kreuzer *et al*. (1998)	*≤ 45 years*				Adjusted for age, region and exposure to asbestos
	Men	≤ 9	2.5	0.7–8.2	
		10–19	8.7	3.5–21.9	
		20–29	19.5	7.5–50.3	
		≥ 30	20.8	7.2–60.5	
	Women	≤ 9	5.7	1.6–16.6	
		10–19	11.8	3.5–29.0	
		20–29	12.1	3.0–48.0	
	55–69 years				
	Men	≤ 9	8.2	5.2–13.0	
		10–19	25.1	16.2–38.7	
		20–29	32.8	20.9–51.4	
		≥ 30	33.3	20.5–54.0	
	Women	≤ 9	2.0	1.2–3.3	
		10–19	5.4	3.5–8.6	
		20–29	7.7	3.5–17.3	
		≥ 30	–	–	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Liu *et al*. (1998)	Men aged 35–69 years	*Urban*[†]			Proportional mortality study
		1–19	2.1	0.05[‡]	Reference level, nonsmoker
		20	3.6	0.06	[†]Most recent smoking habit
		> 20	6.9	0.14	[‡]Standard error
		Rural[†]			Trends: $p < 0.0001$
		1–19	2.2	2.23	
		20	3.7	3.65	
		> 20	7.3	7.26	
Matos *et al*. (1998)	Men	*Current smoker*			Reference level, nonsmoker; adjusted for age and hospital
		1–14	1.6	0.5–5.0	
		15–24	8.0	3.4–16.8	
		≥ 25	15.0	7.1–31.9	
		Former smoker			
		1–14	2.3	0.9–5.6	
		15–24	6.7	2.9–15.4	
		≥ 25	7.4	3.4–16.1	
Wunsch-Filho *et al*. (1998)	Men	< 21 pack–years	1.3	0.7–2.8	Reference level, nonsmoker
		21–40 pack–years	4.2	2.2–8.1	
		41–60 pack–years	6.9	3.6–13.0	
		≥ 61 pack–years	7.7	4.1–14.6	
	Women	< 21 pack–years	3.9	2.0–7.6	
		21–40 pack–years	9.0	3.6–22.5	
		41–60 pack–years	7.4	2.9–19.0	
		≥ 61 pack–years	3.6	1.1–11.4	
Armadans-Gil *et al*. (1999)	Men	1–14	3.3	1.4–7.4	Adjusted for age
		15–24	11.6	5.3–25.3	
		≥ 25	41.2	17.8–95.0	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Mzileni *et al*. (1999)	Men	Former smoker	2.2	1.0–4.6	Reference level, never-smoker; adjusted for age, dusty occupation and exposure to asbestos at birth
		Current smoker			
		< 15 g/day	9.8	5.9–16.4	
		≥ 15 g/day	12.0	6.5–22.3	
	Women	Former smoker[†]	5.8	1.3–25.8	[†]Only 2 former and 5 current smokers among controls
		Current smoker[†]	5.5	2.6–11.3	
Agudo *et al*. (2000)	Women	< 10	2.0	1.6–2.5	Reference level, never-smoker (includes smokers of less than 400 cig during lifetime) adjusted for age and centre
		10–19	5.9	4.8–7.3	
		20–29	9.5	7.0–12.8	
		≥ 30	15.4	9.6–24.7	
Dikshit & Kanhere (2000)	Men	1–10	1.5	0.3–6.7	Adjusted for age and bidi-smoking
		11–20	11.1	3.4–35.9	
		> 20	26.8	6.0–120.2	
Kreuzer *et al*. (2000)	*All*[†]				Reference level, never-smoker Adjusted for age and centre [†]*p* for interaction gender/smoking < 0.0001 [‡]*p* for interaction gender/smoking = 0.8 Analysis restricted to ever-smokers, adjusted also for duration and time since cessation
	Men	< 15	8.6	6.7–10.9	
		15–29	21.7	17.2–27.4	
		≥ 30	25.4	19.4–33.3	
	Women	< 15	2.9	2.4–3.6	
		15–29	7.8	5.8–10.3	
		≥ 30	13.8	6.8–28.1	
	Age < 50[‡]				
	Men	< 15	4.3	2.4–7.5	
		15–29	11.6	7.0–19.3	
		≥ 30	20.7	10.8–39.6	
	Women	< 15	3.8	1.9–7.6	
		15–29	15.0	7.0–32.0	
		≥ 30	23.4	5.9–92.3	
	Ever-smoker				
	Men	< 15	1.0		
		15–29	2.0	1.8–2.2	
		≥ 30	2.4	2.0–2.8	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio			95% CI	Adjustments, comments
	Women	< 15	1.0				
		15–29	2.0			1.4–2.7	
		≥ 30	3.4			1.6–7.3	
Osann *et al.* (2000)	Women	Former smoker	31.5				Small-cell carcinoma only
		Current smoker	278.9				Reference level, never-smoker (1 case/107 controls); adjusted for age and education
		< 12 pack–years	1.0[†]				[†]1 case/146 controls; analysis by pack–years, also adjusted for years since cessation.
		12.1–24.4 pack–years	27.0				
		≥ 24.5 pack–years	56.7				
Simonato *et al.* (2000)	Men and women	*Venice*					Reference level, never-smoker, includes former smokers with > 20 years of cessation; adjusted for age, sex, education, duration, occupation and heating
		Former smoker	4.6			1.3–16.5	
		Current smoker	17.5			4.8–63.4	
		Mestre					
		Former smoker	4.9			2.3–10.5	
		Current smoker	9.7			4.7–19.9	
Boffetta *et al.* (2001)	Women		*< 35 years*	*35–39 years*	*40–44 years*		[†]Reference level, never-smoker, adjusted for center and age
		Current smoker[†]	3.4 (0.6–19)	5.4 (1.9–15)	18 (6.6–50)		[‡]Reference level, < 15 cigarettes/day, further adjusted for duration of smoking
		Former smoker[†]	4.9 (0.5–47)	2.2 (0.6–8.2)	5.3 (1.6–18)		
		1–9 pack–years[†]	3.6 (0.6–21)	1.0 (0.2–4.5)	3.9 (1.2–13)		
		10–14 pack–years[†]	3.7 (0.3–41)	6.6 (1.6–27)	18 (4.9–64)		
		≥ 15 pack–years[†]	4.4 (0.4–48)	6.9 (2.1–22)	33 (10–104)		
		15–24 cig/day[‡]	0.3 (0.1–2.6)	0.1 (0.02–1.0)	2.0 (0.7–5.4)		
		≥ 25 cig/day[‡]	–	0.4 (0.04–4.4)	5.7 (1.0–32)		

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Goldoni *et al.* (2001)	Men	1–9	3.7	0.9–15.8	Reference level, nonsmoker; adjusted for passive smoking, age and diet
		10–19	9.9	3.3–29.5	
		≥ 20	44.9	14.5–139.3	
Lam *et al.* (2001)	*35–69 years*				Reference level, nonsmoker; adjusted for age and education all p for trend < 0.001
	Men	1–14	2.8*		
		15–24	5.6*		
		≥ 25	12.7*		
	Women	1–14	2.4*		
		15–24	4.2*		
		≥ 25	7.5*		
	≥ 70 years				
	Men	1–14	3.4*		
		15–24	6.5*		
		≥ 25	7.3*		
	Women	1–14	3.4*		
		15–24	6.2*		
		≥ 25	5.3*		
Mao *et al.* (2001)	Men	Former smoker	6.4	4.6–8.8	Reference level, never-smoker; adjusted for age group, province, years of exposure to passive smoking, total consumption of vegetables, vegetable juices and meat
		Current smoker	17.3	12.4–24.2	
		≤ 8 pack–years	2.1	1.4–3.2	
		9–18	3.6	2.4–5.2	
		19–32	12.7	9.0–17.9	
		≥ 33	27.9	19.8–39.4	
	Women	Former smoker	4.3	3.5–5.4	
		Current smoker	13.2	10.6–16.4	
		≤ 8 pack–years	1.5	1.2–2.1	
		9–18	4.1	3.1–5.4	
		19–32	13.0	10.2–16.6	
		≥ 33	29.0	22.1–38.0	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Simonato *et al*. (2001)	Men	< 10	13.1	10.1–16.8	Reference level, nonsmoker; adjusted for age, education and centre. There is an increasing risk with duration for each category of average cigarettes/day. Only data for duration ≥ 40 years are shown.
		10–19	29.7	23.9–36.7	
		20–29	44.9	35.7–56.3	
		≥ 30	46.4	29.7–72.5	
	Women	< 10	6.6	4.6–9.5	
		10–19	11.6	8.3–16.1	
		20–29	29.5	18.0–48.1	
		≥ 30	36.4	10.3–129.1	
Stellman *et al*. (2001)	Men USA (hospital controls)	< 20	10.9	4.4–28.0	Reference level, nonsmoker; adjusted for age, education and hospital for hospital controls or residence for community controls
		20–29	53.4	23.1–135.2	
		≥ 30	73.3	32.5–181.6	
	Japan (hospital controls)	< 20	1.6	0.7–3.9	
		20–29	3.5	1.5–8.4	
		≥ 30	6.2	2.6–15.0	
	Japan (community controls)	< 20	2.6	1.4–4.9	
		20–29	4.3	2.4–7.6	
		≥ 30	9.3	5.2–16.7	
Bhurgi *et al*. (2002)	Men and women	Former smoker	16.7	9.8–28.4	Reference level, never-smoker; adjusted for age, sex, hospital [†]Also adjusted for years of smoking
		Current smoker	30.2	17.8–51.3	
		Cig-equivalents/day[†]			
		1–9	4.1	1.8–9.2	
		19–19	14.5	8.0–26.3	
		20–29	36.7	20.1–67.0	
		≥ 30	85.9	43.9–168.3	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Kubik *et al*. (2001, 2002)	Women	Former smoker	7.7	6.7–15.8	Reference level, never-smoker; adjusted for age, residence and education; information on duration and pack–years
		Current smoker	10.3	5.1–11.5	
		1–4	4.6	2.4–9.0	
		5–14	5.7	3.8–8.5	
		> 14	12.6	8.3–19.0	
Pacella-Norman *et al*. (2002)	Men	1–14 g/day[†]	6.3	2.6–15.0	Reference level, never-smoker; adjusted for age, place of birth, education, work category [†]1 cigarette = 1 pipe = 1 hand-rolled cigarette = 1 g
		≥ 15 g/day[†]	23.9	9.5–60.3	
	Women	1–14 gday[†]	10.5	4.1–27.3	
		≥ 15 g/day[†]	50.9	12.6–204.6	
Petrauskaite (2002)	Men	Former smoker	14.0	4.9–40.3	Reference level, never-smoker; adjusted for age and year of death
		Current smoker	21.1	7.5–60.1	
		< 8	9.8	2.9–33.1	
		8–15	21.3	7.1–63.7	
		≥ 16	27.0	9.3–78.5	
Rachtan (2002)	Women	Former smoker	3.3	1.8–5.9	Reference level, never-smoker; adjusted for age
		Current smoker	14.0	9.0–21.7	
		< 11	4.0	2.3–7.0	
		11–20	11.2	7.1–17.6	
		21–30	23.0	8.2–64.3	
		≥ 30	45.8	10.3–204.1	
Sasco *et al*. (2002)	Men and women	Former light	1.8	0.5–6.8	Reference level, never-smoker; adjusted for use of hashish/kif, snuff, history of chronic bronchitis, passive smoking, occupational exposure, cooking and heat source, lighting sources, ventilation of the kitchen
		Former heavy	8.1	2.0–33.1	
		Current light	18.5	4.1–83.5	
		Current heavy	26.1	6.6–103.0	

Table 2.1.1.5 (contd)

Reference	Subjects	Average no. of cigarettes/day[a]	Odds ratio	95% CI	Adjustments, comments
Stellman *et al.* (2002)	*Men* White	Former smoker	7.9	6.0–10.3	Reference level, never-smoker
		Current smoker	21.0	15.8–27.8	
		1–19	8.4	5.9–12.1	
		20	20.0	14.4–27.6	
		≥ 21	29.8	22.1–40.2	
	Black	Former smoker	8.1	3.4–19.4	
		Current smoker	18.2	7.6–43.4	
		1–19	7.5	3.0–18.7	
		20	34.2	13.3–88.3	
		≥ 21	42.2	15.9–111.9	
	Women White	Former smoker	6.3	5.1–7.9	
		Current smoker	19.3	15.4–24.2	
		1–10	6.2	4.4–8.8	
		11–20	19.1	14.6–25.0	
		≥ 21	33.6	25.4–44.4	
	Black	Former smoker	9.3	4.5–19.2	
		Current smoker	17.2	8.7–33.7	
		1–10	8.3	3.8–18.2	
		11–20	21.3	10.0–45.2	
		≥ 21	42.9	17.0–108.4	
Wang *et al.* (2002)	Men and women	Light smoker	1.3	0.8–1.8	Reference level, never-smoker; adjusted for age, sex, prefecture and socioeconomic factors
		≥ 10 cig/day and ≥ 30 years	2.5	1.5–4.1	
		≥ 20 cig/day and ≥ 40 years	5.5	2.2–12.2	

*$p < 0.05$
[a] Unless otherwise specified

Table 2.1.1.6. Case–control studies on tobacco smoking and lung cancer: age at starting smoking

Reference	Subjects	Age at starting smoking (years)	Odds ratio	95% CI	Comments
Gao *et al* (1988)	Men	10–19	5.1	3.6–7.2	Reference level, lifelong nonsmoker; adjusted for age and education
		20–29	4.7	3.3–6.5	
		≥ 30	1.2	0.8–1.9	
	Women	10–19	5.6	3.4–9.0	
		20–29	3.8	2.6–5.8	
		≥ 30	2.0	1.4–3.0	
Jedrychowski *et al.* (1990)	Men	< 17	1.7	1.2–2.3	Reference level, never-smoker; adjusted for age
		17–18	1.3	1.0–1.7	
	Women	< 23	1.8	0.7–4.6	
Liu (1992)	Men and women	< 20	3.3	2.7–4.0	Reference level, nonsmoker; combined analysis of 3 studies; adjusted by city
		20–29	2.4	2.0–2.8	
		≥ 30	1.2	0.9–1.5	
Morabia & Wynder (1992)	Men and women		NCC		Only bronchioloalveolar carcinoma; reference level, never-smoker; adjusted for age and sex
		10–14	2.3	0.9–6.2	
		15–16	5.7	2.5–12.9	
		17–19	2.1	1.0–4.4	
		20–50	2.3	1.1–4.9	
			CC		
		10–14	6.0	2.1–17.3	
		15–16	5.2	2.3–11.3	
		17–19	4.1	1.9–8.7	
		20–50	2.4	1.2–5.1	

Table 2.1.1.6 (contd)

Reference	Subjects	Age at starting smoking (years)	Odds ratio	95% CI	Comments
Gao *et al*. (1993)	Men	< 20	8.6	4.0–18.5	Reference level, nonsmoker; adjusted for age
		20–29	6.4	3.3–12.5	
		≥ 30	2.1	0.4–13.0	
Hegmann *et al*. (1993)	Men	≤ 19	12.7	6.4–25.2	Reference level, nonsmoker; adjusted for age and pack–years
		> 19	6.0	2.8–12.9	[†]Only 2 cases started > 25 years.
	Women	≤ 25	10.0	4.7–21.2	
		> 25[†]	2.6	0.5–12.4	
Pezzotto *et al*. (1993)	Men	< 14	1.0		Adjusted for age, hospital and intensity of cigarette smoking
		14–18	1.4		
		> 18	0.9		
Benhamou & Benhamou (1994)	Men	≤ 19	5.8	3.8–8.8	Reference level, nonsmoker; adjusted for age at diagnosis, hospital, interviewer and pack–years
		> 19	5.9	3.9–8.9	
	Women	≤ 25	2.5	0.9–6.9	
		> 25	1.2	0.4–3.5	
Suzuki *et al*. (1994)	Men and women	< 12	2.4	0.8–7.3	Adjusted for age, sex, race and pack–years
		12–18	2.1	0.9–5.0	
		> 18	1.0		
Yu & Zhao (1996)	Men and women	< 20	3.3	2.4–3.6	Reference level, nonsmoker
		20–29	2.4	1.9–3.1	Meta-analysis of 15 studies
		≥ 30	1.3	0.9–1.9	
	Women	< 20	3.2	2.4–4.3	Meta-analysis of 12 studies
		20–29	2.8	2.2–3.7	
		≥ 30	1.5	1.2–2.0	

Table 2.1.1.6 (contd)

Reference	Subjects	Age at starting smoking (years)	Odds ratio	95% CI	Comments
Barbone *et al*. (1997)	Men	< 15	50.8	27.2–95.0	Reference level, nonsmoker; adjusted for age
		15–19	9.9	6.2–15.8	
		≥ 20	8.2	5.0–13.3	
Rachtan & Sokolowski (1997)	Women	< 20	11.6	5.0–26.7	Reference level never-smoker; adjusted for age
		20–30	5.3	2.8–10.2	
		> 30	5.3	1.5–19.0	
Khuder *et al*. (1998)	Men	< 16	10.3	6.5–16.3	Reference level, nonsmoker; unadjusted odds ratios
		16–19	6.4	4.0–10.2	
		≥ 20	6.4	3.8–10.2	
Liu *et al*. (1998)	Men 35–69 years				Proportional mortality study
	Urban	< 20	4.11	0.07†	Reference level, nonsmoker
		20–24	2.94	0.05†	†standard error
		≥ 25	2.45	0.05†	trends: $p < 0.0001$
	Rural	< 20	3.07	0.11†	
		20–24	2.62	0.09†	
		≥ 25	2.26	0.09†	
Matos *et al*. (1998)	Men				Reference level, nonsmoker; adjusted for age and hospital
	Current smoker	< 15	11.3	5.3–24.3	
		15–19	8.6	4.1–18.4	
		≥ 20	5.3	2.3–12.5	
	Former smoker	< 15	4.9	2.2–11.0	
		15–19	7.5	3.5–16.0	
		≥ 20	2.6	1.0–6.7	

Table 2.1.1.6 (contd)

Reference	Subjects	Age at starting smoking (years)	Odds ratio	95% CI	Comments
Mao *et al*. (2001)	Men	≤ 15	11.5	8.3–16.0	Reference level, never-smoker; adjusted for age group, province, years of exposure to passive smoking, total consumption of vegetables, vegetable juices and meat
		16–19	9.1	5.5–12.7	
		≥ 20	6.3	4.4–9.1	
	Women	≤ 15	8.8	6.9–11.2	
		16–19	8.0	6.4–9.9	
		≥ 20	5.6	4.4–7.1	
Stellman *et al*. (2001)	Men USA (community controls)	≤ 14	1.2	0.4–3.4	Adjusted for age, education and hospital for hospital controls or residence for community controls
		15–17	1.0	Reference	
		18–20	0.6	0.2–1.7	
		> 20	0.5	0.2–1.4	
	Japan (hospital controls)	15–17	1.0	Reference	No controls and only 2 cases started before 15 years in Japan.
		18–20	0.2	0.1–0.6	
		> 20	0.2	0.1–0.8	
	Japan (community controls)	15–17	1.0	Reference	
		18–20	0.8	0.5–1.3	
		> 20	0.5	0.3–0.9	
Petrauskaite *et al*. (2002)	Men	< 20	22.5	7.8–63.9	Reference level not clear; adjusted for age and year of death
		20–24	13.6	4.6–40.0	
		≥ 25	8.6	2.6–28.5	
Rachtan (2002)	Women	≤ 18	13.6	7.6–24.1	Reference level, never-smoker; adjusted for age
		> 18	8.2	5.4–12.4	

CI, confidence interval; NCC, non-cancer controls; CC, cancer controls

Table 2.1.1.7. Case–control studies on tobacco smoking and lung cancer: duration of smoking

Reference	Subjects	Duration (years)	Odds ratio	95% CI	Comments
Pathak *et al.* (1986)	Men				Reference level, never-smoker; adjusted for sex and ethnicity
	< 65 years	1–29	12.9		$p < 0.001$ for linear trend
		30–39	37.3		
		40–49	57.3		
		50–59	91.4		
	≥ 65 years	1–29	22.9		$p < 0.001$ for linear trend
		30–39	6.6		
		40–49	11.7		
		50–59	16.1		
		≥ 60	11.9		
Benhamou *et al.* (1987)	Women	≤ 20	1.0		Matched analysis, adjusted for filter, inhalation, age at starting smoking and type of tobacco used
		21–40	2.1	0.5–9.0	
		> 40	3.3	0.4–24.1	
Benhamou *et al.* (1989)	Men	1–25	1.0		Adjusted for age and daily consumption of cigarettes
		26–35	1.6	1.2–2.3	
		≥ 36	2.1	1.5–2.9	
Katsouyanni *et al.* (1991)	Women	1–30	1.3	0.5–3.3	Reference level, nonsmoker; adjusted for age
		> 30	7.4	2.9–19.1	
Osann (1991)	Women	≤ 20	1.6	0.7–3.5	Reference level, never-smoker; adjusted for age
		> 20	11.6	5.8–23.3	
Liu (1992)	Men and women	< 30	1.0	0.8–1.3	Reference level, nonsmoker; combined analysis of 5 studies
		≥ 30	2.7	2.2–3.2	

Table 2.1.1.7 (contd)

Reference	Subjects	Duration (years)	Odds ratio		95% CI	Comments
Lubin *et al*. (1992)	Men	1–29	1.3			Reference level, nonsmoker; adjusted for age, source of subject, type of respondent and years of work underground
		30–39	2.3			
		40–49	4.4			
		≥ 50	9.6			
						p for trend < 0.01
Morabia & Wynder (1992)	Men and women		NCC	CC		Only bronchioloalveolar carcinoma
		1–19	1.2	1.4		Reference level, never-smoker; adjusted for age and sex
		20–29	2.2	2.5*		
		30–39	2.7*	3.9*		
		40–49	3.4*	5.6*		
		50–80	5.1*	9.1*		
Pezzotto *et al*. (1993)	Men	< 31	1.0			Adjusted for age, hospital and intensity of cigarette smoking
		31–40	3.6		$p < 0.0005$	
		> 40	6.0		$p < 0.005$	
Benhamou *et al.* (1994)	Men	1–25	1.0			Adjusted for age and smoking variables
		26–35	2.4		1.8–3.1	
		36–45	3.0		2.2–4.2	
		≥ 46	4.2		2.7–6.5	
De Stefani *et al*. (1994)	Men	*Manufactured*				Adjusted for age, residence, education and amount of smoking
		1–31	1.0			
		32–43	1.6		0.6–4.0	
		44–52	3.2		0.6–7.4	
		≥ 53	2.9		0.9–17.0	

Table 2.1.1.7 (contd)

Reference	Subjects	Duration (years)	Odds ratio	95% CI	Comments
		Hand-rolled			
		1–31	1.0		
		32–43	2.9	1.7–5.2	
		44–52	5.0	2.8–8.9	
		≥ 53	7.6	4.1–14.0	
Sobue *et al*. (1994)	Men	1–29	1.0		Adjusted for number of cigarettes/day, fraction smoked per cigarette, filter and inhalation
		30–39	1.5	1.0–2.2	
		40–49	2.8	2.0–4.1	
		≥ 50	4.1	2.7–6.2	
De Stefani *et al*. (1996a)	Men	1–29	3.4	1.7–6.8	Reference level, never-smoker; adjusted for age, residence, urban/rural status and education
		30–39	5.2	2.9–8.9	
		40–49	10.4	6.4–16.9	
		≥ 50	10.8	6.6–17.6	
Yu & Zhao (1996)	Men and women	0	1.0		Meta-analysis of 15 studies
		< 30	1.1	0.6–?[†]	[†]Illegible in original article
		≥ 30	2.5	1.7–3.6	
	Women	0	1.0		Meta-analysis of 12 studies
		< 30	1.4	0.5–3.9	
		≥ 30	3.8	1.7–8.5	
Barbone *et al*. (1997)	Men	1–29	3.2	1.8–5.7	Reference level, nonsmoker; adjusted for age
		30–39	7.9	4.7–13.5	
		40–49	11.4	7.0–18.8	
		≥ 50	14.5	9.0–23.3	
Dosemeci *et al*. (1997)	Men	1–10	1.0	0.6–1.7	Adjusted for age and alcohol use
		11–20	3.8	2.6–5.7	
		≥ 21	4.9	3.5–7.0	

Table 2.1.1.7 (contd)

Reference	Subjects	Duration (years)	Odds ratio	95% CI	Comments
Hu *et al*. (1997)	Men	1–19	2.0	0.1–3.9	Reference level, nonsmoker; [variables of adjustment not stated]
		20–29	2.1	1.2–3.7	
		≥ 30	2.2	0.9–5.3	
	Women	1–19	1.7	0.6–5.0	
		20–29	1.9	0.6–6.0	
		≥ 30	1.6	0.3–9.7	
Muscat *et al*. (1997)	Men	1–19	2.9*	1.2–7.3	Large-cell carcinoma only; adjusted for age and education All p for trends < 0.01
		20–39	10.6*	4.9–22.9	
		≥ 40	23.1*	10.4–50.8	
	Women	1–19	2.9*	1.2–6.9	
		20–39	11.5*	6.3–21.1	
		≥ 40	30.1*	15.8–57.4	
Rachtan & Sokolowski (1997)	Women	1–20	2.0	0.9–4.7	Reference level, never-smoker; adjusted for age
		21–40	7.5	3.9–14.6	
		> 40	58.7	7.6–455.6	
Khuder *et al*. (1998)	Men	1–29	3.5	1.8–7.1	Reference level, nonsmoker; unadjusted odds ratios
		30–49	7.5	4.8–11.9	
		≥ 50	9.0	5.7–14.1	
Kreuzer *et al*. (1998)	*≤ 45 years*				Reference level, never-smoker; adjusted for age, region and exposure to asbestos
	Men	≤ 19	4.0	1.6–10.2	
		20–39	26.3	10.3–66.8	
	Women	≤ 19	4.9	1.7–14.2	
		20–39	47.5	13.2–173	
	55–69 years				
	Men	≤ 19	4.9	3.1–7.9	
		20–39	20.9	13.5–32.2	
		≥ 40	54.5	34.9–85.2	

Table 2.1.1.7 (contd)

Reference	Subjects	Duration (years)	Odds ratio	95% CI	Comments
	Women	≤ 19	0.9	0.5–1.6	
		20–39	4.9	3.1–7.6	
		≥ 40	8.3	4.7–14.5	
Matos *et al*. (1998)	Men	*Current smoker*			Reference level, nonsmoker; adjusted for the design variables, age and hospital
		1–24	5.2	1.7–16.4	
		25–39	7.4	3.3–16.6	
		≥ 40	10.2	4.7–22.1	
		Former smoker			
		1–24	1.5	0.6–3.9	
		25–39	7.5	3.4–16.8	
		≥ 40	15.4	6.2–37.9	
Dikshit & Kanhere (2000)	Men	1–20	2.5	1.1–5.6	Reference level, nonsmoker; adjusted for age
		21–30	12.0	5.9–24.0	
		> 30	52.0	24.0–112.8	
Armadans-Gil *et al*. (1999)	Men	1–24	2.6	1.0–6.6	Reference level, nonsmoker; adjusted for age
		25–49	11.9	5.5–25.5	
		≥ 50	26.8	11.0–65.1	
Agudo *et al*. (2000)	Women	< 20	1.3	1.0–1.6	Reference level, never-smoker and smokers who had smoked less than 400 cigarettes in their lifetime; adjusted for age and centre
		20–29	4.5	3.5–5.7	
		30–39	7.6	6.1–9.5	
		≥ 40	12.8	10.1–16.2	
Kreuzer *et al*. (2000)	*All*†				Reference level, nonsmoker; adjusted for age and centre
	Men	< 20	2.4	1.8–3.3	†*p* for interaction gender/smoking < 0.0001
		20–39	16.4	12.9–20.9	
		≥ 40	39.1	30.4–50.3	

Table 2.1.1.7 (contd)

Reference	Subjects	Duration (years)	Odds ratio	95% CI	Comments
	Women	< 20	1.2	0.9–1.7	
		20–39	5.3	4.2–6.8	
		≥ 40	7.0	5.1–9.5	
	< 50 years[‡]				[‡]*p* for interaction gender/smoking = 1.0
	Men	< 20	2.1	1.2–3.8	
		20–39	16.4	9.9–27.2	
	Women	< 20	2.2	1.0–4.7	
		20–39	14.4	7.2–28.6	
	Ever-smoker				Also adjusted for average amount of smoking and time since cessation [There is probably an error in the original table; analysis by duration says adjusted for duration instead average amount of smoking.]
	Men	< 20	1.0		
		20–39	3.2	2.5–4.0	
		≥ 40	4.1	3.1–5.6	
	Women	< 20	1.0		
		20–39	2.7	1.7–4.1	
		≥ 40	3.3	1.9–5.8	
Simonato *et al.* (2000)	Men and women	*Venice*			Reference level, never-smoker and former smoker who quit more than 20 years ago; adjusted for age, sex, education, occupation and heating
		< 20	4.4	0.3–67.4	
		20–40	6.0	1.7–21.9	
		≥ 40	16.9	4.5–63.3	
		Mestre			
		< 20	0.6	0.1–6.0	
		20–40	7.6	3.5–16.4	
		≥ 40	9.3	4.4–19.7	

Table 2.1.1.7 (contd)

Reference	Subjects	Duration (years)	Odds ratio	95% CI	Comments
Boffetta *et al*. (2001)	Women				Reference level < 10 years of smoking; adjusted for centre, age, average number of cigarettes per day
	< 35 years	10–19	1.1	0.1–11	
		≥ 20	2.8	0.1–95	
	35–39 years	10–19	1.8	0.3–12	
		≥ 20	40.0	2.8–584	
	≥ 40 years	10–19	2.3	0.4–13	
		≥ 20	7.1	1.2–42	
Kubik *et al*. (2001)	Women	1–10	3.1	1.2–6.2	Reference level, never-smoker; adjusted for age, residence and education
		11–20	2.2	1.2–4.3	
		21–30	4.0	2.4–6.6	
		31–40	11.7	7.4–18.5	
		> 40	17.6	10.7–28.7	
Simonato *et al*. (2001)	Men	0–19	1.0	–	Adjusted for age, education, average number of cigarettes/day and centre
		20–29	5.0	4.3–5.8	
		30–39	11.0	9.6–12.7	
		≥ 40	21.6	18.6–24.9	
	Women	0–19	1.0	–	
		20–29	4.3	1.3–5.5	
		30–39	7.2	5.6–9.1	
		≥ 40	8.6	6.6–11.3	
Stellman *et al*. (2001)	Men				Reference level, nonsmoker; adjusted for age, education and hospital or residence for community controls
	USA (HC)	≤ 40	25.2	11.9–61.0	
		> 40	57.8	27.4–131.9	
	Japan (HC)	≤ 40	2.2	1.1–5.2	
		> 40	7.4	2.9–19.4	
	Japan (PC)	≤ 40	4.8	2.6–8.9	
		> 40	8.3	4.5–15.4	

Table 2.1.1.7 (contd)

Reference	Subjects	Duration (years)	Odds ratio		95% CI	Comments
Bhurgri *et al*. (2002)	Men and women	1–19	8.4 (3.8–18.5)	1.0†	Reference	Adjusted for age, sex and hospital
		20–29	10.1 (5.0–20.1)	1.3	0.5–3.4	†Also adjusted for average daily amount of smoking; study included all types of smoking.
		30–39	20.7 (11.5–37.2)	2.4	0.9–5.9	
		≥ 40	53.2 (29.4–96.2)	6.0	2.4–14.8	
Petrauskaite *et al*. (2002)	Men	< 41	13.0		4.5–37.7	Reference level not clear; adjusted for age and year of death
		≥ 41	22.2		7.7–63.6	
Rachtan (2002)	Women	< 26	3.0		1.8–5.0	Reference level, never- smoker; adjusted for age
		26–39	15.6		9.1–26.8	
		≥ 40	30.0		14.2–63.4	
Stellman *et al*. (2002)	Men					Reference level, nonsmoker
	White	< 40	15.8		11.5–21.8	
		≥ 40	25.1		18.6–33.8	
	Black	< 40	16.1		6.7–45.7	
		≥40	20.1		8.7–54.7	
	Women					
	White	< 40	13.4		10.2–17.6	
		≥ 40	24.7		19.1–32.0	
	Black	< 40	14.6		6.9–30.9	
		≥ 40	20.7		9.6–44.7	

CI, confidence interval; NCC, non-cancer control; CC, cancer control; HC, hospital control; PC, population control
*$p < 0.05$

Table 2.1.1.8. Case–control studies on tobacco smoking and lung cancer: smoking cessation

Reference	Subjects	Years since quitting	Odds ratio				95% CI	Comments
Gao *et al*. (1988)	Men	Current smoker	3.9				2.9–5.4	Reference level, lifelong nonsmoker; adjusted for age and education
		1–4	6.9				4.4–10.8	
		5–9	3.1				1.7–5.9	
		≥ 10	1.1				0.5–2.2	
	Women	Current smoker	2.9				2.2–3.8	
		1–4	7.2				3.4–15.1	
		5–9	3.9				1.5–9.9	
		≥ 10	2.2				1.0–4.6	
Higgins & Wynder (1988)	Men	1–4	17.4				12.5–24.1	Reference level, nonsmoker; odds ratios not adjusted
		5–9	7.2				5.1–10.3	
		10–19	6.1				4.5–8.4	
		20–29	3.7				2.5–5.5	
		≥ 30	1.9				1.1–3.1	
	Women	1–4	9.3				6.4–13.4	
		5–9	4.8				3.2–7.1	
		10–19	2.2				1.4–3.3	
		20–29	1.6				0.9–2.9	
		≥ 30	2.6				1.2–5.3	
Benhamou *et al*. (1989)	Men		Cigarettes/day					†Adjusted for age and duration
			1–9†	10–19†	≥ 20†	any‡		‡Adjusted for duration and daily consumption of cigarettes
		Current smoker	1.0	2.4*	5.2*	1.0		
		1–4	3.3*	3.8*	5.8*	1.5	1.1–1.9§	§95% CI for any number of cigarettes/day
		5–9	0.5	1.5	3.4*	0.7	0.5–1.0§	
		10–19	0.9	1.0	1.9*	0.5	0.3–0.8§	
		≥ 20	0.5	2.0	1.3	0.4	0.2–0.8§	

Table 2.1.1.8 (contd)

Reference	Subjects	Years since quitting	Odds ratio		95% CI	Comments
Jedrychowski *et al*. (1990)	Men	> 5–10	0.7		0.4–1.0	Reference level, never-smoker; adjusted for age
		> 10	0.4		0.3–0.6	
	Women	> 5	0.5		0.2–1.5	
Becher *et al*. (1991)	Men and women	0–1	1.0			Risks for both sexes and both groups of controls combined; adjusted for lifetime-cumulative cigarette consumption
		2–4	0.9		0.4–2.2	
		5–9	0.7		0.3–1.3	
		≥ 10	0.2		0.1–0.5	
		Nonsmoking interval (years)				[†]Results based on 6 cases and 39 controls
		0–< 1	1.0			
		1–< 3	0.8		0.4–1.9	
		≥ 3	0.2[†]		0.1–0.5	
Jöckel *et al*. (1992)	Men	0–5	1.0			Hospital controls and population controls combined
		> 5–10	0.9		0.4–1.8	
		> 10	0.4		0.2–0.7	
	Women	0–5	1.0			
		> 5	0.2		0.03–1.1	
Morabia & Wynder (1992)	Men and women		CC	NCC		Only bronchioloalveolar carcinoma
		Current smoker	3.7*	2.3		Reference level, never-smoker; adjusted for age and sex
		1–9	2.9*	3.8*		
		10–19	2.6*	2.1		
		20–52	1.5	1.5		
Gao *et al*. (1993)	Men	1–4	5.1		2.3–11.4	Reference level, nonsmoker; adjusted for age
		5–9	3.5		1.1–8.0	
		10–14	3.8		1.5–9.5	

Table 2.1.1.8 (contd)

Reference	Subjects	Years since quitting	Odds ratio	95% CI	Comments
De Stefani *et al*. (1994)	Men	*Manufactured*			Adjusted for age, residence, education and amount of smoking
		Current smoker	1.0		
		1–4	0.5	0.2–1.4	
		5–9	0.7	0.2–1.9	
		≥ 10	0.5	0.2–1.5	
		Hand-rolled			
		Current smoker	1.0		
		1–4	0.9	0.5–1.4	
		5–9	0.5	0.3–1.0	
		≥ 10	0.2	0.1–0.3	
Suzuki *et al*. (1994)	Men and women	Current smoker	1.0		Adjusted for age, sex, race and pack–years; excluding nonsmokers
		1–5	0.5	0.2–1.4	
		5–10	0.5	0.2–1.5	
		> 10	0.2	0.1–0.6	
De Stefani *et al*. (1996a)	Men	Current smoker	10.9	6.9–17.1	Reference level, never-smoker; adjusted for age, residence, urban/rural status and education
		1–4	9.0	5.2–15.9	
		5–9	6.2	3.2–12.2	
		≥ 10	2.8	1.4–5.7	
Barbone *et al*. (1997)	Men	Current smoker	13.8	8.7–21.9	Reference level, nonsmoker; adjusted for age
		1–4	13.9	6.8–28.5	
		5–14	9.1	5.3–15.5	
		15–24	6.8	3.6–12.8	
		> 25	2.1	1.0–4.3	
Muscat *et al*. (1997)	Men	1–5	12.4	5.2–29.6	Only large-cell carcinoma
		6–10	12.9	5.3–31.1	Adjusted for age and education
		> 10	6.1	2.8–13.6	p for trend < 0.01
		Never-smoker	1.0		

Table 2.1.1.8 (contd)

Reference	Subjects	Years since quitting	Odds ratio	95% CI	Comments
	Women	1–5	15.9	7.1–35.4	
		6–10	11.5	5.0–26.7	
		> 10	4.2	3.0–9.0	
		Never-smoker	1.0		
Pohlabeln *et al*. (1997)	Men	Current smoker	1.0		Adjusted for age, region of residence and pack–years
		< 1	20.3	9.8–42.3	
		1	6.9	3.3–14.2	
		2–5	1.6	1.0–2.3	
		6–10	1.0	0.6–1.4	
		11–20	0.5	0.4–0.8	
		> 20	0.2	0.2–0.4	
		Never/occasional smoker	0.2	0.1–0.4	
Khuder *et al*. (1998)	Men	Current smoker	10.4	6.6–16.4	Reference level, nonsmoker; unadjusted odds ratios
		1–4	9.6	5.8–15.9	
		5–14	6.4	3.8–10.7	
		≥ 15	4.0	2.4–6.6	
Matos *et al*. (1998)	Men	1–5	1.4	0.8–2.6	Reference level, current smoker; adjusted for the design variables, age and hospital
		6–10	0.9	0.4–1.6	
		≥ 11	0.3	0.2–0.6	
		Nonsmoker	0.1	0.1–0.2	
Agudo *et al.* (2000)	Women	Current smoker	8.9	7.5–10.6	Adjusted for age and centre; never-smoker includes smokers who had smoked less than 400 cigarettes in their lifetime.
		< 15	3.8	2.9–5.0	
		15–19	1.7	1.2–2.4	
		20–29	0.6	0.4–1.2	
		≥ 30	1.1	0.7–1.8	
		Never-smoker	1.0		

Table 2.1.1.8 (contd)

Reference	Subjects	Years since quitting	Odds ratio	95% CI	Comments
Kreuzer *et al.* (2000)	Men	Current smoker	1.0		Adjusted for age, centre and average amount of smoking
		2–9	0.7	0.6–0.8	
		10–19	0.2	0.2–0.3	
		≥ 20	0.1	0.1–0.1	
	Women	Current smoker	1.0		
		2–9	0.5	0.3–0.7	
		10–19	0.2	0.1–0.3	
		≥ 20	0.2	0.1–0.3	
Osann *et al.* (2000)	Women	Current smoker	14.8	4.3–51.4	Small-cell carcinoma only
		< 12	8.6	2.1–34.9	Adjusted for age, education and pack–years
		> 12	1.0		
Mao *et al.* (2001)	Men	≤ 10	14.5	10.2–20.6	Reference level, never-smoker; adjusted for age group, province, years of exposure to passive smoking, total consumption of vegetables, vegetable juices and meat
		11–19	7.3	5.0–10.5	
		20–28	3.5	2.4–5.2	
		≥ 29	1.5	1.0–2.4	
	Women	≤ 10	11.8	9.0–15.4	
		11–19	3.3	2.4–4.6	
		20–28	1.6	1.0–2.3	
		≥ 29	1.5	1.0–2.3	
Simonato *et al.* (2001)	Men	Current smoker	1.0		Adjusted for age, education and centre
		2–9	0.66	0.59–0.73	
		10–19	0.27	0.24–0.31	
		20–29	0.17	0.14–0.20	
		≥ 30	0.08	0.06–0.10	
		Nonsmoker	0.04	0.03–0.05	

Table 2.1.1.8 (contd)

Reference	Subjects	Years since quitting	Odds ratio	95% CI	Comments
	Women	Current smoker	1.00		
		2–9	0.41	0.31–0.55	
		10–19	0.19	0.14–0.27	
		20–29	0.08	0.05–0.14	
		≥ 30	0.13	0.08–0.21	
		Nonsmoker	0.11	0.10–0.14	
Stellman *et al.* (2001)	Men				Adjusted for age, education and hospital or residence for community controls
	USA (HC)	Current smoker	1.0		
		1–4	0.5	0.3–1.0	
		5–9	0.5	0.2–0.9	
		10–15	0.4	0.2–0.8	
		≥ 16	0.1	0.1–0.2	*p* for trend < 0.001
	Japan (HC)	Current smoker	1.0		
		1–4	0.9	0.3–2.9	
		5–9	0.8	0.3–1.8	
		10–15	0.2	0.1–0.5	
		≥ 16	0.2	0.1–0.4	
	Japan (PC)	Current smoker	1.0		
		1–4	0.9	0.5–1.7	
		5–9	0.8	0.5–1.4	
		10–15	0.2	0.1–0.4	
		≥ 16	0.2	0.1–0.3	

Table 2.1.1.8 (contd)

Reference	Subjects	Years since quitting	Odds ratio	95% CI	Comments
Bhurgri *et al.* (2002)	Men and women	Current smoker	1.0		Adjusted for age, sex and hospital
		2–4	1.7	0.9–3.4	
		5–9	0.9	0.4–1.8	
		10–14	0.3	0.1–0.7	
		15–19	0.2	0.1–0.5	
		≥ 20	0.2	0.1–0.3	
		Never-smoker	0.03	0.02–0.05	
Petrauskaite *et al.* (2002)	Men	Current smoker or < 2 years	1.0		Adjusted for age and year of death
		2–4	1.2	0.6–2.0	
		5–9	0.6	0.3–1.3	
		10–19	0.4	0.2–0.9	
		≥ 20	0.4	0.2–0.9	
Stellman *et al.* (2002)	Men				Reference level, nonsmoker
	White	1–10	14.5	10.9–19.5	
		11–20	7.8	5.8–10.6	
		≥ 21	3.7	2.8–5.1	
	Black	1–10	13.7	5.9–37.5	
		11–20	4.2	1.6–12.7	
		≥ 21	3.9	1.4–12.3	
	Women				
	White	1–5	10.1	7.9–13.0	
		6–15	6.7	4.8–9.4	
		≥ 16	3.4	2.6–4.4	
	Black	1–5	11.0	5.0–24.2	
		6–15	6.5	2.0–20.7	
		≥ 16	7.2	2.9–17.5	

CI, confidence interval; HC, hospital controls; PC, population controls; CC, cancer controls; NCC, non-cancer controls
*$p < 0.05$

Table 2.1.1.9. Case–control studies on tobacco smoking and lung cancer: type of cigarettes

Reference	Subjects	Use of filter-tip	OR	95% CI	Comments
Pathak *et al.* (1986)	Men				Adjusted for age, sex and ethnic variables, ethnicity, amount and duration of smoking and age–duration interaction
	Non-Hispanic whites	Filter-tip only	0.8		
		67–99% filter-tip	0.7		
		34–66% filter-tip	0.6		
		1–33% filter-tip	0.8		
		Untipped only	1.0		
	Hispanic	Filter-tip only	0.04*		
		67–99% filter-tip	0.3*		
		34–66% filter-tip	0.4		
		1–33% filter-tip	0.6		
		Untipped only	1.0		
Benhamou *et al.* (1987)	Women	≤ 50% untipped[†]	1		[†]Includes nonsmokers; adjusted for cigarettes/day, duration of smoking and inhalation
		> 50% untipped	1.3	0.3–6.0	
		100% untipped	3.6	0.7–19.2	
Benhamou *et al.* (1989)	Men	Filter-tipped	1.0		Only current smokers; adjustment not stated
		Mixed	1.8	1.3–2.5	
		Untipped	1.9	1.4–2.5	
Jöckel *et al.* (1992)	Men	Filter-tipped	1		Hospital and population controls combined
		Untipped (last 20 years)	2.4	1.2–4.8	
Pezzotto *et al.* (1993)	Men	Ever filter-tipped	1.0		Adjusted for age, hospital and years of cigarette smoking
		Untipped or both	3.5	$p < 0.0001$	
Sobue *et al.* (1994)	Men, current smokers	All histological types	1.5	0.9–2.6	Untipped versus filter-tipped cigarettes for each type; adjusted for duration, fraction smoked per cigarette, cigarettes/day, cigarette type, inhalation
		SCC	2.2	1.2–4.0	
		AC	1.2	0.6–2.5	
		Small-cell carcinoma	0.6	0.2–2.0	
		Large-cell carcinoma	1.3	0.4–4.5	
De Stefani *et al.* (1996a)	Men	Never-smoker	1.0		Adjusted for age, residence, urban/rural status and education
		Filter-tipped	7.3	4.6–11.8	
		Plain	10.1	6.4–15.6	
De Stefani *et al.* (1996b)	Men and women	Nonsmoker	1.0		Adjusted for age, sex, residence (urban/rural), education, family history of cancer and BMI
		Filter-tipped	7.4	4.2–13.2	
		Plain	10.1	5.7–17.8	

Table 2.1.1.9 (contd)

Reference	Subjects	Use of filter-tip	OR	95% CI	Comments
Kabat (1996)	Men[†]	**Kreyberg I**			[†]Current smokers; reference category untipped only; adjusted for cigarettes/day, age, inhalation and years of education [‡]Reference category; untipped and switchers 1–9 years
		Switchers (1–9 years)	0.8	0.6–1.2	
		Switchers (≥ 10 years)	0.7	0.5–0.9	
		Filter-tip only	0.7	0.4–1.3	
		Kreyberg II			
		Switchers (1–9 years)	1.0	0.6–1.5	
		Switchers (≥ 10 years)	0.8	0.5–1.2	
		Filter-tip only	0.9	0.4–1.5	
	Women[†]	**Kreyberg I**			
		Switchers (1–9 years)	1.0	0.5–2.0	
		Switchers (≥ 10 years)	0.7	0.4–1.4	
		Filter-tip only	0.6	0.3–1.4	
		Kreyberg II			
		Switchers (≥ 10 years)[‡]	1.0	0.8–1.3	
		Filter-tip only	1.0	0.6–1.5	
Stellman *et al*. (1997a,b)	Men[†]	**SCC**			[†]Current smokers Reference level, lifetime smoker of untipped cigarettes; adjusted for age, education and number of cigarettes/day
		Switched	0.9	0.7–1.0	
		Lifetime filter-tip	0.8	0.5–1.2	
		AC			
		Switched	1.0	0.8–1.3	
		Lifetime filter-tip	1.0	0.7–1.5	
	Women[†]	**SCC**			
		Switched	0.6	0.3–0.99	
		Lifetime filter-tip	0.4	0.2–0.8	
		AC			
		Switched	1.2	0.7–2.0	
		Lifetime filter-tip	0.9	0.5–1.7	
Wakai *et al*. (1997)	Men[†]	With filter-tip	1.0		[†]Current smokers; adjusted for age, age at start, cigarettes/day, fraction smoked/cigarette, cigarette type and smoke inhalation
		Without filter-tip	1.0	0.3–3.2	
Khuder *et al*. (1998)	Men	Filter-tip yes	5.3	3.3–8.4	Reference level, nonsmoker
		Filter-tip no	11.4	7.3–18.0	
Armadans-Gil *et al*. (1999)	Men	Lifetime filter-tip			Adjusted for age and cumulative cigarette consumption
		Never	1.0		
		Mixed	1.0	0.6–1.6	
		Always	0.7	0.4–1.2	
Agudo *et al*. (2000)	Women	Never-smoker	1.0		Adjusted for age and centre; never-smoker included smokers who had smoked < 400 cigarettes in their lifetime.
		Only filter-tip	3.4	2.9–4.1	
		Untipped + mixed	7.5	6.0–9.3	

Table 2.1.1.9 (contd)

Reference	Subjects	Use of filter-tip	OR	95% CI	Comments
Simonato *et al*. (2001)	Men	Only filter-tip	1.0		Adjusted for age, education and centre
		Mixed	1.7	1.5–2.0	
		Only untipped	1.1	0.9–1.3	
	Women	Only filter-tip	1.0		
		Mixed	2.4	1.8–3.1	
		Only untipped	2.0	1.3–3.1	
Rachtan (2002)	Women	Nonsmoker	1.0		Adjusted for age
		Filter-tip	9.3	6.2–14.0	
		Untipped	9.8	4.7–20.5	

OR, odds ratio; H, hospital; P, population; SCC, squamous-cell carcinoma; AC, adenocarcinoma; BMI, body mass index; Kreyberg I, squamous-cell carcinoma, large-cell, oat-cell and small-cell carcinoma; Kreyberg II, adenocarcinoma, bronchiolar and alveolar-cell carcinoma
*$p < 0.05$

Table 2.1.1.10. Case–control studies on tobacco smoking and lung cancer: tar levels in cigarettes

Reference	Subjects	Histology/definition of smokers	Odds ratio					Comments
Wilcox *et al.* (1988)	Men	All histologies	Av. mg tar/cigarette (1973–80)					Adjusted for intensity and duration of smoking
			≤ 14	14.1–17.5	17.6–21.0	21.1–28.0		
			0.61	1.04	1.21	1.0		
Kaufman *et al.* (1989)	Men and women	All histologies	Av. mg tar/cigarette		< 22	22–28	≥ 29	Adjusted for age, sex, ethnicity, religion, education and interview
			All cigarettes		1	1.9	3.1*	
			Cigarettes smoked at least 10 years before admission		1	3.0*	4.0*	
Zang & Wynder (1992)	Men	*Kreyberg I*	Kg tar	1–2	3–5	6–8	≥ 9	Kg tar: cumulative measure for lifetime exposure Reference level, never-smoker; adjusted for age; no CI provided
		Current smoker		17.3	29.7	38.7	60.2	
		Former smoker		7.3	19.9	20.0	38.3	
		Kreyberg II						
		Current smoker		6.5	6.5	10.1	12.8	
		Former smoker		2.6	4.4	6.2	7.3	
	Women	*Kreyberg I*						
		Current smoker		23.1	47.6	58.9	102.9	
		Former smoker		7.9	15.3	33.2	22.9	
		Kreyberg II						
		Current smoker		8.3	15.1	11.6	16.3	
		Former smoker		3.2	4.8	8.5	6.8	

Table 2.1.1.10 (contd)

Reference	Subjects	Histology/definition of smokers	Odds ratio					Comments
Harris *et al.* (1993)	Men	*Kreyberg I*	Kg tar	0	1–4	5–8	≥ 9	All linear trends statistically significant at $p < 0.01$; adjustment not clear
		White						
		Current smoker		1.0	11.7*	24.5*	54.3*	
		Ever-smoker		1.0	6.8*	20.2*	42.6*	
		Black						
		Current smoker		1.0	12.8*	25.1*	55.4*	
		Ever-smoker		1.0	10.0*	23.6*	47.0*	
		Kreyberg II						
		White						
		Current smoker		1.0	5.7*	8.3*	13.1*	
		Ever-smoker		1.0	3.1*	6.5*	10.1*	
		Black						
		Current smoker		1.0	10.5*	18.6*	24.9*	
		Ever-smoker		1.0	8.3*	15.2*	24.0*	
	Women	*Kreyberg I*						
		White						
		Current smoker		1.0	13.8*	41.0*	108.7*	
		Ever-smoker		1.0	8.7*	34.9*	75.8*	
		Black						
		Current smoker		1.0	12.4*	72.3*	120.0*	
		Ever-smoker		1.0	11.2*	83.8*	146.7*	
		Kreyberg II						
		White						
		Current smoker		1.0	5.6*	11.4*	24.5*	
		Ever-smoker		1.0	3.9*	9.8*	17.9*	
		Black						
		Current smoker		1.0	3.0*	18.7*	29.1*	
		Ever-smoker		1.0	3.4*	20.8*	29.1*	

Table 2.1.1.10 (contd)

Reference	Subjects	Histology/definition of smokers	Odds ratio				Comments
Benhamou *et al*. (1994)	Men		% years smoking cig. > 30 mg tar	< 51%	51–75%	> 75%	Reference level, lifelong smokers of light, imported cigarettes with unknown tar levels; adjusted for age, daily consumption and duration of smoking
		Use of high-tar cigarettes (≥ 30 mg)		2.4*	3.0*	3.0*	
Kabat (1996)			Quartile tar intake (95% CI)				Reference level, never smoker and first quartile; adjusted for age, education, time period, hospital and smoking status
				2	3	4	
	Men	White		1.9 (1.6–2.2)	2.9 (2.5–3.5)	4.3 (3.6–5.2)	
		Black		2.3 (1.4–3.7)	5.0 (2.9–8.5)	5.7 (3.0–10.9)	
	Women	White		2.3 (1.8–2.9)	4.5 (3.5–5.8)	5.3 (4.1–6.8)	
		Black		2.1 (1.0–4.2)	5.1 (2.4–11.5)	12.8 (4.3–38.7)	
Zang & Wynder (1996)			Kg tar	1–2	3–5	6–8	≥ 9	Current smokers only; reference level, nonsmoker. All dose–response trends statistically significant. Dose–response for women was statistically significantly higher than for men.
	Men	SCC		33.1*	36.8*	54.3*	81.5*	
		AC		7.1*	6.8*	12.4*	14.7*	
	Women	SCC		24.5*	38.5*	56.2*	129.3*	
		AC		11.6*	13.9*	25.4*	33.3*	

CI, confidence interval; Kreyberg I, squamous-cell carcinoma, large-cell, oat-cell and small-cell carcinoma; Kreyberg II, adenocarcinoma and alveolar-cell carcinoma; SCC, squamous-cell carcinoma; AC, adenocarcinoma
*$p < 0.05$

Table 2.1.1.11. Case–control studies on tobacco smoking and lung cancer: type of tobacco

Reference	Subjects	Type	Odds ratio	95% CI	Comments
Benhamou *et al.* (1989)	Men	Light	1.0		Adjusted for age and duration of smoking
		Mixed	2.0	0.9–4.2	
		Dark	2.5	1.3–5.1	
		Manufactured	1.0		[Adjustment variables not stated]
		Mixed	1.2	0.9–1.6	
		Hand-rolled	1.2	0.8–1.7	
De Stefani *et al.* (1994)	Men	*Manufactured cigarettes*			Adjusted for age, residence, education, pack–years and cessation
		Blond	1.0		
		Black	2.1	1.1–3.9	
		Hand-rolled cigarettes			
		Blond	1.0		
		Black	1.2	0.9–1.7	
Suzuki *et al.* (1994)	Men and women	Cigarettes only	1.0		Adjusted for age, sex, race and pack–years, excluding nonsmokers; black tobacco smoked in the form of hand-rolled cigarettes
		Black tobacco and cigarettes	2.8	1.0–7.7	
De Stefani *et al.* (1996a)	Men	Blond	6.1	3.8–9.8	Reference level, never-smoker; adjusted for age, residence, urban/rural status and education
		Mixed	13.6	7.7–23.9	
		Black	10.9	6.8–17.4	
De Stefani *et al.* (1996b)	Men and women	Blond	4.7	2.6–8.6	Reference level, nonsmoker; adjusted for age, sex, residence, urban/rural, education, family history of cancer and body mass index
		Black	11.2	6.4–19.3	
Matos *et al.* (1998)	Men	*Only blond*			Reference level, nonsmoker; adjusted for the design variables, age and hospital
		1–14 cig/day	0.6	0.2–2.2	
		15–24 cig/day	8.4	3.7–18.9	
		≥ 25 cig/day	7.7	3.5–16.7	

Table 2.1.1.11 (contd)

Reference	Subjects	Type	Odds ratio	95% CI	Comments
		Duration			
		1–24 years	1.9	0.7–5.0	
		25–39 years	5.7	2.6–12.5	
		≥ 40 years	10.1	4.3–23.8	
		Only black			
		1–14 cig/day	2.7	0.6–11.5	
		15–24 cig/day	6.8	3.9–32.7	
		≥ 25 cig/day	12.9	5.2–45.0	
		Duration			
		1–24 years	1.2	0.2–6.3	
		25–39 years	11.3	3.9–32.7	
		≥ 40 years	15.5	5.2–45.0	
Armadans-Gil *et al*. (1999)	Men	Blond	1.0		Adjusted for age and cumulative cigarette consumption
		Both	4.9	1.7–13.7	
		Black	5.3	2.1–13.6	
Agudo *et al*. (2000)	Women	Only blond	3.1	2.5–3.7	Reference level, never-smoker and smokers who had smoked less than 400 cigarettes in their lifetime; adjusted for age and centre
		Dark + mixed	10.4	7.9–13.6	
Simonato *et al*. (2001)	Men	Only blond	1.0		Adjusted for age, education and centre
		Mixed	2.2	1.7–2.9	
		Only black	1.6	1.1–2.3	
	Women	Only blond	1.0		
		Mixed	3.9	2.6–5.8	
		Only black	4.8	3.1–7.4	

CI, confidence interval

Table 2.1.1.12. Case–control studies on tobacco smoking and lung cancer: degree of inhalation

Reference	Subjects	Inhalation	Odds ratio	95% CI	Comments
Osann (1991)	Women	No	1.0		Adjusted for age
		Yes	9.6	5.0–18.5	
Pezzotto *et al*. (1993)	Men	Slight or moderate	1.0		Adjusted for age, hospital, duration and intensity of cigarette smoking
		Deep	0.9		
Benhamou *et al*. (1994)	Men	No	1.0		Adjusted for age and smoking variables
		Moderate	1.2	0.9–1.6	
		Deep	1.5	1.2–1.8	
Sobue *et al*. (1994)	Men	All histological types	1.2	0.9–1.6	Reference level, no inhalation; adjusted for number of cigarettes/day, duration, fraction smoked per cigarette, filter
		SCC	1.0	0.7–1.6	
		AC	1.4	0.9–2.0	
		SCLC	1.4	0.8–2.6	
		Large-cell carcinoma	1.8	0.7–4.4	
Suzuki *et al*. (1994)	Men and women	No or slight	1.0		Adjusted for age, sex, race and pack–years, excluding nonsmokers
		Deep	2.6	1.3–5.4	
Rachtan & Sokolowski (1997)	Women	No	4.5	2.2–9.5	Reference level, never-smoker; adjusted for age
		Yes	8.7	4.5–16.7	
Wakai *et al*. (1997)	Men	*All histological types*			Reference level, no inhalation; adjusted for age, age at starting smoking, number of cigarettes per day, fraction of a cigarette smoked and cigarette type
		Moderate	1.1	0.6–2.0	
		Deep	2.1	1.1–3.8	
		SCC			
		Moderate	1.2	0.6–2.4	
		Deep	1.9	0.9–4.3	
		AC			
		Moderate	1.3	0.6–2.8	
		Deep	3.0	1.3–7.0	

Table 2.1.1.12 (contd)

Reference	Subjects	Inhalation	Odds ratio	95% CI	Comments
Khuder *et al*. (1998)	Men	No Yes	1.4 15.4	0.8–2.4 9.8–24.0	Reference level, nonsmoker; unadjusted odds ratios
Agudo *et al*. (2000)	Women	Never inhaled Ever inhaled	2.5 6.9	2.0–3.1 5.9–8.2	Reference level, never-smoker and smokers who had smoked less than 400 cigarettes during their lifetime; adjusted for age and center
Rachtan (2002)	Women	No Yes	5.8 12.4	3.5–9.6 7.9–19.2	Reference level, nonsmoker; adjusted for age

CI, confidence interval; SCC, squamous-cell carcinoma; AC, adenocarcinoma; SCLC, small-cell carcinoma

Table 2.1.1.13. Case–control studies on tobacco smoking and lung cancer: histology

Reference	Subjects	Histology	Odds ratio (95% CI)					Comments
Damber & Larsson (1986)	Men		*Duration (years)*	*< 30*	*31–40*	*41–50*	*≥ 51*	Smoking includes any tobacco. Adjustment variables not stated.
		SCC		4.4*	8.4*	13.8*	16.7*	
		SCLC		3.6	10.5*	19.6*	25.1*	
		AC, alveolar-cell carcinoma, bronchiolar carcinoma		1.8	1.2	3.4*	2.5	
Gao *et al*. (1988)	Men	**SCC**	*Duration (years)*	*1–29*	*30–39*	*≥ 40*		Reference level, lifelong nonsmoker; adjusted for age and education. Confidence interval or statistical significance not provided
		1–19 cig/day		1.1	5.2	7.0		
		20–29 cig/day		4.0	12.6	13.6		
		≥ 30 cig/day		6.1	22.1	25.0		
		AC						
		1–19 cig/day		0.8	1.6	1.9		
		20–29 cig/day		0.9	2.4	2.4		
		≥ 30 cig/day		0.7	4.2	5.5		
	Women	**SCC**	*Duration (years)*	*1–29*	*≥ 30*			
		1–19 cig/day		1.9	2.7			
		20–29 cig/day		4.7	7.0			
		≥ 30 cig/day		16.2	42.4			
		AC						
		1–19 cig/day		0.7	1.2			
		20–29 cig/day		1.3	1.4			
		≥ 30 cig/day		7.0	3.5			
Schoenberg *et al*. (1989)	Women		Cigarettes/day	< 20	≥ 20	< 20	≥ 20	All odds ratios statistically significant at 5% level. Adjusted for age, race and type of respondent
			Duration (years)	*< 35*	*< 35*	*≥ 35*	*≥ 35*	
		SCC		2.7	7.7	12.0	21.4	
		SCLC		19.0	40.6	62.5	140.0	
		AC		2.0	3.4	3.9	6.8	
Svensson *et al*. (1989)	Women		*Cigarettes/day*	*1–10*	*11–20*	*≥ 21*		Reference level, never-smoker; adjusted for age
		SCC		9.7*	36.2*	59.0*		
		SCLC		33.7*	72.1*	215.8*		
		AC		2.2	5.4*	19.7*		

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)				Comments
Xu *et al*. (1989)	Men	**SCC/SCLC**	*Duration (years)*	*1–29*	*30–39*	*≥ 40*	Reference level, nonsmoker; adjusted for age and education
		1–19 cig/day		2.3*	2.9*	5.0*	
		20–29 cig/day		2.6*	3.9*	10.4*	
		≥ 30 cig/day		7.7*	8.3*	31.2*	
		AC					
		1–19 cig/day		1.4	2.2*	2.6*	
		20–29 cig/day		0.7	1.5	3.6*	
		≥ 30 cig/day		5.4*	3.2*	11.8*	
	Women	**SCC/SCLC**					
		1–19 cig/day		1.8*	4.2*	5.3*	
		≥ 20 cig/day		2.5	2.4	19.9*	
		AC					
		1–19 cig/day		0.9	2.2*	1.9*	
		≥ 20 cig/day		–	3.7*	6.8*	
Wu-Williams *et al*. (1990)	Women	**SCC/SCLC**	*Duration (years)*	*1–29*	*30–39*	*≥ 40*	Reference not stated [probably nonsmokers] †Only 9% of the cases and 4% of the controls smoked more than 20 cigarettes per day.
		1–19 cig/day		2.0*	3.9*	4.7*	
		≥ 20 cig/day†		2.0	3.8*	12.0*	
		AC					
		1–19 cig/day		0.8	1.7*	2.0*	
		≥ 20 cig/day†		0.8	3.8*	2.8*	
Morabia & Wynder (1991)	Men†		*Cigarettes/day*	*1–19*	*20–29*	*≥ 30*	Adjusted for age, race and state †Current smokers
		SCC		1.0	1.6	2.3*	
		SCLC		1.0	6.0*	5.5*	
		Large-cell		1.0	1.1	1.0	
		AC		1.0	1.7	1.9*	
	Women†	SCC		1.0	1.5	2.7*	
		SCLC		1.0	1.8	3.2*	
		Large-cell		1.0	1.9	1.4	
		AC		1.0	1.3	1.5	

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)					Comments
Osann (1991)	Women		*Pack/day*	*< 1*		*≥ 1*		Reference level, never-smoker (7 cases and 58 controls for Kreyberg I); adjusted for age
		Kreyberg I		12.1 (1.5–96.3)		71.2 (8.3–609)		
		Kreyberg II		0.9 (0.3–2.7)		3.8 (1.6–8.8)		
			Duration (years)	*≤ 20*		*> 20*		
		Kreyberg I		4.9 (0.5–44.6)		101.1 (8.3–1230)		
		Kreyberg II		0.7 (0.2–1.9)		4.1 (1.8–9.4)		
			Inhalation	*No*		*Yes*		
		Kreyberg I		13.3 (1.7–106)		52.0 (6.6–408)		
		Kreyberg II		0.6 (0.2–1.9)		3.5 (1.5–8.0)		
Jedrychowski *et al.* (1992)	Men		*Cigarettes/day*	*1–19*	*20–29*	*≥ 30*		Adjusted for age, education and occupation
		SCC		7.5*	13.5*	21.4*		
		SCLC		7.8*	11.6*	16.8*		
		AC		2.2	4.4*	5.1*		
			Duration (years)	*1–19*	*20–39*	*≥ 40*		
		SCC		5.8*	12.4*	13.0*		
		SCLC		5.5*	11.4*	11.8*		[Adjustments not clear]
		AC		1.1	3.5*	4.4*		
Zang & Wynder (1992)	Men	**Kreyberg I**	*Cigarettes/day*	*1–10*	*11–20*	*21–40*	*≥ 41*	
		Current smoker		14.4	22.3	41.4	74.0	Odds ratios adjusted for age; no CI provided
		Former smoker		4.1	9.0	16.6	23.5	
		Kreyberg II						
		Current smoker		3.9	6.0	10.3	15.8	
		Former smoker		1.0	3.5	5.6	4.6	
	Women	**Kreyberg I**						
		Current smoker		7.5	33.6	76.0	153.9	
		Former smoker		1.2	13.8	14.2	12.4	
		Kreyberg II						
		Current smoker		3.6	9.3	20.5	30.5	
		Former smoker		2.2	5.0	5.4	1.8	

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)				Comments
Ger *et al*. (1993)	Men and women		*Cigarettes/day*	*1–10*	*11–20*	*≥ 21*	
		AC (H)		0.8	1.04	0.7	Matched odds ratios (see Table 2.1.1.4)
		AC (N)		0.8	1.7	1.05	
		SCC + small-cell (H)		1.8	3.6*	20.9*,†	†Based on 19 cases/6 hospital and 7 neighbourhood controls nonsmokers
		SCC + small-cell (N)		2.3	2.9	19.8*,†	
			Duration (years)	*1–30*	*≥ 31*		
		AC (H)		1.4	0.6		
		AC (N)		1.4	1.06		
		SCC + small-cell (H)		1.9	6.0*		
		SCC + small-cell (N)		1.3	6.8*		
Osann *et al*. (1993)	Men		*Pack/day*	*< 2*		*≥ 2*	
		SCC		35.3 (17.0–73.3)		76.0 (36.8–157)	Adjusted for age and race
		AC		16.5 (9.3–29.3)		37.5 (21.3–66.0)	
		SCLC		27.6 (9.8–77.4)		95.3 (34.7–262)	
	Women	SCC		24.0 (12.7–45.5)		72.3 (36.8–142)	
		AC		8.8 (6.1–12.8)		24.2 (15.8–37.2)	
		SCLC		76.7 (27.5–21.5)		316.1 (111–900)	
Pezzotto *et al*. (1993)	Men		*Cigarettes/day*	*< 21*	*21–40*	*> 40*	All odds ratios adjusted for age and hospital
		SCC		1.0	9.7*	15.4*	
		AC		1.0	11.6*	11.6*	Cigarettes/day: also adjusted for years of cigarette smoking
		SCLC		1.0	14.9*	54.2*	
			Duration (years)	*< 31*	*31–40*	*> 40*	Duration: also adjusted for intensity of smoking
		SCC		1.0	9.7*	11.2*	
		AC		1.0	3.5*	4.7*	Years since cessation: reference level, current smoker; also adjusted for intensity of smoking
		SCLC		1.0	1.2	3.5	
			Years since cessation		*1–10*	*> 10*	
		SCC			0.8	0.05*	
		AC			0.2*	0.08*	
		SCLC			0.2*	0.007*	

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)					Comments
			Filter	*Yes*	*No or yes/no*			Filter: also adjusted for intensity and duration of smoking
		SCC		1.0	4.9*			
		AC		1.0	2.6*			
		SCLC		1.0	4.0*			
Risch *et al*. (1993)			*Ever versus never*	*Current smokers at 40 pack–years versus non-smoker*[†]				[†]Both cumulative cigarette consumption and duration since cessation were modelled as continuous variables and were included simultaneously in the models.
	Men	AC	8.00*	5.44*				
		SCC	18.00*	15.5*				
		SCLC/large-cell	6.33*	14.9*				
		Giant-cell carcinoma	6.00*	11.7*				
	Women	AC	3.45*	8.75*				
		SCC	25.5*	101.0*				
		SCLC/large-cell	4.8*	87.3*				
		Giant-cell carcinoma	6.50*	18.0*				
De Stefani *et al*. (1994)	Men, smokers		*Mixed cigarettes*		*Hand-rolled*			Reference level, manufactured cigarettes; adjusted for age, residence, pack–years, cessation and type (black/blond); mixed: manu-factured or hand-rolled.
					Life-time	*Ever*		
		AC	3.3		1.8	2.3*		
		SCC	1.6		0.9	1.2		
		SCLC	5.3		4.1*	4.5*		
		Large-cell carcinoma	1.4*		0.6	0.8		
Sobue *et al*. (1994)	Men		*Cigarettes/day*	*1–19*	*20–29*	*≥ 30*		Adjusted for duration, fraction smoked per cigarette, filter-tip and inhalation
		AC		1.0	1.2	1.2		
		SCC		1.0	1.5	1.9*		
		SCLC		1.0	0.8	2.3*		
		Large-cell carcinoma		1.0	2.1	2.6		
			Duration (years)	*1–29*	*30–39*	*40–49*	*≥ 50*	
		AC		1.0	1.1	2.0*	2.1*	
		SCC		1.0	2.1*	4.3*	8.0*	
		SCLC		1.0	2.4	4.3*	7.6*	
		Large-cell carcinoma		1.0	1.3	2.1	1.6	

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)						Comments
Shimizu *et al.* (1994)	Men		*Cigarettes/day*	*1–20*	*≥ 21*				Reference level, nonsmoker; adjusted for age and education
		AC		1.1	2.1				
		Central SCC		5.0*	18.6*				
		Peripheral SCC		8.2*	15.5*				
			Duration (years)	*1–40*	*≥ 41*				
		AC		1.1	2.2				
		Central SCC		5.1*	16.5*				
		Peripheral SCC		6.0*	20.7*				
Kabat (1996)	Men[†]		*Cigarettes/day*	*1–10*	*11–20*	*21–30*	*31–40*	*≥ 41*	[†]Only current smokers
		Kreyberg I		13.3*	15.8*	29.6*	37.7*	64.1*	Reference category, never-smoker
		Kreyberg II		2.4*	8.4*	15.4*	11.1*	18.4*	
	Women[†]	Kreyberg I		6.6*	18.2*	26.5*	95.2*	88.7*	[Adjustments not stated]
		Kreyberg II		3.1*	4.5*	9.4*	13.4*	20.7*	
Xu *et al*. (1996)	Men	**SCC**	*Duration (years)*		*1–29*	*30–39*	*≥ 40*		Adjusted for age and education
		1–19 cig/day			2.3*	2.9*	5.0*		
		20–29 cig/day			2.6*	3.9*	10.4*		
		≥ 30 cig/day			7.7*	8.3*	31.2*		
		AC							
		1–19 cig/day			1.4	2.2*	2.6*		
		20–29 cig/day			0.7	1.5	3.6*		
		≥ 30 cig/day			5.4*	3.2*	11.8*		
	Women	**SCC**							
		1–19 cig/day			1.8*	4.2*	5.3*		
		≥ 20 cig/day			2.5	2.4	19.9*		
		AC							
		1–19 cig/day			0.9	2.2*	1.9*		
		≥ 20 cig/day			–	3.7*	6.8*		
Yu & Zhao (1996)	Men and women	AC	1.0 (0.9–1.2)						Meta-analysis of 15 studies
		SCC	4.8 (4.0–5.7)						
	Women	AC	1.1 (0.8–1.4)						Meta-analysis of 12 studies
		SCC	7.4 (4.2–10.7)						

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)						Comments
Zang & Wynder (1996)	Men		*Pack–years*	*1–19*	*20–39*	*40–49*	*≥ 50*		Only current smokers; reference level, nonsmoker; odds ratios adjusted for age
		SCC		6.5*	24.1*	48.9*	82.1*		
		AC		2.4*	5.6*	11.6*	13.8*		
	Women	SCC		11.9*	26.4*	48.8*	95.2*		
		AC		6.8*	11.2*	21.4*	32.7*		
			Most recent no. of cigarettes smoked/day	*1–10*	*11–20*	*21–40*	*≥ 41*		The dose–response relationships for women were statistically significantly higher than those for men.
	Men	SCC		14.1*	16.0*	38.9*	66.8*		
		AC		4.4*	7.2*	12.1*	19.3*		
	Women	SCC		9.3*	33.0*	74.9*	85.3*		
		AC		4.5*	14.2*	27.2*	34.3*		
Barbone *et al.* (1997)	Men		*Cigarettes/day*	*1–9*	*10–19*	*20–29*	*30–39*	*≥ 40*	Reference level, nonsmoker; adjusted for age
		SCC		3.9*	13.2*	15.2*	18.5*	23.4*	
		SCLC		1.1	9.2*	11.8*	13.4*	19.8*	
		AC		2.2	7.4*	6.5*	9.7*	9.6*	
			Duration (years)	*1–29*	*30–39*		*40–49*	*≥ 50*	
		SCC		2.1	9.6*		14.6*	21.2*	
		SCLC		3.1*	8.8*		12.6*	15.5*	
		AC		3.7*	5.1*		8.2*	8.3*	
			Age at start (years)	*≥ 20*	*15–19*		*< 15*		
		SCC		9.4*	13.7*		71.3*		
		SCLC		8.8*	10.4*		47.5*		
		AC		5.7*	6.0*		33.4*		
			Years since cessation	*≥ 25*	*15–24*	*5–14*	*1–4*	*0*	
		SCC		1.9	8.1*	11.9*	18.7*	9.3*	
		SCLC		2.2	7.6*	7.7*	10.9*	14.5*	
		AC		1.8	4.6*	7.3*	9.4*	8.2*	

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)							Comments
Dosemeci *et al*. (1997)	Men		*Cigarettes/day*	*1–10*	*11–20*	*≥ 21*				Adjusted for age and alcohol use; for all types *p* for trend < 0.001
		SCC		2.6*	3.2*	7.0*				
		SCLC		1.7	5.0*	13.5*				
		Other histology		1.8	2.7*	3.2*				
			Duration (years)	*1–10*	*11–20*	*≥ 21*				
		SCC		1.2	3.9*	4.9*				
		SCLC		1.7	7.0*	8.4*				
		Other histology		0.8	3.3*	4.1*				
Pohlabeln *et al*. (1997)	Men		Years since cessation							Reference level, current smoker; adjusted for age, region of residence and pack–years
			< 1	*1*	*2–5*	*6–10*	*11–20*	*> 20*		
		SCLC	16.8*	4.0*	1.2	0.4	0.4*	0.1*		
		SCC	19.9*	6.8*	1.6	1.0	0.3*	0.1*		
		AC	24.1*	10.2*	1.8	1.0	0.8	0.5		
Schwartz & Swanson (1997)	African–American men		*Age 40–54 years*	*55–84 years*						Risk for African Americans compared with whites; odds ratios adjusted for age, education, number of cigarettes smoked, number of years of smoking and number of years since quitting
		All lung carcinoma	3.2 (2–5.1)	0.9 (0.8–1.1)						
		AC	2.8 (1.6–5.1)	0.9 (0.7–1.1)						
		SCC	4.0 (2.2–7.2)	1.1. (0.9–1.4)						
		Large-cell carcinoma	2.1 (0.9–4.8)	1.1 (0.7–1.6)						
		SCLC	2.5 (1.2–4.9)	0.7 (0.5–1)						
	Women	All lung carcinoma	1.3 (0.8–2.1)	1.0 (0.8–1.2)						
		AC	0.9 (0.5–1.8)	0.9 (0.7–1.2)						
		SCC	3.7 (2.5–8.9)	1.3 (1–1.9)						
		Large-cell carcinoma	1.6 (0.4–6.4)	0.5 (0.2–1)						
		SCLC	2.7 (1.0–7.3)	0.9 (0.6–1.3)						
Wakai *et al*. (1997)	Men		*Cigarettes/day*	*1–19*	*20–29*	*≥ 30*				Current smokers; reference level, nonsmoker; adjusted for age
		SCC		3.9*	10.4*	24.0*				
		AC		1.3	1.9	4.5*				
			Years since cessation	*5–9*	*10–19*	*≥ 20*				
		SCC		7.5*	8.9*	2.0				
		AC		1.2	2.5	0.5				

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)				Comments
Khuder *et al*. (1998)	Men		*Cigarettes/day*	*1–39*	*≥ 40*		Adjusted for duration, number of cigarettes/day, age at start and whether or not subject had quit smoking
		SCC		1	8.7*		
		SCLC		1	11.5*		
		AC		1	3.5*		
			Duration (years)	*1–29*	*≥ 30*		
		SCC		1	1.9		
		SCLC		1	2.6		
		AC		1	2.7*		
			Age at start (years)	*≥ 20*	*16–19*	*< 16*	
		SCC		1	0.8	1.0	
		SCLC		1	1.6	3.0*	
		AC		1	0.7	0.8	
			Cessation	*Yes*	*No*		
		SCC		1	0.6*		
		SCLC		1	1.1		
		AC		1	0.6*		
Matos *et al*. (1998)	Men		*Cigarettes/day*	*1–14*	*15–24*	*≥ 25*	Adjusted for age and hospital
		SCC		1.4	7.8*	9.7*	
		AC		2.8	7.0*	8.4*	
			Duration (years)	*1–24*	*25–39*	*≥ 40*	
		SCC		1.2	5.8*	18.5*	
		AC		1.7	7.3*	10.7*	
Kreuzer *et al*. (2000)			*Cigarettes/day*	*< 15*	*15–29*	*≥ 30*	Reference level, occasional smoker; 95% CI not provided; adjusted for age, centre and duration/average amount of smoking and time since quitting
	Men	SCLC		1.0	2.2	2.6	
		SCC		1.0	2.2	3.0	
		AC		1.0	1.6	1.6	
	Women	SCLC		1.0	2.0	4.7	
		SCC		1.0	1.8	3.8	
		AC		1.0	2.1	4.6	

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)					Comments
Kreuzer *et al.*			*Duration (years)*	*< 20*	*20–39*	*≥ 40*		
(2000) (contd)	Men	SCLC		1.0	3.3	3.8		
		SCC		1.0	3.2	4.1		
		AC		1.0	3.4	4.0		
	Women	SCLC		1.0	3.9	3.6		
		SCC		1.0	2.4	4.2		
		AC		1.0	2.2	2.3		
Lee *et al.* (2001)	Men and		*Cigarettes/day*	*1–10*	*11–20*	*≥ 21*		
	women	SCC/SCLC		2.9*	3.1*	5.6*		
		AC		1.6	2.0	2.9*		
			Duration (years)	*1–30*	*31–40*	*≥ 41*		Adjusted for education,
		SCC/SCLC		2.8*	4.3*	5.0*		residence, socioeconomic
		AC		1.7	1.8	3.0*		status
			Age started (years)	*> 20*	*12–20*			
		SCC/SCLC		4.0*	4.3*			
		AC		1.6	2.8*			
			Inhalation	*Light†*	*Deep‡*	*Light*	*Deep*	†'Uncertain but light more'
		SCC/SCLC		1.6	5.0	3.4*	6.8*	[sic]
		AC		1.6	0.7	1.9	2.5*	‡'Uncertain but deep more' [sic]
Simonato *et al.* (2001)			*Former smoker*	*Current smoker*				Reference category, non-smoker; adjusted for age, education and centre
	Men	SCC/SCLC	16.2	57.9				
		AC	3.5	8.0				
	Women	SCC/SCLC	3.8	18.2				
		AC	1.1	4.1				

Table 2.1.1.13 (contd)

Reference	Subjects	Histology	Odds ratio (95% CI)					Comments
Stellman *et al.* (2001)	Men		*Cigarettes/day*	*< 20*	*20–29*	*≥ 30*		
	USA	AC		7.0*	37.3*	54.6*		Adjusted for age and education and hospital for hospital controls (H)
	Japan	AC (H)		0.6	2.2	3.3*		
		AC (CC)[†]		1.2	2.9*	5.5*		
		SCC (H)		7.4*	13.7*	31.8*		
		SCC (CC)[†]		10.2*	14.1*	35.7*		
			Duration (years)	*≤ 40*	*> 40*			SCC could not be evaluated for USA (0 controls)
	USA	AC		15.1*	34.7*			
	Japan	AC (H)		1.1	3.9*			[†]Community controls
		AC (CC)[†]		2.6*	4.1*			
		SCC (H)		6.3*	19.3*			
		SCC (CC)[†]		13.1*	22.8*			
Rachtan (2002)	Women		*Cigarettes/day*	*< 11*	*11–20*	*21–30*	*> 30*	Adjusted for age
		SCC		3.3*	13.5*	30.2*	74.0*	[†]Only 1 case
		AC		1.7	3.4*	8.5*	5.3[†]	
		SCLC		12.9*	31.6*	43.5*	108.8*	
			Duration (years)	*< 26*	*26–39*	*≥ 40*		
		SCC		2.5*	18.2*	35.2*		
		AC		1.4	4.8*	9.6*		
		SCLC		7.7*	44.7*	98.5*		
			Age started (years)	*> 18*	*≤ 18*			
		SCC		8.4*	21.0*			
		AC		2.6*	4.2*			
		SCLC		25.1*	29.5*			
			Inhalation	*No*	*Yes*			
		SCC		6.4*	15.8*			
		AC		2.2	3.6*			
		SCLC		16.6*	34.6*			

SCC, squamous-cell carcinoma; SCLC, small-cell carcinoma; AC, adenocarcinoma; Kreyberg I, squamous-cell carcinoma, small-cell and large-cell carcinoma; Kreyberg II, adenocarcinoma and alveolar-cell/bronchioalveolar carcinoma; H, hospital control; N, neighbourhood control
*$p < 0.05$

Table 2.1.1.14. Approximate[a] effects of various durations of cigarette smoking on annual excess incidence of lung cancer

Years of cigarette smoking	Annual excess incidence	
	Moderate smokers (%)	Heavy smokers (%)
15	0.005	0.01
30	0.1	0.2
45	0.5	1

[a] Estimated by Peto and Doll (1984) from the model reported by Doll and Peto (1978) fitted to incidence data for male UK doctors

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2.1.2 *Cancer of the lower urinary tract*

The 'lower urinary tract' comprises the renal pelvis, ureter, bladder and urethra. Cancers originating in the urothelium at these sites are mostly transitional-cell carcinomas or squamous-cell carcinomas. These cancers are discussed together, unless a particular distinction has been made in the studies that were considered.

In the previous *IARC Monograph* on tobacco smoking (IARC, 1986), cancer of the lower urinary tract was identified as being causally associated with cigarette smoking.

(*a*) *Analytical studies*

Results in support of the association of cigarette smoking with cancer of the lower urinary tract have been reported from cohort studies conducted in the United Kingdom (British Doctors' Study), Sweden (Swedish Twin Registry Study, Swedish Census Study), Norway (Norwegian Cohort Study), Iceland (Reykjavík Study), the USA (American Cancer Society Study, US Veterans' Study, Californian Study, Cancer Prevention Study I, American Men of Japanese Ancestry Study, MRFIT Study, Adventists' Health Study), Canada (Canadian War Veterans' Study), China (Shanghai Men's Study), China, Province of Taiwan (Taiwanese Study), Japan (Life Span Study, Six-prefecture Study, Chiba Center Association Study). The design of these studies is described in the introduction to Section 2 and Table 2.1.

The designs of the available case–control studies are summarized in Table 2.1.2.1.

With the exception of the study by Anthony and Thomas (1970), in Leeds (United Kingdom) and the very small study of Liaw and Chen (1998) in China, Province of Taiwan, all the others have shown an association between cancer of the lower urinary tract and cigarette smoking. Irrespective of the design (cohort, hospital-based or population-based case–control), all other studies have found a positive association, and this overall result cannot be explained by bias. Potential confounders — in addition to age and gender — that may be considered are certain occupational exposures, particularly to aromatic amines, and schistosomiasis in developing countries.

However, Akiba and Hirayama (1990) and Momas *et al.* (1994a) reported estimates adjusted by occupation, which did not differ from other estimates. Two studies from Egypt (Makhyoun, 1974; Bedwani *et al*., 1998) and one study from Zimbabwe (Vizcaino *et al*., 1994) investigated smoking after stratification by bilharziasis (schistosomiasis); the risk of cancer of the lower urinary tract in smokers remained elevated after adjustment for urinary bilharziasis.

(i) *Number of cigarettes smoked and duration of cigarette smoking*

Tables 2.1.2.2 and 2.1.2.3 give the relative risks according to average daily number of cigarettes smoked. One case–control study conducted in Leeds, United Kingdom (Cartwright *et al*., 1983), failed to show a clear-cut dose–response relationship in men, although a statistically significant overall relative risk of 1.6 was found. [The Working

Group noted that the control group used in this study included patients with tobacco-related diseases, a choice that could have biased the result.] Considerable variations in the relationship between relative risks and average daily number of cigarettes smoked are evident. For male smokers of more than 20 cigarettes/day, the relative risks tend to be around 5.0 or higher in studies in Europe, and lower in studies in America and Japan. High estimates have been reported in particular from Uruguay (De Stefani *et al.*, 1991), France (Clavel *et al.*, 1989; Momas *et al.*, 1994b), Denmark (Lockwood, 1961) and Italy (Vineis *et al.*, 1984; Donato *et al.*, 1997).

Twelve of the 42 studies with a case–control design and 10/24 of those with a cohort design reported a levelling-off of the dose–response curve. This phenomenon can be interpreted either as an effect of bias (underestimation of consumption by heavy smokers) or as a genuine effect, due, for example, to the saturation of metabolic enzymes (Vineis *et al.*, 2000). [The Working Group noted that the wide variations in the dose–response relationship could be explained by a number of factors, namely, different study designs, different ways of smoking or different types of tobacco smoked. It was noted that the apparent levelling-off of the dose–response curve could reflect an artefact in data collection, due to under-reporting of levels of consumption by the interviewees.]

The 24 cohort studies have consistently shown an excess of deaths from bladder cancer among smokers; the relative risks were between 3.0 and 5.4 for smokers of 20 or more cigarettes/day (Table 2.1.2.2).

Duration of cigarette smoking showed a positive relationship with relative risks for bladder cancer in all the studies that have examined it (Table 2.1.2.4). Also, age at starting smoking (Table 2.1.2.4) has been found to be positively associated with risk; smokers who started smoking at an earlier age were at a higher risk for bladder cancer. However, duration, age at starting and age at stopping are closely correlated variables, and few studies have tried to disentangle them (Hartge *et al.*, 1993).

When cancers of the renal pelvis and of the ureter are considered separately, a dose–response relationship with daily or cumulative consumption of tobacco is found, and relative risks are similar to those reported for cancer of the bladder (McCredie *et al.*, 1982, 1983; McLaughlin *et al.*, 1983, 1992).

(ii) *Effect of stopping cigarette smoking*

A lowering of risk after stopping cigarette smoking is seen in almost all the studies (Table 2.1.2.5), and it is particularly evident from studies conducted in the USA (Kahn, 1966; Wynder & Goldsmith, 1977; Rogot & Murray, 1980; Morrison *et al.*, 1984; Mills *et al.*, 1991), Canada (Howe *et al.*, 1980), France (Clavel *et al.*, 1989), Italy (Vineis *et al.*, 1984; D'Avanzo *et al.*, 1990; Donato *et al.*, 1997), Germany (Pommer *et al.*, 1999), the United Kingdom (Doll & Peto, 1976; Cartwright *et al.*, 1983; Morrison *et al.*, 1984), Japan (Morrison *et al.*, 1984) and Sweden (Steineck *et al.*, 1988).

(iii) *Type of cigarette and effect of inhaling*

In six studies (Vineis *et al.*, 1984; Clavel *et al.*, 1989; D'Avanzo *et al.*, 1990; De Stefani *et al.*, 1991; Lopez-Abente *et al.*, 1991; Momas *et al.*, 1994b) (Table 2.1.2.6), separate estimates were reported for the relative risks for lower urinary tract cancers for smokers of black (air-cured) and blond (flue-cured) tobacco. Relative risks for smokers of black tobacco were 1.5 to two times higher than those for smokers of blond tobacco, after adjustment for age, occupation, average daily consumption of cigarettes, years since stopping and use of a filter tip.

A strong effect of inhaling was shown in the studies by Clavel *et al.* (1989) and Lopez-Abente *et al.* (1991). A slight effect of inhaling was reported by Cole *et al.* (1971), Howe *et al.* (1980), Morrison *et al.* (1984) and Burch *et al.* (1989) but not by Lockwood (1961) (Table 2.1.2.6).

The effects of filter-tipped cigarettes have been analysed in several studies, with conflicting results (Table 2.1.2.7). A weak effect of filter-tipped cigarettes was reported by Howe *et al.* (1980), Cartwright *et al.* (1983), Vineis *et al.* (1984), López-Abente *et al.* (1991) and De Stefani *et al.* (1991), whereas no difference between the effects of smoking filter-tipped and untipped cigarettes was found in the studies by Wynder and Goldsmith (1977), Morrison *et al.* (1984) or Momas *et al.* (1994b).

(iv) *Histology*

Almost all of the cancers of the lower urinary tract encompassing bladder, renal pelvis and ureter are transitional-cell cancers in industrialized countries, but squamous-cell carcinomas are common in developing countries. One pooled analysis by Fortuny *et al.* (1999) (Table 2.1.2.3) considered non-transitional-cell bladder cancers, mainly epidermoid cancers, and found elevated relative risks in association with smoking and a positive dose–response relationship. A small study in Zimbabwe (Vizcaino *et al.*, 1994) found that the association with smoking was present (but not statistically significant) only in transitional-cell carcinomas.

(*b*) *Population characteristics*

(i) *Effect of gender*

Tables 2.1.2.2 and 2.1.2.3 show the relative risks according to the number of cigarettes smoked, by gender. There are only slight differences between men and women, and this holds true for subsequent tables. The differences seem to be attributable more to chance (specifically because there have been fewer studies among women) than to real differences in susceptibility to the effects of tobacco smoking.

A population-based study was conducted in Los Angeles, USA, with the aim of addressing the gender differences in susceptibility to bladder cancer (Castelao *et al.*, 2001). The risk for women was statistically significantly higher than that for men ($p = 0.016$ for interaction). Biochemical evidence was also provided: the slopes of the regression lines of 3-aminobiphenyl (3-ABP–) and 4-ABP–haemoglobin adducts by number of cigarettes smoked per day were statistically significantly steeper in women than in men ($p < 0.001$ and 0.006, respectively).

(ii) *Effect of race/ethnicity*

Two studies considered the dose–response relationship in both whites and blacks living in the USA (Dunham *et al.*, 1968; Burns & Swanson, 1991). One study was conducted in Egypt (Makyoun, 1974), one in Iran (Sadeghi *et al.*, 1979), and several were conducted among Asians (e.g. Hirayama, 1977; Morrison *et al.*, 1984; Akiba & Hirayama, 1990; Yuan *et al.*, 1996). The differences between the various races and ethnic groups observed for the dose–response relationship are compatible with chance variation.

(*c*) *Pooled analysis*

The original data from 11 of the case–control studies of bladder cancer together with those from one unpublished study have been analysed together as part of a pooled analysis consisting of 3285 cases of bladder cancer (2600 men, 685 women) and 7940 controls (5524 men, 2416 women) (Brennan *et al.*, 2000, 2001). These studies were selected as they were participating in a parallel reanalysis of data on occupational exposures and bladder cancer in Europe. Two case–control studies each were from France, Spain and Italy, three from Germany and one each from Denmark and Greece (Vineis *et al.*, 1985; Rebelakos *et al.*, 1985; Claude *et al.*, 1986; Jensen *et al.*, 1987; Lopez-Abente *et al.*, 1991; Clavel *et al.*, 1989; Bolm-Audorff *et al.*, 1993; Hours *et al.*, 1994; Greiser & Molzahn, 1997; Donato *et al.*, 1997; Serra *et al.*, 2000). All studies included both men and women.

(i) *Duration of smoking*

An increasing risk of bladder cancer was observed with increasing duration of smoking. The relationship appeared to be approximately linear for both men and women. The relative increase in risk was approximately 100% after 10–19 years of smoking (odds ratio, 2.0; 95% CI, 1.5–2.6 for men; odds ratio, 2.2; 95% CI, 1.4–3.5 for women), 200% after 20–29 years of smoking (odds ratio, 3.1; 95% CI, 2.5–3.9 for men; odds ratio, 2.5; 95% CI, 1.7–3.8 for women) and 300% after 40 years of smoking (odds ratio, 3.8; 95% CI, 3.1–4.6 for men; odds ratio, 3.9; 95% CI, 2.8–5.4 for women).

(ii) *Intensity of smoking*

A dose–relationship was observed between number of cigarettes smoked per day and bladder cancer up to an apparent threshold of 15–19 cigarettes per day (odds ratio, 4.5; 95% CI, 3.8–5.3 for men; odds ratio, 3.8; 95% CI, 2.7–5.4 for women), after which a plateau in the risk was observed for both male and female smokers of more than 20 cigarettes per day.

(iii) *Smoking cessation*

An immediate decrease in risk of bladder cancer was observed among men who gave up smoking. Compared with current smokers, this fall was close to 40% for male smokers who had stopped smoking between 1 and 4 years prior to diagnosis (odds ratio, 0.65;

95% CI, 0.53–0.79) and reached 60% after 25 years of cessation (odds ratio, 0.37; 95% CI, 0.30–0.45). However, even after 25 years, the risk was not as low as that for non-smokers (odds ratio, 0.20; 95% CI, 0.17–0.24). Among women, the immediate decrease in risk was approximately 30% for smokers who stopped smoking between 1 and 4 years prior to diagnosis. The risk did not appear to decrease substantially after this and, even after 25 years of cessation, it remained considerably above the level found for never-smokers.

(iv) *Attributable fraction*

The proportion of bladder cancer cases attributable to ever smoking, i.e. the population attributable risk (PAR), was calculated as 0.66 for men (95% CI, 0.61–0.70) and 0.30 (95% CI, 0.25–0.35) for women. Similarly, the PAR of bladder cancer cases attributable to current smoking was calculated as 0.32 (95% CI, 0.28–0.35) for men and 0.18 (95% CI, 0.14–0.22) for women. [The Working Group noted that the lower attributable proportions among women reflect the earlier stage of the smoking-related disease epidemic among women, and these attributable fractions may be expected to increase in the future as this epidemic becomes more widespread among women.]

Table 2.1.2.1. Case–control studies on tobacco smoking and lower urinary tract cancer: main characteristics of study design

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Lilienfeld *et al.* (1956) USA 1945–55	Men: 321 cases and 663 controls; women: 118 cases and 1205 controls	Hospital-based study; controls: 287 men with prostate cancers, 39 men with benign bladder conditions and 337 healthy men; 776 women with breast cancers, 110 women with benign bladder conditions and 319 healthy women
Lockwood (1961) Denmark 1956–57	Men: 282 cases and 282 controls; women: 87 cases and 87 controls	Population-based study; living cases from the Danish Cancer Registry (1956–57); controls selected from Population Registry
Schwartz *et al.* (1961) France Study started in 1954	Men: 214 cases and 214 controls	Hospital-based study; age-matched controls were subjects admitted to hospitals for accidents
Wynder *et al.* (1963a) USA 1960–61	Men: 300 cases and 300 controls; women: 70 cases and 70 controls	Hospital-based study, papillomas excluded; sex- and age-matched controls: cancers of respiratory system, upper alimentary tract and myocardial infarction excluded
Cobb & Ansell (1965) USA 1951–61	Men and women: 136 cases and 342 controls	Hospital-based study; 120 colon cancer controls and 222 controls with ‘pulmonary problems’; data on smoking available for 131 cases
Staszewski (1966) Poland 1958–64	Men: 150 cases and 750 controls	Hospital-based study; age-matched controls with cancer or other diseases
Dunham *et al.* (1968) USA 1958–64	Men: 334 cases and 350 controls; women: 159 cases and 177 controls	402 incident cases in New Orleans and 91 prevalent cases or cases not living in the city; hospital controls, including unspecified numbers of patients with bronchitis, emphysema, myocardial infarction; 162 (29%) of eligible cases not interviewed
Anthony & Thomas (1970) UK 1958–67	Men: 381 cases and 275 controls	Hospital-based study; surgical controls (excluding patients with chest, genitourinary and malignant disease) in 1955–58

Table 2.1.2.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Cole *et al*. (1971) USA 1967–68	Men: 360 cases and 381 controls; women: 108 cases and 117 controls	Cases randomly selected among all (668) eligible incident cases occurring in 1967–68 in 87 cities of the Boston area (20–89 years old); controls: random sample of 20–89-year-old residents, matched for sex and age; interviews of 140/470 cases and 78/500 controls conducted with spouse or next of kin
Tyrell *et al*. (1971) Ireland 1967–68	Men: 200 cases and 200 controls; women: 50 cases and 50 controls	Hospital-based study; age- and sex-matched urological controls
Makhyoun (1974) Egypt 1966–71	Men: 365 cases and 365 controls	Hospital-based study; age-matched non-cancer controls; 278 cases and 278 matched controls had previous urinary bilharziasis
Morgan & Jain (1974) Canada	Men: 158 cases and 158 controls; women: 74 cases and 74 controls	Hospital-based study; controls matched for sex and age; postal questionnaires: responses were 67% (cases) and 57% (controls) among men; 73% (cases) and 57% (controls) among women
Schmauz & Cole (1974) USA	Men: 18 cases and 376 controls	Population-based study of cancer of the renal pelvis and ureter (see Cole *et al*., 1971, for design)
Wynder & Goldsmith (1977) USA 1969–74	Men: 574 cases and 574 controls; women: 158 cases and 158 controls	Hospital-based study on cases aged 40–80 years and controls matched for sex, ethnic group, hospital and age; controls had no ‘tobacco-related condition’.
Miller *et al*. (1978) Canada	Men: 188 cases and 564 controls; women: 77 cases and 231 controls	Hospital-based study, using self-completed questionnaires of subjects over 40 years; two sex- and age-matched controls for each case
Sadeghi *et al*. (1979) Iran 1969–76	Men: 88 cases and 88 controls	Hospital-based study; sex- and age-matched hospital controls; patients with cancer, pulmonary and bladder disease excluded (23/122 cases excluded due to poor information)

Table 2.1.2.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Howe *et al*. (1980) Canada 1974–76	Men: 480 cases and 480 controls; women: 152 cases and 152 controls	Population-based study; eligible cases were all patients with newly diagnosed bladder cancer in 3 Canadian provinces (77% interviewed); controls matched for sex, age and neighbourhood (controls who refused were substituted); male cases had a higher level of education and income than controls.
Tola *et al*. (1980) Finland 1975–76	Men: 134 cases and 134 controls; women: 46 cases and 46 controls	Originally eligible cases were all those (274) reported to the Finnish Cancer Registry for 5 Finnish provinces; postal questionnaires sent to 269 cases and 271 sex- and age-matched hospital controls or their relatives; response rates were 80% (cases) and 81% (controls); source of information was a relative for 39% of cases and 12% of controls.
McCredie *et al*. (1982) Australia 1977–80	Men: 27 cases and 70 controls; women: 40 cases and 110 controls	Cancer registry and hospital-based study; renal pelvis cancer cases; first control group were friends or relatives of other patients; second control group were subjects attending a screening clinic; 24 cases interviewed by their doctors, remaining cases and all controls interviewed by researchers; higher socio-economic status among screening clinic controls
Najem *et al*. (1982) USA 1978	Men: 65 cases and 123 controls; women: 10 cases and 19 controls	Hospital-based study; prevalent cases only; 2 controls per case matched for sex, age, ethnic group, place of birth and place of residence (patients with cancer and tobacco-related heart disease excluded)
Cartwright *et al*. (1983) UK 1978–81	Men: 932 cases and 1402 controls; women: 327 cases and 579 controls	90% of incident cases in West Yorkshire (1978–81) and prevalent cases included; sex- and age-matched hospital controls (25% arterial disease; 60% accident, minor surgery; 10% chest conditions)

Table 2.1.2.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
McCredie *et al*. (1983) Australia 1977–82 (ureter), 1980–82 (renal pelvis)	Men: 65 cases and 307 controls	Population-based (cancer registry) study; cancers of the ureter (36 cases) and renal pelvis (29 cases) only; controls were a random sample of the general population; questionnaires posted to cases and controls (no. of non-respondents not given); higher educational level among controls
McLaughlin *et al*. (1983) USA 1974–79	Men: 50 cases and 428 controls; women: 24 cases and 269 controls	Population-based study on cancer of the renal pelvis (71/74 were transitional-cell carcinomas); controls were (1) a random sample of the general population and (2) a group of deceased individuals matched to the deceased cases
Møller-Jensen *et al*. (1983) Denmark 1979–81	Men: 286 cases and 574 controls; women: 95 cases and 193 controls	Cases, two-thirds of all incident cases in Greater Copenhagen (under age 75 years); controls, a random sample of the general population (out of 1052 controls approached, 109 refused, 114 were not located and 39 were too ill)
Mommsen & Aagaard (1983) Denmark 1977–79 (men), 1977–80 (women)	Men: 165 cases and 165 controls; women: 47 cases and 94 controls	Population-based study; controls: random sample of general population; cases interviewed in hospital, controls by phone
Morrison *et al*. (1984) Japan and UK, 1976–78; USA, 1976–77	Men: Greater Manchester, 398 cases, 490 controls; Nagoya (Japan), 224 cases, 442 controls; Boston area, 427 cases, 391 controls Women: Greater Manchester, 155 cases, 241 controls; Nagoya, 66 cases, 146 controls; Boston area, 165 cases, 142 controls	Population-based study in Japan, UK and USA; 96% (Manchester), 84% (Nagoya) and 81% (Boston) of all incident cases (aged 21–89 years) were interviewed; controls were randomly selected from electoral registers; in Nagoya most cases were interviewed in hospital, all other groups at home; 95% of tumours were of the bladder.

Table 2.1.2.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Vineis *et al*. (1984) Italy 1978–83	Men: 512 cases and 596 controls	Hospital-based study; 210/512 prevalent cases; 225 age-matched controls (with urological disease); 287 cases and 371 unmatched controls from surgical departments (87 hernias, 41 peripheral arteriopathies and other diagnoses)
Rebekalos *et al.* (1985) Greece 1980–82	Men: 250 cases and controls; women: 50 cases and controls	Hospital-based study. Histologically confirmed cases of bladder cancer. Sex- and age-matched controls from accidents centre of another hospital (traumatic fractures, 185; other traumatic conditions, 30; osteoarthrosis, 32; rheumatoid arthritis, 28; other orthopaedic conditions, 24).
Claude *et al.* (1986) Germany 1977–82	Men: 340 cases and controls; women: 91 cases and controls	Hospital-based study; 21% of controls selected from homes for the elderly. Interviews carried out by medical students using a standardized questionnaire. 90% of cases had bladder tumours (remainder had cancers of renal pelvis, ureter or urethra or combinations of these). Male controls had prostate adenomas and infections (70%), urinary tract infections (20%). Female controls had urinary tract infections (68%) or no particular illness (24%).
Burch *et al.* (1989) Canada 1979–82	781 cases and 781 matched controls	Population-based study. Only 67% of eligible cases were interviewed. Response rate for controls, 53%.
Clavel *et al.* (1989) France 1984–87	477 cases and 477 matched controls	Hospital-based study using interview; 157 prevalent cases; controls: patients with tobacco-related conditions were excluded. Refusal rate not given
D'Avanzo *et al.* (1990) Italy 1985–89	337 cases and 392 controls	Hospital-based study using interviews. Refusals < 3%. Controls had trauma (30%), orthopaedic conditions (17%) and surgical conditions.

Table 2.1.2.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Harris *et al*. (1990) USA 1969 onwards	White men: 1114 cases, 3252 controls; black men, 84 cases, 271 controls; white women: 420 cases, 1289 controls; black women, 45 cases, 118 controls	Hospital-based study. Incident cases. Controls included gastrointestinal disease, infections, leukaemia, benign prostatic hypertrophy, benign neoplastic disease, other cancers and other causes. Controls were matched on sex, age, race, year of interview and hospital of diagnosis.
Burns & Swanson (1991) USA	White men: 1410 cases, 1615 controls; black men: 161 cases, 382 controls; white women: 504 cases, 1600 controls; black women, 85 cases, 382 controls	Population-based study; controls: incident cases of colorectal cancer. Telephone interviews. Response rates, 94% (cases) and 95% (controls)
De Stefani *et al*. (1991) Uruguay 1987–89	Men: 91 cases and 182 controls; women: 20 cases and 40 controls	Hospital-based study, only incident cases; 29% of controls had malignant tumours, 22% eye diseases. No refusals
López-Abente *et al*. (1991) Spain 1983–86	430 cases, 405 hospital controls and 386 population controls	Hospital and population-based study; 49% were prevalent cases. Controls matched by sex and age. Refusals: 5% of cases, 7% of hospital controls, 7% of population controls. Hospital controls: patients with tobacco-related diagnoses excluded
Kunze *et al*. (1992) Germany 1977–85	Men: 531 cases and 531 controls; women: 144 cases and 144 controls	Hospital-based study. Controls matched by sex and age; diagnoses included prostate hyperplasia (64% of men) or infection of urinary tract (73% of women)
McLaughlin *et al.* (1992) USA 1983–86	Men: 331 cases and 315 controls; women: 171 cases and 181 controls	Population-based study in New Jersey, Iowa and California. Incident cases of cancers of the renal pelvis and ureter, microscopically confirmed, aged 20–79 years, identified using the local population-based cancer registries; 58% of ascertained cases participated. Controls selected by random-digit dialling (< 65 years) or Health Care Financial Administration rosters (≥ 65 years), frequency-matched on age (5-year groups) and sex; response rate, 54–66%

Table 2.1.2.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Hartge *et al*. (1993) USA Study started in 1978	White men: 1925 cases, 3642 controls; black men: 88 cases, 277 controls; white women: 633 cases, 1295 controls; black women: 33 cases, 106 controls	Population-based study. Cases drawn from 5 states and 5 metropolitan areas in the SEER network of cancer registries in 1978; controls selected by random-digit dialling or Health Care Financing Administration files
Vena *et al*. (1993) USA 1979–85	White men: 351 cases and 855 controls	Population-based study. Only incident cases. Controls were matched on sex, age and neighbourhood. Response rates were 42% in controls and 76% in cases [sampling of controls not described].
Barbone *et al.* (1994) Italy 1986–90	273 cases and 573 controls	Hospital-based study using interviews. Controls had trauma (20%), orthopaedic conditions (35%), surgical conditions (26%).
Hours *et al*. (1994) France 1984–87	Men and women: 116 cases and 232 controls	Hospital-based study. Two groups of controls with diseases other than cancer, matched for sex, hospital, age and nationality, one from same hospital ward and one from another ward of same hospital as case; most frequent diagnoses among urological ward controls were benign adenoma of the prostate (48/116) and urinary lithiasis (22/116); most common among general hospital controls were cardiovascular (42/116), digestive system (10/116) and endocrine (11/116) diseases. Job/other histories obtained by interview. Papillomas of urinary bladder included; 30–75 years of age
Momas *et al*. (1994a,b) France 1987–89	219 cases and 794 controls	Population-based study. Controls sought from electoral rolls. Only incident cases. Cases and 558 controls interviewed by telephone, 236 controls by post. Response rate, 81% (telephone), 72% (postal) in controls and 219/272 (80.5%) cases
Sorahan *et al.* (1994) UK 1985–87	989 cases, 2059 population controls and 1599 patients of general practitioners	Mixed design (population controls and patients of general practitioners). Postal questionnaires. Response rate not given

Table 2.1.2.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Vizcaino *et al.* (1994) Zimbabwe 1963–77	Black men: 494 cases and 4412 controls; black women: 186 cases and 3789 controls	Analysis of data from Bulwayo cancer registry; controls comprised all other registered cancer cases excluding 'tobacco-related sites' (oesophagus, larynx and lung); interviews conducted either with subject at time of hospitalization or with relatives; individuals with current bilharzia or haematuria were excluded. Complete interview obtained for 72.2% of cases and 70.3% of controls
McCarthy *et al.* (1995) USA 1975–92	Men: 217 cases and 860 controls; women: 84 cases and 336 controls	Population-based study. Controls sampled from private census (covering 90% of residents), including information on smoking
Donato *et al.* (1997) Italy 1991–92	Men: 135 cases and 398 controls; women: 37 cases and 180 controls	Hospital-based study. Only incident cases. Controls had prostate adenoma (40%), urolithiasis (48%). Response rate not given.
Bedwani *et al.* (1998) Egypt 1994–96	Men: 151 cases and 157 controls	Hospital-based study; controls had traumatic and other orthopaedic conditions (35%), acute surgical diseases (27%), eye diseases (8%), miscellaneous (30%). Women were excluded due to low proportion of current smokers (1/39 cases); questionnaires completed by trained interviewers.
Pohlabeln *et al.* (1999) Germany 1989–92	Men: 239 matched pairs; women: 61 matched pairs (age and area of residence)	Hospital-based study. Incident cases. Response rate, 93% in cases and 98% in controls. Male controls had prostate adenoma (41%) or kidney stones (30%). Female controls had kidney stones (62%). Interviews
Pommer *et al.* (1999) Germany 1990–94	Men: 415 cases and 415 controls; women: 232 cases and 232 controls	Population-based study. Incident cases. Controls sought from municipality registry, matched on sex and age; 11% of cases and 29% of controls refused to participate.
Serra *et al.* (2000) Spain 1993–95	Men: 196 cases and 314 controls; women: 22 cases and 30 controls	Population-based study. Incidence cases, all histologically confirmed (93.6% transitional-cell carcinomas). Controls with no known benign or malignant tumour of the urinary tract, from the same county, selected using municipal-based census lists. Matched by sex, age and residence

Table 2.1.2.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Castelao *et al*. (2001) USA 1987–96	Men and women: 1514 cases and 1514 controls	Population-based study. Non-Asian patients with histologically confirmed bladder cancer. Controls matched by sex, age, race (non-Hispanic white, Hispanic, African American) and neighbourhood of residence. Structured questionnaires were completed at an interview in the participant's home. Peripheral blood samples collected to measure 3- and 4-aminobiphenyl–haemoglobin adducts.
Combined analyses		
Fortuny *et al*. (1999) Europe 1983–95	Men and women: 146 cases and 292 controls	Combined analysis of 9 case–control studies (9/11 described in Brennan *et al*., 2000). Non-transitional-cell carcinoma of the bladder only.
Brennan *et al*. (2000, 2001) Europe 1976–96	Men: 2600 cases and 5524 controls; women: 685 cases and 2416 controls	Combined analysis of 11 case–control studies. Recruitment of cases was hospital-based, that of controls either hospital-based (7 centres), population-based (3 centres) or both (1 centre). Diseases of hospital-based controls varied among centres, although all subjects were affected by diseases unrelated to smoking.

Table 2.1.2.2. Cohort studies on tobacco smoking and cancer of the lower urinary tract: intensity of smoking

Reference Country and years of study	Cohort study Subjects	Smoking categories	Relative risk (no. of cases or 95% CI)	Comments
Hammond & Horn (1958a,b) USA 1952–55	American Cancer Society (9-state) Study 187 783 men	Cig/day		Microscopically verified cancer of the genitourinary system
		1–9	2.0 (14)	
		10–20	2.0 (42)	
		> 21	3.4 (41)	
		Smoker	2.2 (59)	Microscopically verified bladder cancer only
Hammond (1966) USA 1959–63	Cancer Prevention Study (CPS) I 440 558 men	Ever-smoker		Relative risks calculated by the Working Group as ratios of age-adjusted annual death rates
		aged 45–64 years	1.8 (59)	
		aged 65–79 years	2.9 (56)	
Kahn (1966) USA 1954–62	US Veterans' Study 293 658 men	Cig/day		
		< 10	1.0 (11)	
		10–20	2.3 (71)	
		21–39	3.1 (51)	
		≥ 40	3.0 (9)	
Lossing *et al.* (1966) Canada 1956–62	Canadian War Veterans' Cohort 78 000 men	Cig/day		Mortality ratios; genitourinary cancers
		< 10	1.3 (29)	
		10–20	1.4 (57)	
		> 20	1.4 (17)	
Weir & Dunn (1970) USA 1954–62	Californian Study 68 153 men	Cig/day		
		1–9	1.5	
		10–20	2.8	
		≥ 21	5.4	
Cederlöf *et al.* (1975) Sweden 1963–72	Swedish Census Study 25 444 men, 26 467 women	Men		
		Cig/day		
		1–7	1.5 (6)	
		8–15	1.6 (6)	
		≥ 16	2.7 (6)	
		Women		
		Cig/day		
		1–7	1.2 (2)	
		8–15	2.1 (4)	
		≥ 16	0.8 (1)	
Doll & Peto (1976) UK 1951–71	British Doctors' Study 34 440 men	Cig/day		Relative risks, calculated by the Working Group, are ratios of age-adjusted annual death rates.
		1–14	2.2	
		15–24	2.2	
		> 25	1.4	
Hirayama (1977, 1985) Japan 1965–81	Six-prefecture Study 122 261 men	Current smoker	1.4 (59)	

Table 2.1.2.2 (contd)

Reference Country and years of study	Cohort study Subjects	Smoking categories	Relative risk (no. of cases or 95% CI)	Comments
Doll *et al*. (1980) UK 1951–1973	British Doctors' Study 6194 women	Current smoker	0.6 (5)	
Rogot & Murray (1980) USA 1954–69	US Veterans' Study 293 958 men	Current smoker	SMR 2.2 (326)	Standardized mortality ratio
Steineck *et al*. (1988) Sweden 1967–82 (14 years)	Swedish Twin Registry Study 16 477 persons	Men Cig/day		Adjusted for age
		1–9	4.5 (2.1–9.9)	
		≥ 10	4.7 (2.0–10.8)	
		Women Ever-smoker	1.6 (0.5–5.2)	
Akiba & Hirayama (1990) Japan 1965–81	Six-prefecture Study 122 261 men, 142 857 women	Men Cig/day		Adjusted for residence, age, occupation and observation period
		1–4	1.8 (0.4–5.0)	
		5–14	1.4 (0.9–2.3)	
		15–24	2.0 (1.3–3.3)	
		25–34	1.7 (0.6–4.1)	
		≥ 35	2.1 (0.5–6.1)	*p* for trend = 0.005
		Women		
		1–4	0.9 (0.1–4.0)	
		5–14	2.2 (1.1–4.1)	
		≥ 15	1.2 (0.1–5.7)	
Kuller *et al*. (1991) USA 1975–85	MRFIT Study 12 866 men		Mortality rate	Annual mortality rates/10 000 men; adjusted for age, blood pressure, cholesterol and ethnicity
		Nonsmoker	1.6 (39)	
		1–15	1.8 (5)	
		16–25	3.1 (13)	
		26–35	4.4 (12)	
		36–45	3.9 (9)	
		> 45	3.6 (3)	
Mills *et al*. (1991) USA 1976–82	Adventists' Health Study 34 198 men and women	1–14	1.6 (0.6–4.1)	Adjusted for age and sex
		15–24	4.3 (1.9–9.7)	
		≥ 25	3.3 (1.3–8.6)	
Chyou *et al*. (1993) USA 1954–80	American Men of Japanese Ancestry Study 8006 men	Pack–years		Adjusted for relevant variables
		> 0–30	2.1 (1.2–3.8)	
		> 30	2.3 (1.3–4.1)	*p* for trend = 0.004
Doll *et al*. (1994) UK 1951–91	British Doctors'Study 34 439 men	Cig/day	Mortality rate	Annual mortality rate per 100 000 men
		0	13	
		1–14	29	
		15–24	29	
		≥ 25	37	*p* for trend < 0.01

Table 2.1.2.2 (contd)

Reference Country and years of study	Cohort study Subjects	Smoking categories	Relative risk (no. of cases or 95% CI)	Comments
McLaughlin *et al*. (1995) USA 1954–80	US Veterans' Study 293 958 men	Cig/day 1–9 10–20 31–39 ≥ 40	 1.1 (0.8–1.5) 2.3 (1.9–2.7) 2.7 (2.2–3.3) 2.2 (1.5–3.3)	Adjusted for age and calendar period p for trend ≤ 0.01
Engeland *et al*. (1996) Norway 1966–93	Norwegian Cohort Study 11 857 men, 14 269 women	Men Cig/day 1–4 5–9 10–14 ≥ 15	 2.5 (1.5–4.0) 2.7 (1.6–4.5) 3.4 (2.1–5.4) 5.1 (3.1–8.4)	Adjusted for age
		Women Cig/day 1–4 5–9 10–14 ≥ 15	 1.5 (0.7–3.2) 2.2 (1.0–4.7) 5.4 (2.8–11) 7.9 (3.3–19)	
Murata *et al*. (1996) Japan 1984–93	Chiba Center Association Study 17 200 men	1–10 11–20 ≥ 21	2.6 2.3 1.3	Adjusted for age and county
Yuan *et al*. (1996) China 1986–93	Shanghai Men's Study 18 244 men	Cig/day < 20 ≥ 20	 2.1 1.7	Adjusted for age
Nordlund *et al*. (1997) Sweden 1963–89	Swedish Census Study 25 829 women	Cig/day 1–7 8–15 ≥ 16	 1.9 (0.98–3.6) 2.9 (1.4–5.8) 3.4 (1.2–9.7)	
Tulinius *et al*. (1997) Iceland 1968–95	Reykjavík Study 11 366 men	Cig/day 1–14 15–24 ≥ 25	 1.5 (0.7–3.0) 2.6 (1.4–4.7) 4.6 (2.4–6.9)	
Liaw & Chen (1998) China, Province of Taiwan 1982–94	Taiwanese Study 11 096 men	Smoker	0.5 (0.2–1.7)	Very small study

Table 2.1.2.3. Case–control studies on tobacco smoking and cancer of the lower urinary tract: intensity of smoking

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Lilienfeld *et al*. (1956)	Men	Nonsmoker	1.0 (51)	Crude risks calculated by the Working Group; unadjusted
USA		Smoker	2.1 (151)	
1945–55	Women	Nonsmoker	1.0 (108)	
		Smoker	0.4 (10)	
Lockwood (1961)	Men	Nonsmoker	1.0 (24)	Crude risks calculated by the Working Group
Denmark		1–10 g tobacco/day	1.3 (16)	
1956–57		11–20 g tobacco/day	3.3 (40)	
		21–30 g tobacco/day	9.5 (18)	
		≥ 31 g tobacco/day	15.8 (10)	
	Women	Nonsmoker	1.0 (49)	
		1–10 g tobacco/day	0.9 (8)	
		11–20 g tobacco/day	4.6 (4)	
		≥ 21 g tobacco/day	–	No cases or controls
Schwartz *et al*. (1961)	Men	Nonsmoker	1.0 (24)	Crude risks calculated by the Working Group
France		1–9	1.4 (31)	
1954 onwards		10–19	2.1 (69)	
		20–29	2.6 (63)	
		≥ 30	3.8 (15)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Wynder *et al*. (1963a) USA 1960–61	Men	Nonsmoker	1.0 (21)	Crude risks calculated by the Working Group
		1–9	2.1 (12)	
		10–15	1.5 (15)	
		16–20	2.8 (86)	
		21–34	5.2 (63)	
		≥ 35	5.7 (78)	
	Women	Nonsmoker	1.0 (43)	
		1–9	3.1 (9)	
		10–20	3.3 (14)	
		≥ 21	–	4 cases, 0 controls
Cobb & Ansell (1965) USA 1951–61	Men and women	Nonsmoker	1.0 (6)	Hospital controls with colon cancer only; heavy smokers smoked > 1 pack of cigarettes/day for ≥ 30 years; age-adjusted relative risks calculated by the Working Group
		Light and medium smoker	3.0 (21)	
		Heavy smoker	10.3 (104)	
Staszewski (1966) Poland 1958–64	Men	Nonsmoker	1.0 (10)	Nonsmoker included smokers of < 1 g tobacco per day for < 1 year.
		Smoker	2.7 (140)	
Dunham *et al*. (1968) USA 1958–64	Men			
	White	Nonsmoker	1.0 (55)	Crude risks calculated by the Working Group
		< 10	1.2 (19)	
		10–19	2.1 (76)	
		≥ 20	1.1 (114)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
	Black	Nonsmoker	1.0 (14)	
		< 10	0.9 (9)	
		10–19	2.7 (25)	
		≥ 20	1.9 (21)	
	Women			
	White	Nonsmoker	1.0 (77)	
		< 10	0.7 (6)	
		10–19	1.0 (12)	
		≥ 20	1.9 (17)	
	Black	Nonsmoker	1.0 (28)	
		< 10	1.0 (8)	
		10–19	1.0 (5)	
		≥ 20	1.9 (6)	
Anthony & Thomas (1970) UK 1958–67	Men aged 40–69 years	Nonsmoker	1.0 (18)	Only controls with surgical conditions considered; age-adjusted relative risks calculated by the Working Group
		< 15 g/day	0.7 (81)	
		≥ 15 g/day	1.1 (104)	
Cole *et al.* (1971) USA 1967–68	Men aged 20–89 years	Nonsmoker	1.0 (70)	Smoker defined as smoking at least 100 cigarettes in lifetime; amount considered is maximum amount smoked per day during life
		≤ ½ pack/day	1.0 (36)	
		½–1½ packs/day	2.0 (140)	
		1½–2½ packs/day	2.2 (85)	
		> 2½ packs/day	1.8 (25)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
	Women aged 20–89 years	Nonsmoker	1.0 (50)	
		≤ ½ pack/day	1.5 (13)	
		½–1½ packs/day	2.0 (30)	
		> 1½ packs/day	3.8 (12)	
Tyrrell *et al*. (1971)	Men	Nonsmoker	1.0 (7)	Crude relative risks calculated by the Working Group
		Smoker	3.7 (163)	
Ireland	Women	Nonsmoker	1.0 (31)	
1967–68		Smoker	0.8 (19)	
Makhyoun (1974)	Men with urinary bilharziasis	Nonsmoker	1.0 (66)	Moderate smokers: (average number of cigarettes per day × duration of smoking) = 300–600; heavy smokers: > 600; crude relative risks calculated by the Working Group
		Moderate smoker	1.5 (42)	
Egypt		Heavy smoker	1.4 (21)	
1966–71	Men without urinary bilharziasis	Nonsmoker	0 (15)	
		Moderate smoker	2.3 (41)	
		Heavy smoker	3.3 (28)	
Morgan & Jain (1974)	Men	Nonsmoker	1.0 (22)	
		1–14	2.6 (57)	
Canada		15–24	2.7 (42)	
		≥ 25	6.4 (37)	
	Women	Nonsmoker	1.0 (45)	
		1–14	1.2 (16)	
		15–24	1.1 (9)	
		≥ 25	4.4 (4)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Schmauz & Cole	Men	Nonsmoker	1.0 (4)	Cancer of the renal pelvis and ureter
(1974)		≤ ½ pack/day	1.2 (2)	
USA		½–1½ pack/day	1.3 (5)	
		1½–2½ packs/day	1.1 (2)	
		> 2½ packs/day	10.0 (5)	
Wynder &	Men	Nonsmoker	1.0 (65)	
Goldsmith		1–10	1.4 (0.9–2.2)	
(1977)		11–20	2.4 (1.7–3.3)	
USA		21–30	2.7 (1.8–4.1)	
1969–74		31–40	2.3 (1.5–3.4)	
		≥ 41	3.3 (2.1–5.3)	
	Women	Nonsmoker	1.0 (67)	
		1–10	1.7 (0.9–3.3)	
		11–20	2.3 (1.3–4.2)	
		≥ 21	2.4 (1.1–5.1)	
Miller *et al.*	Men	Nonsmoker	1.0	
(1978)		Ever-smoker	1.6	
Canada	Women	Nonsmoker	1.0	
		Ever-smoker	0.8	
Sadeghi *et al.*	Men	Nonsmoker	1.0 (17)	
(1979)		Smoker	2.0 (27)	
Iran				
1969–76				

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Howe *et al.* (1980) Canada 1974–76	Men	Nonsmoker	1.0	
		< 10	2.6 (1.7–4.4)	
		10–20	3.8 (2.6–6.0)	
		> 20	5.1 (3.5–8.6)	
	Women	Nonsmoker	1.0	
		≤ 15	2.3 (1.3–4.6)	
		> 15	2.6 (1.4–6.9)	
Tola *et al.* (1980) Finland 1975–76	Men	Nonsmoker	1.0 (19)	Crude relative risks calculated by the Working Group
		Ever-smoker	1.9 (114)	
	Women	Nonsmoker	1.0 (25)	
		Ever-smoker	5.4 (17)	
McCredie *et al.* (1982) Australia 1977–80	Men	Nonsmoker	1.0	Cancer of renal pelvis; first set of controls, 'contacts'; second set of controls, 'screening clinic'; relative risks adjusted for consumption of analgesics
		Smoker (contacts)	1.0 (0.2–4.3)	
		Smoker (screening clinic)	2.8 (0.7–10.4)	
	Women (cancer of renal pelvis)	Nonsmoker	1.0	
		Smoker (contacts)	2.2 (0.8–5.9)	
		Smokers (screening clinic)	7.0 (2.5–19.7)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Mommsen *et al*. (1982); Mommsen & Aagaard (1983); Mommsen *et al*. (1983) Denmark 1977–80	Men	Nonsmoker Smoker	1.0 1.9 (1.2–3.0)	Crude odds ratios; Figure 1 in Mommsen & Aagaard (1983) suggests that relative risks are around 6.5 for smokers of 201–300 and 9.5 for smokers of 301–400 (years × no. of cigarettes/day) during lifetime
	Women	Nonsmoker Smoker	1.0 1.9 (0.9–3.9)	
Najem *et al*. (1982) USA 1978	Men and women	Nonsmoker Smoker	1.0 2.0 (1.1–3.7)	Data not given separately
Cartwright *et al*. (1983) UK 1978–81		Duration of cigarette smoking (years)		Incident and prevalent cases considered together; reference category included nonsmokers (< 1000 cigarettes in lifetime)

Subjects	Cigarettes/day	≤ 5	6–15	16–25	26–35	36–45	≥ 46
Men	< 10	1.0	0.85	1.3	1.6	1.3	1.9
	10–20	1.0	1.8	1.8	1.5	1.7	1.8
	≥ 21	1.0	1.4	1.1	1.3	1.5	0.85
Women	< 10	1.0	2.4	1.2	1.4	1.4	1.6
	10–20	1.0	1.0	2.0	1.5	1.6	1.5
	≥ 21	Insufficient data					

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
McCredie *et al*. (1983) Australia 1977–82	Men	Nonsmoker	1.0	Cancer of the ureter; relative risks adjusted for phenacetin consumption and age
		1–249 kg tobacco in lifetime	1.9	
		≥ 250 kg tobacco in lifetime	4.6	
		Nonsmoker	1.0	Cancer of renal pelvis
		1–249 kg tobacco in lifetime	1.3	
		≥ 250 kg tobacco in lifetime	4.2	
McLaughlin *et al*. (1983) USA 1974–79	Men	Nonsmoker	1.0 (3)	Cancer of renal pelvis; smoking categories: light, ≤ 32 pack–years of cigarettes; moderate, 33–57; heavy, ≥ 58; relative risks adjusted for age and type of respondent (living case/control or next of kin)
		Light smoker	5.5 (1.4–25.5)	
		Moderate smoker	9.6 (2.5–43.4)	
		Heavy smoker	10.7 (2.7–48.9)	
	Women	Nonsmoker	1.0 (8)	
		Light smoker	4.9 (1.2–20.2)	
		Moderate smoker	7.6 (1.9–31.3)	
		Heavy smoker	11.1 (1.8–68.7)	
Møller-Jensen *et al*. (1983) Denmark 1979–81	Men	Nonsmoker	1.0 (9)	Crude relative risks calculated by the Working Group
		1–14	4.2 (82)	
		15–24	4.9 (112)	
		≥ 25	4.3 (54)	
	Women	Nonsmoker	1.0 (23)	
		1–14	2.0 (30)	
		≥ 15	2.5 (42)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Morrison *et al*. (1984) UK and Japan, 1976–78 USA, 1976–77	Boston area			
	Men	Nonsmoker	1.0 (53)	
		Current smoker		
		< 1 pack/day	1.4 (25)	
		1 pack/day	3.2 (91)	
		≥ 2 packs/day	4.7 (67)	
		Former and current smoker	1.9 (1.3–2.8)	
	Women	Nonsmoker	1.0 (49)	
		Current smoker		
		< 1 pack/day	4.3 (18)	
		≥ 1 pack/day	6.2 (48)	
		Former and current smoker	4.2 (2.5–7.1)	
	Manchester area			
	Men	Nonsmoker	1.0 (28)	
		Current smoker		
		< 1 pack/day	1.9 (85)	
		1 pack/day	3.2 (104)	
		≥ 2 packs/day	4.0 (31)	
		Former and current smoker	2.2 (1.4–3.5)	
	Women	Nonsmoker	1.0 (63)	
		Current smoker		
		< 1 pack/day	2.1 (40)	
		≥ 1 pack/day	2.2 (26)	
		Former and current smoker	1.3 (0.8–2.0)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
	Nagoya area			
	Men	Nonsmoker	1.0 (24)	
		Current smoker		
		< 1 pack/day	1.6 (47)	
		1 pack/day	2.1 (92)	
		≥ 2 packs/day	2.8 (33)	
		Former and current smoker	1.7 (1.1–2.9)	
	Women	Nonsmoker	1.0 (45)	
		Current smoker		
		< 1 pack/day	4.4 (11)	
		≥ 1 pack/day	4.2 (7)	
		Former and current smoker	4.3 (2.0–9.2)	
Vineis *et al*. (1984) Italy 1978–83	Men	Nonsmoker	1.0 (19)	
		1–14	4.0 (2.4–6.8)	
		15–29	5.7 (3.5–9.3)	
		≥ 30	10.1 (4.9–20.7)	
Rebekalos *et al*. (1985) Greece 1980–82	Men < 50–> 70 years	Never-smoker	1.0	
		1–10	1.6 (0.9–3.1)	
		11–20	2.9 (1.9–4.6)	
		21–30	4.4 (2.4–8.0)	
		≥ 31	4.4 (2.2–8.8)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
	Men and women	Never-smoker	1.0	
	< 59–> 70 years	1–10	1.6 (0.9–2.9)	
		11–20	2.8 (1.8–4.4)	
		21–30	4.4 (2.4–8.0)	
		≥ 31	4.4 (2.2–8.8)	
Claude *et al*.	Men	Nonsmoker	1.0	
(1986)		1–10	1.7 (1.1–2.7)	$p < 0.05$
Germany		11–20	2.4 (1.6–3.7)	$p < 0.01$
1977–82		> 20	3.2 (1.9–5.0)	$p < 0.001$
	Women	Nonsmoker	1.0	
		1–10	2.4 (1.1–5.5)	$p < 0.05$
		> 10	4.9 (1.3–18.8)	$p < 0.05$
Clavel *et al*.	Men	0	1.0	Adjusted for hospital, age and residence
(1989)		1–19	3.3 (2.1–5.1)	
France		20–39	4.4 (2.8–6.9)	
1984–87		≥ 40	6.9 (3.7–12.9)	
D'Avanzo *et al*.	Men	< 10	2.5 (1.1–6.0)	Adjusted for age
(1990)		10–19	2.3 (1.2–4.4)	
Italy		≥ 20	4.0 (2.3–6.8)	
1985–89				

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Harris *et al.* (1990) USA 1969 onwards	White men	Nonsmoker	1.0	Adjusted for age, education and years since quitting
		1–10	1.5 (1.1–2.2)	
		11–20	3.0 (2.5–3.7)	
		21–30	3.7 (3.0–4.5)	
		> 30	3.6 (3.0–4.4)	
	Black men	Nonsmoker	1.0	
		1–10	1.6 (0.7–3.6)	
		11–20	1.9 (0.9–3.9)	
		21–30	2.7 (1.1–6.6)	
		> 30	2.0 (0.7–5.9)	
	White women	Nonsmoker	1.0	
		1–10	1.7 (1.2–2.5)	
		11–20	3.3 (2.4–4.1)	
		21–30	4.7 (3.1–6.9)	
		> 30	2.3 (1.3–4.0)	
	Black women	Nonsmoker	1.0	
		Ever-smoker	3.9 (1.5–6.8)	
Burns & Swanson (1991) USA	White men	Nonsmoker	1.0	Adjusted for age
		1–19	1.7 (1.3–2.1)	
		20	2.4 (1.9–2.9)	
		> 20	2.6 (2.1–3.1)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
	Black men	Nonsmoker	1.0	
		1–19	2.3 (1.3–4.0)	
		20	3.6 (2.0–6.1)	
		> 20	4.3 (2.3–7.9)	
	White women	Nonsmoker	1.0	
		1–19	1.9 (1.4–2.5)	
		20	2.6 (2.0–3.4)	
		> 20	3.0 (2.1–4.1)	
	Black women	Nonsmoker	1.0	
		1–19	3.7 (2.0–6.7)	
		20	2.5 (1.1–5.6)	
		> 20	3.7 (1.4–9.5)	
De Stefani *et al*. (1991) Uruguay 1987–89	Men	Nonsmoker	1.0	Adjusted for age, residence, sex and hospital
		1–14	4.7 (1.3–16.9)	
		15–29	11.5 (3.3–40.6)	
		≥ 30	8.2 (2.2–30.2)	
Lopez-Abente *et al*. (1991) Spain 1983–86	Men	Nonsmoker	1.0	Adjusted for age and residence
		1–10	1.9 (1.1–3.2)	
		11–20	4.8 (3.0–7.8)	
		21–30	4.1 (2.4–7.1)	
		> 30	4.2 (2.1–8.4)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Kunze *et al.* (1992) Germany 1977–85	Men	Nonsmoker	1.0	Adjusted for sex and age
		1–9	1.7 (1.1–2.5)	
		10–19	2.5 (1.7–3.6)	
		20–29	3.6 (2.4–5.4)	
		30–39	9.3 (4.3–20.0)	
		≥ 40	1.9 (1.1–3.5)	
	Women	Nonsmoker	1.0	
		1–9	2.2 (1.1–4.7)	
		10–19	3.3 (1.2–9.2)	
		≥ 20	6.3 (1.7–22.9)	
McLaughlin *et al.* (1992) USA 1983–86		Ever-smoker	3.9 (2.1–7.3)	Adjusted for age and study area
		Current smoker	6.5 (1.2–12.7)	
	Men (*n* = 193)	< 20	3.2 (1.4–7.2)	Renal pelvis
		20–39	3.8 (1.9–7.6)	
		≥ 40	5.1 (2.4–10.9)	
	Women (*n* = 115)	Ever-smoker	2.0 (1.2–3.5)	
		Current smoker	2.4 (1.3–4.3)	
		< 20	1.4 (0.7–3.0)	
		20–39	2.7 (1.4–5.2)	
		≥ 40	3.4 (0.9–13.4)	
	Men (*n* = 138)	Ever-smoker	5.2 (2.4–11.9)	Ureter
		Current smoker	11.4 (4.4–31.5)	
		< 20	5.6 (2.0–16.0)	
		20–39	5.4 (2.3–13.1)	
		≥ 40	7.7 (2.6–24.7)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
	Women (*n* = 56)	Ever-smoker	3.1 (1.4–7.0)	
		Current smoker	4.1 (1.7–10.2)	
		< 20	2.4 (0.9–6.4)	
		20–39	4.2 (1.6–11.3)	
		≥ 40	3.7 (0.4–38.9)	
Hartge *et al*. (1993) USA 1978 onwards	Men			Adjusted for age, geographical area, occupational risk and pipe or cigar use
	Black	Never-smoker	1.0	
		< 20	2.2 (1.0–4.8)	
		≥ 20	4.5 (2.1–9.3)	
	White	Never-smoker	1.0	
		< 20	2.1 (1.7–2.6)	
		≥ 20	3.0 (2.6–3.6)	
	Women			
	Black	Never-smoker	1.0	
		< 20	1.7 (0.6–4.7)	
		≥ 20	2.1 (1.4–10)	
	White	Never-smoker	1.0	
		< 20	2.0 (1.5–2.7)	
		≥ 20	3.1 (2.4–4.2)	
	Men	Former smoker		
	Black	< 20	1.6 (0.7–3.9)	
		≥ 20	1.8 (0.8–4.1)	
	White	< 20	1.3 (1.1–1.6)	
		≥ 20	1.9 (1.6–2.2)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
	Women			
	Black	< 20	3.6 (1.0–13)	
		≥ 20	5.0 (0.9–28)	
	White	< 20	2.0 (1.4–2.7)	
		≥ 20	1.3 (0.9–2.0)	
Vena *et al*. (1993) USA 1979–85	White men	0–2 pack–years	1.0	Adjusted for age, education and consumption of coffee, other liquids, carbonated drinks, carotene and calorie intake
		3–28 pack–years	1.7 (1.1–2.6)	
		29–48 pack–years	2.1 (1.4–3.1)	
		49–144 pack–years	2.7 (1.8–4.0)	p for trend < 0.001
Hours *et al*. (1994) France 1984–87	Men and women	≤ 10 pack–years	1.0	Ward controls
		11–30 pack–years	2.5 (1.2–5.4)	
		> 30 pack–years	3.6 (1.9–7.0)	
		≤ 10 pack–years	1.0	General controls
		11–30 pack–years	1.7 (0.8–3.6)	
		> 30 pack–years	2.3 (1.2–4.3)	
Momas *et al*. (1994a) France 1987–89	Men	Lifetime no. of cigarettes		
		< 365	1.0	
		365–146 000	3.4 (1.6–7.8)	
		146 000–320 000	5.0 (2.4–10.7)	
		> 320 000	8.7 (4.2–17.8)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Momas *et al*. (1994b) France 1987–89	Men	1–10 11–30 > 30	3.6 (1.8–7.2) 5.9 (3.1–11.1) 8.4 (4.0–17.8)	Adjusted for age, occupation coffee intake, alcohol intake and diet
Sorahan *et al*. (1994) UK 1985–87	Men	< 10 10 20 30 ≥ 40	1.5 (1.0–2.1) 1.9 (1.4–2.6) 2.3 (1.8–3.0) 2.0 (1.4–2.8) 2.2 (1.5–3.3)	Adjusted for age
Vizcaino *et al*. (1994) Zimbabwe 1963–77	Men	Never-smoker Former smoker Current smoker < 15 g tobacco/day ≥ 15 g tobacco/day	1.0 0.3 (0.1–1.4) 1.1 (0.8–1.4) 1.0 (0.7–1.3) 1.4 (0.9–2.3)	Adjusted for age group, province, past history of bilharzia, education and drinking habits
	Women	Never-smoker Ever-smoker	1.0 1.4 (0.4–4.7)	Adjusted for age group, province, bilharzia and education
McCarthy *et al*.(1995) USA 1975–92	Men and women	< 14 15–24 > 24	1.5 (0.9–2.6) 1.6 (1.1–2.4) 2.0 (1.3–3.1)	Adjusted for sex and age

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Donato *et al*.		Lifetime no. of cigarettes		
(1997)	Men	1000–99 000	1.8 (0.6–4.9)	Adjusted for age, residence, education, date
Italy		100 000–199 000	5.7 (2.4–13.7)	of interview, and coffee and alcohol intake
1991–92		200 000–299 000	7.2 (2.9–17.8)	
		≥ 300 000	11.1 (4.7–26.4)	
	Women	1000–99 000	6.6 (1.8–24.7)	
		100 000–199 000	7.1 (1.4–36.9)	
		≥ 200 000	12.6 (2.0–77)	
Bedwani *et al*.	Men	Never-smoker	1.0	Adjusted for age, education, type of house,
(1998)		Current smoker	6.6 (3.1–13.9)	history of schistosomiasis and high-risk
Egypt		< 20	5.4 (2.4–12.1)	occupation; *p* for trend < 0.001
1994–96		≥ 20	7.6 (3.4–16.8)	
Pohlabeln *et al*.	Men	1–9	2.5 (1.4–4.5)	Adjusted for age, sex and residence
(1999)		10–19	2.6 1.4–4.9)	
Germany		≥ 20	3.4 (1.8–6.2)	
1989–92				
Pommer *et al*.	Men and women	Never/rare	1.0	Adjusted for age and sex [results for
(1999)		Former smoker	1.6 (1.1–2.2)	bladder; results also given for renal pelvis
Germany		Current smoker	3.2 (2.3–4.5)	and renal pelvis or ureter]
1990–94				

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Castelao *et al*. (2001) USA 1987–96	Men	< 10	1.2 (0.8–1.8)	Adjusted for age, occupation, diet and medical drugs
		10–< 20	1.4 (1.0–2.0)	
		20–< 30	2.2 (1.7–2.8)	
		30– <40	3.1 (2.3–4.2)	
		≥ 40	4.0 (3.0–5.3)	
	Women	< 10	1.7 (1.0–3.0)	
		10–< 20	2.0 (1.2–3.3)	
		20–< 30	3.2 (2.1–4.9)	
		30–< 40	6.9 (2.8–16.9)	
		≥ 40	4.2 (2.2–7.7)	
Non-transitional-cell bladder cancer				
Fortuny *et al*. (1999) Europe 1983–95	Men and women	Former smoker		Pooled analysis; adjusted for age, gender and study centre
		0.06–21.51 pack–years	1.6 (0.8–3.0)	
		21.52–40.51 pack–years	1.4 (0.6–3.3)	
		≥ 40.52 pack–years	1.6 (0.7–3.9)	
		Current smoker		
		0.06–21.51 pack–years	2.2 (1.0–4.8)	
		21.52–40.51 pack–years	2.7 (1.3–5.6)	
		≥ 40.52 pack-years	7.0 (3.6–13.7)	

Table 2.1.2.3 (contd)

Reference Country and years of study	Subjects	Smoking categories[a]	Relative risk (no. of cases/deaths or 95% CI)	Comments
Combined analysis				
Brennan *et al*. (2000, 2001) Europe 1976–96	Men	1–2	1.0	Adjusted for age, centre and duration of smoking
		3–4	1.6 (0.9–2.8)	
		5–9	2.1 (1.3–3.5)	
		10–14	2.4 (1.5–4.0)	
		15–19	3.0 (1.8–5.0)	
		20–24	3.1 (1.8–5.3)	
		25–29	3.2 (1.9–5.5)	
		30–34	3.2 (1.8–5.8)	
		35–39	2.8 (1.6–5.8)	
		≥ 40	3.1 (1.7–5.5)	
	Women	1–4	1.0	
		5–9	1.4 (0.9–2.2)	
		10–14	1.6 (1.0–2.7)	
		15–19	1.6 (1.0–2.7)	
		20–24	1.6 (0.7–4.1)	
		25–29	1.8 (0.6–5.1)	
		≥ 30	1.6 (0.6–4.0)	

[a] Cigarettes/day, unless otherwise specified

Table 2.1.2.4. Studies on tobacco smoking and cancer of the bladder: duration of smoking and age at starting smoking

Reference Country and years of study	Subjects	Duration/age at starting smoking (years)	Relative risk (95% CI)	*p* for trend
Cohort studies				
Mills *et al*. (1991) USA 1976–82	Adventists' Health Study 34 198 men and women	Duration		
		< 5	1.9 (0.6–5.7)	
		5–14	0.9 (0.2–4.0)	
		≥ 15	4.2 (2.1–8.4)	0.0006
Nordlund *et al*. (1997) Sweden, Swedish Census Study II 1964–89	Swedish Census Study 25 829 women	Age at starting smoking		
		20–23	3.3 (1.2–9.2)	0.018
		≤ 19	3.4 (1.2–9.5)	
Case–control studies				
Burch *et al*. (1989) Canada 1979–82		Duration		
	Men	1–10	1.6 (0.9–2.7)	
		11–20	1.5 (0.9–2.5)	
		21–30	1.8 (1.2–2.9)	
		≥ 31	2.3 (1.6–3.4)	< 0.001
	Women	1–10	0.8 (0.3–2.0)	
		11–20	1.1 (0.5–2.8)	
		21–30	3.4 (1.4–7.9)	
		≥ 31	2.2 (1.3–3.7)	< 0.001
		Age at starting smoking		
	Men	≥ 20	1.6 (1.1–2.4)	0.025
		15–19	2.3 (1.6–3.3)	
		< 15	2.4 (1.6–3.6)	
	Women	≥ 20	1.5 (0.9–2.5)	0.044
		15–19	2.7 (1.4–5.0)	
		< 15	2.4 (0.9–6.4)	
Claude *et al*. (1986) Germany 1977–82	Women	Duration		
		0	1.0	
		1–20	5.4 (1.4–21.0)	$p < 0.05$
		21–40	1.1 (0.4–3.1)	
		> 40	10.4 (1.9–56.0)	$p < 0.01$

Table 2.1.2.4 (contd)

Reference Country and years of study	Subjects	Duration/age at starting smoking (years)	Relative risk (95% CI)	*p* for trend
Clavel *et al.* (1989) France 1984–87	Men	Duration		
		1–9	1.8 (0.9–3.6)	
		10–19	1.9 (1.0–3.5)	
		20–29	2.8 (1.7–4.8)	
		30–39	5.2 (3.22–8.39)	
		40–49	5.2 (3.2–8.5)	
		≥ 50	4.8 (2.6–8.9)	< 0.001
		Age at starting smoking		
		> 30	2.0 (0.8–5.0)	< 0.001
		25–30	1.5 (0.6–3.4)	
		21–24	3.5 (2.0–6.4)	
		18–20	4.0 (2.6–6.2)	
		≤ 17	4.9 (3.1–7.8)	
D'Avanzo *et al.* (1990) Italy 1985–89		Duration		
	Men	< 30	1.7 (0.9–3.1)	
		≥ 30	3.1 (1.9–4.9)	
	Women	< 30	1.5 (0.3–6.8)	
		≥ 30	4.6 (1.6–13.8)	
		Age at starting smoking		
	Men and women	> 20	1.8 (0.9–3.8)	
		≤ 20	2.7 (1.8–4.1)	
Burns & Swanson (1991) USA	Men	Duration		
	White	1–10	1.1 (0.7–1.7)	
		11–20	1.3 (0.9–1.8)	
		21–30	2.0 (1.5–2.6)	
		31–40	2.3 (1.8–2.9)	
		> 40	2.9 (2.3–3.5)	
	Black	1–10	2.1 (0.7–6.4)	
		11–20	2.0 (0.7–5.5)	
		21–30	1.9 (0.9–4.0)	
		31–40	2.4 (1.2–4.6)	
		> 40	4.1 (2.4–6.8)	
	Women			
	White	1–10	0.8 (0.4–1.6)	
		11–20	1.1 (0.6–2.0)	
		21–30	1.6 (0.9–2.8)	
		31–40	2.5 (1.9–3.5)	
		> 40	3.3 (2.5–4.3)	

Table 2.1.2.4 (contd)

Reference Country and years of study	Subjects	Duration/age at starting smoking (years)	Relative risk (95% CI)	*p* for trend
	Black	1–10	0.6 (0.1–4.5)	
		11–20	1.6 (0.3–8.1)	
		21–30	2.9 (1.1–7.5)	
		31–40	2.0 (0.8–4.8)	
		> 40	7.4 (3.8–14.2)	
De Stefani *et al.* (1991) Uruguay 1987–89	Men	Duration		
		1–29	2.7 (0.6–11.6)	
		30–39	9.5 (2.3–39.4)	
		40–49	9.4 (2.6–34.2)	
		≥ 50	8.7 (2.5–30.7)	< 0.001
		Age at starting smoking		
		≥ 20	1.0	
		15–19	2.1 (0.9–4.6)	
		≤ 14	1.8 (0.8–4.2)	0.24
Lopez-Abente *et al.* (1991) Spain 1983–86	Men	Duration		
		1–19	1.8 (0.9–3.5)	
		20–39	3.9 (2.4–6.5)	
		40–59	4.7 (2.9–7.5)	
		≥ 60	4.4 (2.0–9.8)	< 0.0001
Kunze *et al.* (1992) Germany 1977–85		Duration		
	Men	1–19	1.1 (0.7–1.7)	
		20–39	2.6 (1.6–3.3)	
		≥ 40	3.7 (2.6–5.3)	
	Women	1–19	3.8 (1.4–10.3)	
		20–39	1.3 (0.5–3.4)	
		≥ 40	5.6 (2.0–15.4)	
		Age at starting smoking		
	Men	≥ 21	2.2 (1.6–3.2)	
		16–20	2.6 (1.8–3.6)	
		≤ 15	6.2 (3.4–11.1)	
	Women	≥ 21	2.5 (1.3–5.0)	
		16–20	4.8 (1.7–13.3)	
		≤ 15	1.6 (0.2–12.2)	

Table 2.1.2.4 (contd)

Reference Country and years of study	Subjects	Duration/age at starting smoking (years)	Relative risk (95% CI)	*p* for trend
McLaughlin *et al.* (1992)[a] USA 1983–86		Duration		
	Men	< 26	2.4 (1.1–5.5)	
		26–37	3.1 (1.5–6.7)	
		38–45	4.7 (2.1–10.7)	
		≥ 46	5.9 (2.6–13.7)	< 0.001
	Women	< 26	0.9 (0.3–2.2)	
		26–37	1.4 (0.6–3.4)	
		38–45	2.2 (1.0–4.9)	
		≥ 46	7.9 (2.8–22.6)	< 0.001
		Age at starting smoking		
	Men	≥ 25	0.4 (0.7–6.6)	0.10
		15–24	1.2 (2.3–8.4)	
		≤ 14	1.0	
	Women	≥ 25	0.4 (0.0–7.2)	0.002
		15–24	1.0 (0.1–7.4)	
		≤ 14	1.0	
Momas *et al.* (1994b) France 1987–89	Men	Duration		
		1–39	2.9 (1.2–6.8)	
		40–55	5.3 (2.8–9.9)	
		> 55	7.1 (3.3–15.2)	< 0.0001
		Age at starting smoking		
		≥ 21	4.6 (2.0–10.4)	
		17–20	4.9 (2.6–9.2)	
		13–16	5.4 (2.8–10.6)	
		≤ 12	20.3 (6.9–59.8)	
Sorahan *et al.* (1994) UK 1985–87	Men	Duration		
		1–9	0.9 (0.6–1.5)	
		10–19	1.4 (1.0–1.9)	
		20–29	1.8 (1.4–2.5)	
		30–39	2.5 (1.8–3.3)	
		> 40	2.9 (2.2–3.8)	< 0.001
		Age at starting smoking		
		≥ 21	2.0 (1.4–2.8)	0.175
		17–20	1.9 (1.4–2.4)	
		7–16	2.3 (1.7–2.9)	

Table 2.1.2.4 (contd)

Reference Country and years of study	Subjects	Duration/age at starting smoking (years)	Relative risk (95% CI)	*p* for trend
Pohlabeln *et al*. (1999) Germany 1989–92	Men	Duration		
		1–19	1.8 (0.9–3.3)	
		20–39	2.8 (1.5–5.2)	
		≥ 40	5.0 (2.6–9.6)	
		Age at starting smoking		
		≥ 21	2.1 (1.1–3.9)	
		16–20	3.0 (1.7–5.4)	
		≤ 15	3.4 (1.6–7.2)	
	Women	Duration		
		1–19	5.2 (0.9–30.7)	
		20–39	5.7 (1.0–32.2)	
		≥ 40	5.2 (0.9–30.7)	
		Age at starting smoking		
		≥ 21	2.4 (0.6–9.9)	
		≤ 20	16.6 (2.0–136.7)	
Castelao *et al*. (2001) USA 1987–96	Men	Duration		Adjusted by age, medical drugs, occupation, diet
		Never-smoker	1.0	
		< 10	1.2 (0.8–1.7)	
		10–19	1.4 (1.1–1.9)	
		20–29	2.4 (1.8–3.2)	
		30–39	3.3 (2.5–4.3)	
		≥ 40	4.2 (3.1–5.6)	
	Women	Duration		
		Never-smoker	1.0	
		< 10	0.8 (0.4–1.7)	
		10–19	1.5 (0.9–2.8)	
		20–29	2.3 (1.4–3.9)	
		30–39	5.4 (3.2–9.2)	
		≥ 40	6.0 (3.1–11.7)	
Brennan *et al*. (2000, 2001) Europe 1976–96	Men	Duration	*1–9 cigarettes/day*	
		1–9	1.3 (0.8–1.9)	
		10–19	2.0 (1.4–2.8)	
		20–29	2.0 (1.4–2.7)	
		30–39	2.2 (1.7–2.9)	
		≥ 40	3.2 (2.6–4.1)	
			10–19 cigarettes/day	
		1–9	1.4 (0.7–2.5)	
		10–19	2.1 (1.5–2.9)	
		20–29	2.8 (2.1–3.6)	
		30–39	4.3 (3.5–5.2)	
		≥ 40	5.1 (4.3–6.1)	

Table 2.1.2.4 (contd)

Reference Country and years of study	Subjects	Duration/age at starting smoking (years)	Relative risk (95% CI)	*p* for trend
			20–29 cigarettes/day	
		1–9	0.9 (0.3–3.2)	
		10–19	1.5 (0.8–3.0)	
		20–29	3.6 (2.5–5.3)	
		30–39	5.8 (4.3–7.8)	
		≥ 40	5.7 (4.4–7.4)	
			≥ 30 cigarettes/day	
		1–9	0.4 (0.1–3.5)	
		10–19	2.2 (1.2–3.9)	
		20–29	4.2 (2.8–6.4)	
		30–39	4.3 (3.1–6.0)	
		≥ 40	5.2 (3.9–6.9)	
	Women	Duration		Adjusted for age, centre and number of cigarettes/day
		1–9	1.0	
		10–19	1.2 (0.6–2.3)	
		20–29	1.3 (0.7–2.5)	
		30–39	1.9 (1.1–3.5)	
		≥ 40	2.0 (1.1–3.5)	

CI, confidence interval
[a] Renal pelvis; similar data available for ureter

Table 2.1.2.5. Studies on tobacco smoking and cancer of the bladder: smoking cessation

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)	*p* for trend/Comments
Cohort studies				
Kahn (1966) USA 1954–62	US Veterans' Study 293 958 men	Current smoker Former smoker	2.2 (82) 1.6 (51)	 *p* for trend < 0.01
Doll & Peto (1976) UK 1957–71	British Doctors' Study 34 440 men	 Current smoker Former smoker	Mortality ratio [2.1] (80) [1.2]	Ratios of annual mortality rates per 100 000 men
Rogot & Murray (1980) USA 1954–69	US Veterans Study 293 958 men	 Current smoker Former smoker	SMR 2.2 (326) 1.4 (126)	Standardized mortality ratio
Steineck *et al*. (1988) Sweden 1967–82 (14 years)	Swedish Twin Registry Study 16 477 persons	Former smoker Ever-smoker	1.9 (0.8–4.7) 3.3 (1.7–6.7)	Analysis for men only
Mills *et al*. (1991) USA 1976–82	Adventist Health Study 34 198 men and women	Former smoker Current smoker	2.4 (1.3–4.7) 5.7 (1.7–18.6)	 *p* for trend = 0.001
Chyou *et al*. (1993) USA 1965–95	American Men of Japanese Ancestry Study 8006 men	Former smoker Current smoker	1.4 (0.7–2.6) 2.9 (1.7–4.9)	
Doll *et al.* (1994) UK 1951–91	British Doctors' Study 34 439 men	 Former smoker Current smoker	Mortality rate 13 21	Annual mortality rate per 100 000 men

Table 2.1.2.5 (contd)

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)	*p* for trend/Comments
Mc Laughlin *et al.* (1995) USA 1954–80	US Veterans' Study 293 958 men	Former smoker Current smoker	1.3 (1.1–1.6) 2.2 (1.9–2.6)	
Engeland *et al*. (1996) Norway 1966–93	Norwegian Cohort Study 11 857 men, 14 269 women	Former smoker Men Women	 2.1 (1.3–3.2) 1.5 (0.6–3.5)	Relative risks for current smoker by no. of cigarettes/day are given in Table 2.1.2.2.
Nordlund *et al*. (1997) Sweden 1963–89	Swedish Census Study 25 829 women	Former smoker Current smoker	2.5 (1.1–5.9) 2.3 (1.4–3.8)	
Tulinius *et al.* (1997) Iceland 1968–95	Reykjavík Study 11 580 men	Former smoker	2.3 (1.4–3.9)	Relative risks for current smoker by no. of cigarettes/day are given in Table 2.1.2.2.
Case–control studies				
Anthony & Thomas (1970) UK 1958–67	Men	Current smoker Fomer smoker	0.9 (185) 1.2 (43)	Age-adjusted relative risks calculated by the Working Group

Table 2.1.2.5 (contd)

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)	*p* for trend/Comments
Tyrell *et al*. (1971) Ireland 1967–68	Men	0	3.9 (129)	Crude relative risks calculated by the Working Group
		0.1–3.9	1.5 3)	
		4.0–6.9	2.9 (5)	
		7.0–12.9	4.1 (6)	
		13.0–21.9	6.2 (9)	
		≥ 22.0	2.7 (11)	
Wynder & Goldsmith (1977) 1969–74	Men	1–3	2.6 (1.6–4.5)	
		4–6	2.9 (1.7–5.2)	
		7–9	1.5 (0.8–3.0)	
		10–12	1.6 (0.8–3.1)	
		13–15	1.2 (0.6–2.5)	
		≥ 16	1.1 (0.7–1.8)	
Howe *et al*. (1980) Canada 1974–76	Men	Current smoker	1.0	Relative risks calculated by the Working Group from logistic regression coefficients
		2–15	0.6 (0.4–0.9)	
		> 15	0.5 (0.4–0.8)	
	Women	Current smoker	1.0	
		Former smoker	0.2 (0.1–0.5)	
Cartwright *et al*. (1983) UK 1978–81	Men (current and former smokers)	≤ 5	1.7	
		6–15	1.0	
		16–25	1.1	
		26–35	0.9	
		> 35 and never-smoker	1.0 (reference)	

Table 2.1.2.5 (contd)

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)	*p* for trend/Comments
McLaughlin *et al*. (1983)[b] USA 1974–79	Men	Current and former smokers	7.6 (47)	
		≥ 10	4.3	
	Women	Current and former smokers	5.8 (16)	
		≥ 10	3.9	
Morrison *et al*. (1984) Japan and UK, 1976–78 USA, 1976–77	Men, former smokers			Relative risks adjusted for intensity of smoking
	Boston area	Versus nonsmokers	1.5 (191)	
		Versus current smokers	0.5 (0.4–0.8)	
	Manchester area	Versus nonsmokers	1.8 (150)	
		Versus current smokers	0.7 (0.5–0.9)	
	Nagoya area	Versus nonsmokers	1.0 (28)	
		Versus current smokers	0.5 (0.3–0.8)	
	Women, former smokers			
	Boston	Versus nonsmokers	3.4 (50)	
	Manchester	Versus nonsmokers	0.7 (26)	
Vineis *et al*. (1984) Italy 1978–83	Men aged < 60	0–2	10.2 (5.0–21.2)	
		3–9	3.3 (1.2–9.2)	
		10–14	1.6 (0.3–8.2)	
		≥ 15	1.9 (0.5–7.9)	
	Men aged > 60	0–2	3.8 (2.0–7.2)	
		3–9	2.8 (1.2–6.6)	
		10–14	2.4 (0.9–6.3)	
		≥ 15	2.5 (1.0–5.8)	

Table 2.1.2.5 (contd)

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)	*p* for trend/Comments
Clavel *et al*. (1989) France 1984–87	Men	0–2 (reference)	1.0	
		3–9	1.0 (0.6–1.3)	
		10–14	0.7 (0.4–1.2)	
		≥ 15	0.4 (0.3–0.6)	< 0.001
Burch *et al*. (1989) Canada 1979–82	Men	1–5	1.1 (0.6–1.9)	
		> 5–10	0.8 (0.4–1.7)	
		> 10	1.4 (0.7–2.8)	0.16
		Current	1.6 (0.8–3.0)	
	Women	1–5	0.4 (0.2–1.2)	
		> 5–10	0.7 (0.1–4.1)	
		> 10	0.8 (0.2–3.7)	0.09
		Current	1.0 (0.3–3.4)	
Harris *et al*. (1990) USA 1969 onwards	White men	Former	2.1 (1.7–2.6)	
		Current	3.2 (2.6–3.9)	
	Black men	Former	1.6 (0.8–3.4)	
		Current	2.0 (1.0–3.9)	
	White women	Former	1.3 (1.0–1.8)	
		Current	3.2 (2.4–4.1)	
	Black women	NA		
D'Avanzo *et al*. (1990) Italy 1985–89	Men and women	> 15	1.2 (0.6–2.5)	
		5–14	1.8 (1.0–3.2)	< 0.01
		2–14	3.1 (1.6–6.2)	

Table 2.1.2.5 (contd)

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)	p for trend/Comments
De Stefani *et al*. (1991) Uruguay 1987–89	Men	1–4	0.5 (0.2–1.3)	
		5–9	0.5 (0.2–1.3)	
		≥ 10	0.4 (0.2–0.8)	0.009
López–Abente *et al*. (1991) Spain 1983–86	Men	0–5	4.4 (2.8–7.0)	
		6–15	3.0 (1.7–5.2)	
		≥ 16	2.4 (1.3–4.3)	< 0.0001
Kunze *et al*. (1992) Germany 1977–85	Men	1–9	1.3 (0.9–1.8)	
		10–19	0.7 (0.5–1.0)	
		≥ 20	0.6 (0.4–0.9)	
	Women	1–9	0.8 (0.3–2.7)	
		10–19	1.7 (0.4–7.0)	
		≥ 20	2.2 (0.8–6.3)	
Mc Laughlin *et al*. (1992)[b] USA 1983–86	Men	Current smoker (reference)	1.0	
		< 10	0.5 (0.1–1.6)	
		10–24	0.3 (0.2–0.6)	
		≥ 25	0.2 (0.1–0.6)	< 0.001
	Women	Current smoker (reference)	1.0	
		< 10	1.1 (0.3–4.2)	
		10–24	0.4 (0.1–1.2)	
		≥ 25	0.7 (0.1–4.7)	0.10

Table 2.1.2.5 (contd)

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)	*p* for trend/Comments
Momas *et al*. (1994b) France 1987–89	Men	≤ 2 3–15 > 15	5.0 (2.6–9.7) 7.1 (3.6–13.9) 4.6 (2.3–9.1)	
Sorahan *et al*. (1994) UK 1985–87	Men	Current smoker 1–9 10–19 ≥ 20	3.1 (2.4–4.1) 1.9 (1.4–2.6) 1.5 (1.1–2.1) 1.2 (0.9–1.7)	
Mc Carthy *et al*. (1995) USA 1975–92	Men and women	Former smoker Current smoker	1.3 (1.0–1.7) 1.7 (1.2–2.3)	
Donato *et al*. (1997) Italy 1991–92	Men	Former smoker Current smoker	4.8 (2.2–10.7) 8.4 (3.7–19)	
Bedwani *et al*. (1998) Egypt 1994–96	Men	< 10 ≥ 10	5.8 (1.6–21.0) 3.4 (1.0–10.7)	Adjusted for age, education, type of house, history of schistosomiasis, high-risk occupation
Pohlabeln *et al*. (1999) Germany 1989–92	Men	Former smoker (1–9) Fomer smoker (> 10) Current smoker	3.4 (1.6–6.9) 1.7 (0.9–3.0) 5.2 (2.7–9.7)	
	Women	Former smoker Current smoker	5.2 (1.3–20.2) 5.6 (1.1–27.3)	

Table 2.1.2.5 (contd)

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)	*p* for trend/Comments
Pommer *et al*. (1999) Germany 1990–94	Men women	Former smoker	1.6 (1.1–2.2)	
		Current smoker	3.2 (2.3–4.5)	
Castelao *et al*. (2001) USA 1987–96	Men	Never-smoker (reference)	1.0	
		Ever-smoker	2.5 (2.1–3.0)	
		Former smoker	1.7 (1.4–2.1)	
		< 10	2.3 (1.8–2.9)	
		10–19	1.9 (1.5–2.5)	
		≥ 20	1.1 (0.9–1.5)	< 0.001
		Current smoker	3.6 (2.8–4.6)	
	Women	Never-smoker (reference)	1.0	
		Ever-smoker	2.8 (2.0–4.0)	
		Former smoker	1.5 (1.0–2.4)	
		< 10	2.7 (1.5–4.8)	
		10–20	1.1 (0.6–2.1)	
		≥ 20	1.1 (0.6–2.0)	0.008
		Current smoker	4.6 (3.0–7.0)	
Combined analyses				
Fortuny *et al*. (1999) Europe 1983–85	Men and women	Nonsmoker	1.0	Adjusted for age, gender, study centre
		Former smoker	1.4 (0.8–2.5)	Non-cancer controls
		Current smoker	3.6 (2.1–6.3)	
		Former smoker	0.6 (0.3–1.3)	Cancer controls
		Current smoker	0.8 (0.4–1.4)	

Table 2.1.2.5 (contd)

Reference Country and years of study	Subjects	Years since cessation[a]	Relative risk (no. of cases or 95% CI)			
			Average consumption (cigarettes/day)[c]			
			1–9	10–19	20–29	≥ 30
Brennan *et al*. (2000, 2001) Europe 1976–96	Men	Current smoker	1.0	1.0	1.0	1.0
		1–4	0.64 (0.53–0.79)	1.01 (0.36–2.82)	0.62 (0.43–0.89)	0.67 (0.52–0.86)
		5–9	0.67 (0.55–0.82)	0.21 (0.05–0.95)	0.63 (0.47–0.85)	0.87 (0.66–1.16)
		10–14	0.61 (0.50–0.75)	0.57 (0.25–1.28)	0.65 (0.49–0.86)	0.76 (0.54–1.08)
		15–19	0.46 (0.36–0.59)	0.61 (0.29–1.27)	0.57 (0.41–0.79)	0.33 (0.17–0.65)
		20–24	0.45 (0.35–0.58)	0.50 (0.25–1.01)	0.58 (0.39–0.78)	0.82 (0.27–2.47)
		> 24	0.37 (0.30–0.45)	0.57 (0.34–0.97)	0.49 (0.34–0.70)	0.65 (0.24–1.78)
		Nonsmoker	0.20 (0.17–0.24)	0.34 (0.21–0.55)	0.21 (0.17–0.26)	0.20 (0.16–0.23)
	Women	Current smoker	1.0			
		< 5	0.63 (0.28–1.1)			
		5–9	0.56 (0.28–1.1)			
		10–14	0.52 (0.26–1.0)			
		15–19	1.1 (0.53–2.2)			
		20–24	0.52 (0.23–1.2)			
		> 24	0.84 (0.48–1.5)			
		All former smokers	0.67 (0.48–0.93)			

[a] The reference category is nonsmoker, unless otherwise specified.
[b] Cancer of the renal pelvis, similar results obtained for cancer of the ureter
[c] Adjusted for age, centre and number of cigarettes per day

Table 2.1.2.6. Case–control studies on tobacco smoking and cancer of the lower urinary tract: type of tobacco and inhalation

Reference Country and years of study	Subjects	Type of tobacco/type of inhalation	Relative risk[a] (95% CI or no. of cases/deaths)	Comments/*p* for trend
Lockwood (1961) Denmark 1956–57	Men	Non-inhalers (ref.) Inhalers	1.0 [0.7] (65)	Age-adjusted relative risks calculated by the Working Group
Cole *et al*. (1971) USA 1967–68	Men	Non-inhalers (ref.) Somewhat inhalers Deep inhalers	1.0 1.0 1.4	
	Women	Non-inhalers (ref.) Somewhat inhalers Deep inhalers	1.0 1.8 2.5	
Howe *et al*. (1980) Canada 1974–76	Men	Inhale untipped moderately Inhale untipped heavily Inhale filter-tipped moderately Inhale filter-tipped heavily	0.7 1.1 1.2 1.1	Calculated by the Working Group from regression coefficients; reference category is all other smokers of the same amount
	Women	Inhale untipped moderately Inhale untipped heavily Inhale filter-tipped moderately Inhale filter-tipped heavily	1.1 0.8 1.1 2.4	

Table 2.1.2.6 (contd)

Reference Country and years of study	Subjects	Type of tobacco/type of inhalation	Relative risk[a] (95% CI or no. of cases/deaths)	Comments/*p* for trend
Morrison *et al*. (1984) UK and Japan, 1976–78 USA, 1976–77	Men			Relative risks are for deep inhalers versus inhaling somewhat or not at all and adjusted for current intensity of smoking
	Boston area	Non-inhalers (ref.)	1.0	
		Inhalers	1.4 (0.8–2.3)	
	Manchester area	Non-inhalers (ref.)	1.0	
		Inhalers	1.3 (0.8–1.9)	
	Nagoya area	Non-inhalers (ref.)	1.0	
		Inhalers	1.4 (1.0–2.1)	
	Women			
	Boston area	Non-inhalers (ref.)	1.0	
		Inhalers	2.4 (0.7–7.8)	
	Manchester area	Non-inhalers (ref.)	1.0	
		Inhalers	0.7 (0.3–1.8)	
Burch *et al*. (1989) Canada 1979–82	Men	Non-inhalers	1.1 (0.7–2.0)	
		Somewhat inhalers	1.4 (0.9–2.2)	
		Deep inhalers	1.5 (0.9–2.4)	0.11
	Women	Non-inhalers	0.9 (0.4–2.2)	
		Somewhat inhalers	0.7 (0.3–1.6)	
		Deep inhalers	0.4 (0.1–1.0)	0.028
Clavel *et al*. (1989) France 1984–87	Men	Blond	1.9 (1.2–2.9)	
		Mixed	3.0 (1.6–5.7)	
		Black	4.4 (2.3–8.3)	
		Non-inhalers	2.1 (1.3–3.4)	
		Inhalers	5.7 (3.7–8.8)	

Table 2.1.2.6 (contd)

Reference Cuntry and years of study	Subjects	Type of tobacco/type of inhalation	Relative risk[a] (95% CI or no. of cases/deaths)	Comments/*p* for trend
D'Avanzo *et al*. (1990) Italy 1985–89	Men and women	Blond/mixed Black	2.7 (1.8–4.0) 3.8 (2.0–7.4)	
De Stefani *et al*. (1991) Uruguay 1987–89	Men	Blond Mixed Black	1.0 2.4 (1.0–5.6) 2.7 (1.3–5.4)	
López-Abente *et al*. (1991) Spain 1983–86	Men	No inhalation Moderate inhalation Deep inhalation Blond Black	1.5 (0.9–2.7) 3.7 (2.2–6.2) 4.9 (3.0–7.8) 3.2 (1.5–6.6) 3.7 (2.4–5.8)	
Momas *et al*. (1994b) France 1987–89	Men	Blond Black	3.1 (1.3–7.8) 6.7 (3.1–10.4)	
Castelao *et al*. (2001) USA 1987–86	Men and women	Light inhalation (ref.) Moderate inhalation Deep inhalation	1.0 1.2 (0.9–1.6) 1.1 (0.5–1.8)	

[a] Unless otherwise specified, the reference is nonsmoker.

Table 2.1.2.7. Case–control studies on tobacco smoking and cancer of the lower urinary tract: type of cigarette

Reference Country and years of study	Subjects	Use of filter-tipped cigarettes	Relative risk (95% CI or no. of cases/deaths)	Comments
Wynder & Goldsmith (1977) USA 1969–74	Men	Filter-tipped (> 10 years) Untipped (> 10 years)	3.0 (2.1–4.3) 3.1 (2.1-4.7)	
Howe *et al*. (1980) Canada 1974–76	Men	Filter-tipped Untipped	1.0 1.1	Calculated by the Working Group from regression coefficients; reference category, all other smokers of the same amount
	Women	Filter-tipped Untipped	1.0 1.1	
Cartwright *et al*. (1983) UK 1978–81	Men and women	Filter-tipped Untipped Both types	1.05 (0.7–1.5) 1.4 (1.1–1.7) 1.6 (1.3–2.0)	Adjusted for age and sex
Morrison *et al*. (1984) UK and Japan, 1976–78 USA, 1976–77	Men Boston area	Filter-tipped Untipped (reference)	1.3 (0.7–2.3) 1.0	Adjusted for current intensity of smoking
	Manchester area	Filter-tipped Untipped (reference)	1.2 (0.8–1.8) 1.0	
	Nagoya area	Filter-tipped Untipped (reference)	1.0 (0.5–1.9) 1.0	
Vineis *et al*. (1984) Italy 1978–83	Men	100% filter-tipped 75–99% filter-tipped 50–74% filter-tipped 50% filter-tipped	0.3 0.5 1.1 1.0	Relative risks adjusted for age, high-risk occupation, average daily amount of smoking, years since stopping and type of tobacco

Table 2.1.2.7 (contd)

Reference Country and years of study	Subjects	Use of filter-tipped cigarettes	Relative risk (95% CI or no. of cases/deaths)	Comments
Burch *et al*. (1989) Canada 1979–82	Men and women	Nonsmoker (reference)	1.0	
		Current smoker:		
		Filter-tipped only	1.4 (0.7–2.6)	
		Untipped only	1.0	
		Former smoker (quit < 10 years ago)		
		Filter-tipped only	1.4 (0.6–3.0)	
		Untipped only	0.9 (0.4–1.8)	
Clavel *et al*. (1989) France 1984–87	Men	Total life-long consumption		
		100% filter-tipped	3.1 (1.9–5.3)	
		75–99% filter-tipped	5.0 (2.5–10.4)	
		50–74% filter-tipped	4.8 (2.1–10.8)	
		< 50% filter-tipped	4.0 (2.6–6.2)	
De Stefani *et al*. (1991) Uruguay 1987–89	Men	Filter-tipped	0.7 (0.4–1.5)	
		Untipped (reference)	1.0	
López-Abente *et al*. (1991) Spain 1983–86	Men	Filter-tipped	0.6 (0.3–1.0)	
		Mixed use (reference)	1.0	
		Untipped	1.1 (0.6–2.5)	
Momas *et al*. (1994b) France 1987–89	Men	Nonsmoker (reference)	1.0	
		Filter-tipped	5.1 (2.6–10.0)	
		Untipped	5.5 (3.0–10.2)	

Table 2.1.2.7 (contd)

Reference Country and years of study	Subjects	Use of filter-tipped cigarettes	Relative risk (95% CI or no. of cases/deaths)	Comments
Sorahan *et al*. (1994) UK 1985–87	Men	Nonsmoker (reference) Filter-tipped Untipped	1.0 2.2 (1.7–2.8) 1.9 (1.4–2.4)	
Castelao *et al*. (2001) USA 1987–96	Men and women	Filter-tipped Untipped (reference)	1.2 (0.9–1.5) 1.0	

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2.1.3 *Renal-cell carcinoma*

The evidence available at the time of the *IARC Monograph* on tobacco smoking (IARC, 1986) did not allow the conclusion that there is a causal association between kidney cancer and tobacco smoking.

The designs of the cohort studies are described in the introduction to Section 2 and Table 2.1 and those of the available case–control studies are summarized in Table 2.1.3.1.

Tables 2.1.3.2 and 2.1.3.3 summarize the results of the cohort and case–control studies. Most (12/21) of these studies show a significant increase in risk and a positive association with the number of cigarettes smoked, although tests for trend were rarely reported. The increase in risk associated with smoking 20 cigarettes per day is above 1.3 (e.g. Benhamou *et al*., 1993; Kreiger *et al*., 1993; Nordlund *et al*., 1997). The results are consistent across study designs (cohort studies, hospital- and population-based case–control studies) and in both sexes.

Studies that looked at the effect of duration of smoking and/or age at starting smoking (La Vecchia *et al.*, 1990; McCredie & Stewart, 1992; Benhamou *et al.*, 1993; Kreiger *et al.*, 1993; McLaughlin *et al.*, 1995a; Nordlund *et al.*, 1997; Yuan *et al.*, 1998) found only a weak association. The relative risk for former smokers was investigated in most studies, and all but three studies (Talamini *et al.*, 1990; Schlehofer *et al.*, 1995; Nordlund *et al.*, 1997) showed a lower risk than in current smokers, although it was not always below unity. A significant negative trend was observed with increasing number of years since quitting in five (McLaughlin *et al.*, 1984; La Vecchia *et al.*, 1990; McCredie & Stewart, 1992; McLaughlin *et al.*, 1995a; Yuan *et al.*, 1998) of six studies.

Other known risk factors for kidney cancer include raised body-mass index (obesity) and hypertension. A few studies have adjusted for these potential confounders. La Vecchia *et al.* (1990), Talamini *et al.* (1990), McCredie and Stewart (1992), Kreiger *et al.* (1993), McLaughlin *et al.* (1995a), Yuan *et al.* (1998) and Chow *et al.* (2000) adjusted for body-mass index, whereas Kuller *et al.* (1991) and Chow *et al.* (2000) adjusted for blood pressure. Their results suggest that there is no confounding effect of body-mass index or hypertension. It should be noted that confounding from body-mass index is likely to attenuate the association between kidney cancer and smoking, because smoking tends to induce a decrease in body-mass index. Therefore, an assessment of risk stratified by body-mass index would be more appropriate than adjustment for it. A large cohort study has evaluated the changes in body-mass index and blood pressure on the risk for kidney cancer (Chow *et al.*, 2000). As compared with men in the lowest three-eighths of the cohort for body-mass index, men in the middle three-eighths had a 30–60% greater risk for renal-cell cancer, and men in the highest two-eighths had nearly double the risk. After adjustment for body-mass index and hypertension, current and former smokers still had a greater risk for renal-cell cancer.

Table 2.1.3.1. Case–control studies on tobacco smoking and renal cancer: main characteristics of study design

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
Schwartz *et al*. (1961) France started 1954	Men: 69 cases and 69 controls	Hospital-based study; controls had been admitted to hospitals for accidents; matched on age, hospital group, interviewer and date of interview
Bennington & Laubscher (1968) USA 1951–66	Men: 88 cases and 170 controls; women: 12 cases and 20 controls	Hospital-based study; information on smoking habits retrieved from clinical records; information lacking for 22/122 cases and 70/190 controls (the latter were replaced)
Wynder *et al*. (1974) USA 1965–73	Men: 129 cases and 256 controls; women: 73 cases and 138 controls	Hospital-based study; controls were patients admitted for conditions not related to smoking (75% of which were malignant neoplasms) and age-matched to the cases.
Armstrong *et al*. (1976) UK 1972–74	Men: 74 cases and 74 controls; women: 32 cases and 32 controls	Hospital-based study; age- and sex-matched hospital controls (tobacco-related diseases not excluded); 48% of eligible cases in Oxford area and 44% in London could not be interviewed (mostly because of death); 19 lost controls replaced
McLaughlin *et al*. (1984) USA 1974–79	Men: 313 cases and 428 controls; women: 182 cases and 269 controls	Population-based study; all newly diagnosed cases in the Minneapolis-St Paul area; controls: age- and sex-stratified random sample of the population and 495 randomly selected deceased individuals matched (for age, sex and year of death) to deceased cases
La Vecchia *et al.* (1990) Italy 1985–89	Men: 85 cases; women: 46 cases; 394 matched controls	Hospital-based study using interviews. Incident cases confirmed histologically; median age, 60 years. Controls with traumas (30%), non-traumatic orthopaedic conditions (17%), acute medical (13%) and surgical (6%) diseases and others (34%); median age, 60 years. > 97% participation rate for cases and controls
Talamini *et al*. (1990) Italy 1986–89	Men: 150 cases and 445 controls; women: 90 cases and 220 controls	Hospital-based study using interviews. Cases confirmed histologically; aged 20–74 years; 97% response rate. Controls mainly with non-traumatic orthopaedic, traumatic and surgical conditions and eye diseases; matched by age (5-year groups), sex, area of residence and hospital; tobacco-, alcohol- and hormone-related diseases excluded; 96% participation rate

Table 2.1.3.1 (contd)

Reference Country and years of study	Numbers of cases and controls	Criteria for eligibility and comments
McCredie & Stewart (1992) Australia 1989–90	Men: 310 cases and 231 controls; women: 179 cases and 292 controls	Population-based study using interviews. Cases ascertained from Cancer Registry, confirmed by histology (87%), fine needle aspiration cytology (1%) or computerized tomography, ultrasound or contrast radiography (8%); aged 20–79 years; 66% of eligible cases. Controls randomly selected from electoral roll; 65% participation rate
Benhamou *et al.* (1993) France 1987–91	Men: 138 cases and 235 controls; women: 58 cases and 112 controls	Hospital-based study. Interviews. Cases confirmed histologically; 100% of eligible cases. Controls with malignant diseases (161) and non-malignant diseases (186). Individually matched by age (± 5 years), sex, hospital and interviewer; tobacco-related diseases, liver cirrhosis and diabetes excluded; 99% participation rate
Kreiger *et al.* (1993) Canada 1986–87	Men: 312 cases and 664 controls; women: 201 cases and 705 controls	Population-based study using a questionnaire. Incident cases confirmed histologically; aged 25–69 years; 81% of eligible cases. Controls randomly selected from general population matched (1:1) for men and (1:2) for women by age, sex and area of residence; 72% participation rate
McLaughlin *et al.* (1995a) Australia, Denmark, Germany, Sweden and USA 1989–92	Men: 1050 cases and 1429 controls; women: 682 cases and 880 controls	Population-based study using interviews. Cases ascertained from cancer registries, confirmed by histology or cytology; aged 20–79 years; 72% of eligible cases. Controls selected from different population rosters, matched by age (5-year groups) and study area; 75% of eligible controls
Schlehofer *et al.* (1995) Germany 1989–91	Men: 185 cases; women: 92 cases; 286 matched controls	Population-based study using interviews. Cases confirmed histologically; 70% aged ≥ 55 years; 85% participation rate. Controls randomly selected from population register, matched for age (± 1 year) and sex; 75% participation rate
Yuan *et al.* (1998) USA 1986–94	Men: 781 cases and 781 controls; women: 423 cases and 423 controls	Population-based study using interviews. Cases ascertained through Cancer Registry, confirmed histologically; non-Asian, aged 25–74 years; 70% of eligible cases. Controls selected from residence area of cases at the time of diagnosis; individually matched on age (± 5 years), sex, race and neighbourhood; 70% were first chosen controls.

Table 2.1.3.2. Cohort studies on tobacco smoking and kidney cancer: intensity of smoking

Reference Country and years of study	No. of subjects (M, F)	No. of events	Smoking categories	Relative risk (95% CI)	Comments
McLaughlin *et al.* (1990) USA 1954–80	US Veterans' Study 248 046 men	719 deaths	Ever-smoker	1.3 (1.1–1.6)	Adjusted for age at follow-up, calendar time and year of response to questionnaire
			Former smoker	1.1 (0.9–1.4)	
			Current smoker	1.5 (1.2–1.8)	
			Cigarettes/day		
			1–9	1.3 (0.9–1.8)	
			10–20	1.4 (1.1–1.7)	
			21–39	1.6 (1.2–2.1)	
			≥ 40	2.1 (1.3–3.3)	*p* for trend < 0.001
Kuller *et al.* (1991) USA 1975–85	MRFIT Study 12 866 men	219 deaths		Mortality rate	Annual mortality rate/10 000 men. Numbers in parentheses represent number of subjects. [†]RR adjusted for age, blood pressure, cholesterol and ethnicity
			Nonsmoker	4.8 (113)	
			Current smoker	1.9[†]	
			Cigarettes/day		
			1–15	4.1 (11)	
			16–25	7.0 (30)	
			26–35	12.9 (34)	
			36–45	10.6 (23)	
			> 45	10.1 (8)	
Doll *et al.* (1994) UK 1951–91	British Doctors' Study 34 439 men	113 deaths		Mortality rate	Annual mortality rate/ 10 000 men
			Nonsmoker	9	
			Former smoker	11	
			Current smoker	13	
			Cigarettes/day		
			1–14	13	
			15–24	14	
			≥ 25	12	χ^2 for trend 0.8 ($p > 0.05$)

Table 2.1.3.2 (contd)

Reference Country and years of study	No. of subjects (M, F)	No. of events	Smoking categories	Relative risk (95% CI)		Comments
McLaughlin *et al*. (1995b) USA 1954–80	US Veterans' Study 177 903 men	511 deaths	Ever-smoker	1.4 (1.1–1.6)		Adjusted for age attained and calendar year time period (5-year groups)
			Former smoker	1.1 (0.9–1.4)		
			Current smoker	1.5 (1.2–1.9)		
			Cigarettes/day			
			1–9	1.3 (0.9–2.0)		
			10–20	1.4 (1.1–1.8)		
			21–39	1.6 (1.3–2.2)		
			≥ 40	2.2 (1.4–3.5)		*p* for trend < 0.01
Engeland *et al*. (1996) Norway 1966–93	Norwegian Cohort Study 11 863 men, 14 269 women	147 cases (87 men, 60 women)		Men	Women	Adjusted for age
			Former smoker	1.3 (0.8–2.4)	0.2 (0.0–1.7)	
			Current smoker	–	1.1 (0.6–2.0)	
			Cigarettes/day			
			0–4	0.9 (0.4–2.1)		
			5–9	1.8 (0.9–3.6)		
			≥ 10	1.3 (0.7–2.5)		
Heath *et al*. (1997) USA 1982–89	Cancer Prevention Study II 434 339 men, 564 565 women	335 deaths (212 men, 123 women)		Men	Women	
			Current smoker	1.7 (1.2–2.6)	1.4 (0.9–2.3)	Adjusted for age
			Former smoker	1.7 (1.1–2.4)	1.2 (0.7–1.9)	

Table 2.1.3.2 (contd)

Reference Country and years of study	No. of subjects (M, F)	No. of events	Smoking categories	Relative risk (95% CI)	Comments
Nordlund *et al.* (1997) Sweden 1963–89	Swedish Census Study 26 032 women	94 cases	Former smoker	1.9 (0.8–4.7)	Adjusted for age and place of residence
			Current smoker	1.1 (0.6–2.0)	
			Cigarettes/day		
			1–7	0.8 (0.3–1.9)	
			8–15	1.0 (0.4–2.9)	
			≥ 16	3.1 (1.1–8.7)	
			Age at start (years)†		†Relative risk adjusted for age, place of residence and cigarettes/day
			> 24	1.0	
			20–23	2.6 (0.7–9.1)	
			< 19	1.4 (0.3–6.1)	*p* for trend = 0.522
Chow *et al.* (2000) Sweden 1971–92	Swedish Construction Worker Cohort 363 992 men	759 cases	Former smoker	1.3 (1.0–1.6)	Adjusted for age, body mass index and blood pressure
			Current smoker	1.6 (1.3–1.9)	

CI, confidence interval

Table 2.1.3.3. Case–control studies on tobacco smoking and kidney cancer: intensity of smoking

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)		Comments
Schwartz *et al.*	Men		Cases	Controls	[†]Values represent percentages.
(1961)		Smoker	78[†]	83[†]	Matched analysis; all $p > 0.05$
France		Equivalent cigs/day	15.0	15.0	
started 1954		Inhaler	44[†]	46[†]	
Bennington &	Men and women	All tobacco use	5.4		[†]Values represent percentages.
Laubscher (1968)		> 10 cigs/day	5.1		No statistical analysis performed
USA			Cases	Controls	on data for women
1951–66		Men	93[†]	75[†]	$p < 0.0005$
		Women	66[†]	50[†]	
		Men only			
		> 10 cigs/day	68[†]	54[†]	$p < 0.0005$
		< 10 cigs/day	3.4[†]	4.7[†]	
		Former smoker	1.1[†]	6.5[†]	$p < 0.05$
Wynder *et al.*	Men and women		Men	Women	
(1974)		Cigarettes only	2.0	1.5	$p < 0.005$
USA		All tobacco	1.7		
1965–73		*Cigarettes/day*			
		1–9	1.5	1.1	
		10–20	1.9	1.5	
		> 20	2.2	1.2	
Armstrong *et al.*	Men and women	Current smoker			
(1976)		Men	1.1 (0.5–2.2)		
UK		Women	1.0 (0.3–3.4)		
1972–74					

Table 2.1.3.3 (contd)

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)		Comments
McLaughlin *et al.* (1984) USA 1974–79	Men and women	Men			Odds ratio adjusted for age and type of interview (with subject or next of kin)
		Ever-smoker	1.6 (1.1–2.4)		
		Pack–years			
		0–25.5	1.2 (0.8–2.0)		Relative risk increased with intensity (cigarettes/day) and duration (years smoked) [data not shown]; *p* for trend < 0.01
		> 25.5–50	1.3 (0.8–2.1)		
		> 50	2.3 (1.4–3.8)		
		Women			
		Ever-smoker	1.9 (1.3–3.1)		
		Pack–years			
		0–12	1.8 (1.0–3.9)		
		> 12–33	1.9 (1.0–3.5)		
		> 33	2.1 (1.1–4.6)		*p* for trend < 0.01
		Men			
		Cigarettes only	1.7 (1.1–2.6)		
		Cigarettes and cigars	2.2 (1.1–4.3)		
		Cigarettes and pipes	1.2 (0.7–2.1)		
		Cigarettes, cigars and pipes	1.3 (0.6–3.0)		
		Years since quitting	Men	Women	
		> 10	1.1	1.6	
		≤ 10	1.7	1.7	
		Current	1.8	2.0	

Table 2.1.3.3 (contd)

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)		Comments
La Vecchia *et al*. (1990) Italy 1985–89	Men and women	*Cigarettes/day*	Univariate	Multivariate	Univariate analysis adjusted for age and sex; multivariate analysis adjusted for area of residence, education and body-mass index
		< 15	1.3 (0.6–2.6)	1.1 (0.5–2.5)	
		15–24	2.0 (1.1–3.8)	1.9 (1.0–3.6)	
		≥ 25	2.1 (1.0–4.6)	2.3 (1.0–5.3)	
		p for trend	0.02	0.02	
		Duration (years)			
		< 30	2.0 (1.1–3.6)	1.7 (0.9–3.0)	
		≥ 30	2.2 (1.2–3.9)	1.8 (1.0–3.2)	
		p for trend	0.01	0.04	
		Age at starting smoking (years)			
		> 20	1.8 (1.0–3.2)	1.7 (1.0–3.0)	
		≤ 20	2.5 (1.3–4.6)	2.0 (1.1–3.7)	
		Years since quitting			
		≥ 10	1.3 (0.6–3.0)	1.3 (0.6–2.7)	
		< 10	2.6 (1.1–5.7)	2.2 (1.1–4.4)	
		Former smoker		1.7 (1.0–3.1)	
Talamini *et al*. (1990) Italy 1986–89	Men and women	Former smoker	1.4 (0.8–2.2)		Adjusted by age, sex, education, body-mass index and residence χ^2 for trend = 0.9
		Current cigarettes/day			
		< 15	1.1 (0.6–1.8)		
		15–24	1.3 (0.8–2.1)		
		≥ 25	1.2 (0.6–2.4)		

Table 2.1.3.3 (contd)

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)		Comments
McCredie & Stewart (1992) Australia 1989–90	Men and women		Former	Current	Adjusted for age, sex, body-mass index and method of interview Model 1 adjusted for duration, cigarettes/day and years since cessation. Model 2 adjusted for age at start, cigarettes/day and years since cessation
		All tobacco	1.4 (1.03–2.0)	2.2 (1.6–3.0)	
		Cigarettes only	1.3 (0.9–1.9)	2.2 (1.5–3.1)	
		Men	1.5 (1.01–2.4)	2.9 (1.8–4.8)	
		Women	1.3 (0.8–2.2)	1.6 (1.00–2.6)	
		Age at diagnosis			
		≤ 58 years	1.3 (0.8–2.4)	2.3 (1.4–3.8)	
		59–67 years	1.7 (0.96–3.0)	2.0 (1.1–3.6)	
		≥ 68 years	1.2 (0.7–2.1)	2.3 (1.1–4.6)	
		Ever-smoker			
		Duration (years)	Model 1	Model 2	
		1–19	1		
		20–34	1.5 (0.9–2.4)		
		≥ 35	1.5 (0.8–3.0)		
		p for trend	0.25		
		Age at starting smoking (years			
		9–17		1	
		≥ 18		1.1 (0.7–1.6)	
		Cigarettes/day			
		1–12	1	1	
		13–20	1.2 (0.7–1.8)	1.2 (0.8–1.9)	
		≥ 21	1.4 (0.9–2.3)	1.5 (0.9–2.4)	
		p for trend	0.14	0.12	
		Years since quitting			
		≥ 25	0.5 (0.2–1.0)	0.4 (0.2–0.7)	
		13–24	0.9 (0.5–1.5)	0.8 (0.5–1.4)	
		1–12	0.9 (0.5–1.4)	0.9 (0.5–1.4)	
		p for trend	0.13	0.003	

Table 2.1.3.3 (contd)

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)		Comments
McCredie & Stewart (1992) (contd)		**Current smoker**			
		Filter status			
		with	2.3 (1.6–3.3)		
		without	2.8 (1.3–6.4)		
		with and without	1.8 (0.95–3.6)		
		Inhalation			
		yes	2.3 (1.6–3.3)		
		no	1.7 (0.8–4.0)		
		Pattern of inhalation			
		deep	1		
		moderate	0.8 (0.4–1.5)		
		light	0.6 (0.3–1.4)		
Benhamou *et al.* (1993) France 1987–91	Men and women		Men	Women	Matched analysis
		Ever-smoker	0.9 (0.6–1.5)	0.7 (0.4–1.5)	
		Current smoker	0.9 (0.4–1.8)	0.8 (0.3–1.8)	
		Cigarettes/day			3 cases and 12 controls excluded; adjusted for education, Quetelet index and duration of smoking
		< 20	0.9 (0.3–3.0)		
		≥ 20	1.2 (0.4–3.7)		
		Duration (years)			Adjusted for education, Quetelet index and cigarettes/day
		< 30	0.7 (0.2–2.0)		
		≥ 30	0.6 (0.2–1.8)		
		Age at starting smoking (years)			Adjusted for education, Quetelet index, cigarettes/day and duration of smoking
		≥ 20	0.7 (0.2–2.9)		
		< 20	0.9 (0.2–3.4)		

Table 2.1.3.3 (contd)

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)		Comments
Kreiger *et al.* (1993) Canada 1986–87	Men and women		Men	Women	Adjusted by age and body-mass index
		Ever-smoker	2.0 (1.4–2.8)	1.9 (1.3–2.6)	
		Current smoker	2.3 (1.5–3.4)	2.2 (1.5–3.2)	
		< 20 years			
		< 20 cigs/day	1.6 (0.9–2.8)	1.5 (0.8–2.9)	
		≥ 20 cigs/day	1.0 (0.5–1.8)	1.8 (0.8–4.2)	
		≥ 20 years			
		< 20 cigs/day	2.2 (1.4–3.5)	1.7 (1.1–2.7)	
		≥ 20 cigs/day	2.2 (1.5–3.3)	2.2 (1.4–3.4)	
		Years since quitting			
		≥ 20	1.3 (0.8–2.1)	1.5 (0.7–3.1)	
		10–19	2.1 (1.3–3.4)	1.9 (0.8–4.2)	
		5–9	1.8 (1.0–3.3)	1.6 (0.7–3.7)	
		1–4	2.1 (1.2–3.8)	1.4 (0.6–2.9)	
McLaughlin *et al.* (1995a) Australia, Denmark, Germany, Sweden and USA 1989–92	Men and women	Ever-smoker	1.3 (1.1–1.5)		Adjusted for age, sex, body-mass index and study centre
		Current smoker	1.4 (1.2–1.7)		
		Former smoker	1.2 (1.0–1.4)		
		Cigarettes/day	Ever-smoker	Current smoker	
		1–10	1.1 (0.9–1.3)	1.1 (0.9–1.5)	
		11–20	1.3 (1.1–1.6)	1.3 (1.1–1.6)	
		> 20	1.5 (1.2–1.9)	2.1 (1.6–2.8)	
		p for trend	< 0.001	< 0.001	
		Pack–years			
		Ever-smoker			
		≤ 9	1.1 (0.9–1.3)		
		9.1–20.1	1.1 (0.9–1.4)		
		20.2–36.9	1.3 (1.0–1.6)		
		≥ 37	1.7 (1.4–2.1)		*p* for trend < 0.001

Table 2.1.3.3 (contd)

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)		Comments
McLaughlin *et al.* (1995a) (contd)		Current smoker			
		< 16	1.1 (0.8–1.5)		
		16–< 28	1.1 (0.8–1.5)		
		28–42.2	1.4 (1.1–1.9)		
		> 42.2	2.0 (1.6–2.7)		*p* for trend < 0.001
		Years since quitting			
		> 25	0.85 (0.6–1.1)		*p* for trend = 0.09
		16–25	0.75 (0.6–1.0)		
		6–15	0.84 (0.7–1.1)		
		≤ 5	0.90 (0.7–1.2)		
		Current	1.0 (reference)		
		Age at starting smoking (years)			
		> 24	0.67 (0.3–1.3)		
		21–24	0.76 (0.4–1.5)		
		17–20	0.77 (0.4–1.4)		
		13–16	0.83 (0.4–1.6)		
		≤ 12	1.0		*p* for trend = 0.20
Schlehofer *et al.* (1995) Germany 1989–91	Men and women	*Pack–years*	Current smoker	Former smoker	Adjusted for age
		Men	1.4 (0.8–2.5)	1.1 (0.6–1.9)	
		< 20	1.4 (0.7–3.0)	0.9 (0.5–1.8)	
		20–< 40	1.1 (0.5–2.1)	1.0 (0.4–2.2)	
		≥ 40	2.2 (0.99–4.7)	2.3 (0.9–6.2)	
		Women	0.8 (0.4–1.8)	1.0 (0.4–1.4)	
		< 10	0.5 (0.1–1.9)	0.9 (0.3–2.3)	
		10–< 20	0.3 (0.1–1.2)	0.7 (0.1–4.7)	
		≥ 20	2.2 (0.7–6.8)	3.0 (0.3–30.2)	

Table 2.1.3.3 (contd)

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)	Comments
Yuan *et al*. (1998) USA 1986–94	Men and women		Total	Adjusted for age, sex and education No effect of age at starting smoking [data not shown]. No modifying effect of body-mass index, history of hypertension, regular use of analgesics or use of amphetamines in stratified analysis or in multivariate conditional analysis
		Ever-smoker	1.4 (1.1–1.6)	
		Former smoker	1.2 (1.02–1.5)	
		Current smoker	1.5 (1.2–1.9)	
		Cigarettes/day		
		1–19	1.5 (1.04–2.1)	
		20–39	1.5 (1.1–1.9)	
		≥ 40	1.9 (1.3–2.9)	
		Lifetime exposure (no. of cigs)		
		< 117 000	1.2 (0.97–1.5)	
		117 000–283 000	1.3 (0.99–1.6)	
		≥ 283 000	1.6 (1.3–2.0)	
		Duration (years)		
		< 20	1.1 (0.8–1.4)	
		20–39	1.1 (0.9–1.5)	
		≥ 40	1.2 (0.9–1.7)	
		Years since quitting		
		≥ 20	1.2 (0.9–1.5)	
		10–19	1.3 (0.9–1.6)	
		1–9	1.3 (1.02–1.7)	
		Years since quitting		Compared with current smokers; adjusted for age, sex, education, body-mass index and number of cigarettes/day *p* for trend = 0.01
		≥ 20	0.7 (0.5–1.0)	
		10–19	0.7 (0.5–1.0)	
		< 10	0.8 (0.6–1.1)	

Table 2.1.3.3 (contd)

Reference Country and years of study	Sex	Smoking categories	Relative risk (95% CI)		Comments
Yuan *et al*. (1998)			Men	Women	
(contd)		Ever-smoker	1.4 (1.1–1.8)	1.2 (0.9–1.6)	
		Former smoker	1.3 (1.1–1.7)	1.1 (0.8–1.5)	
		Current smoker	1.6 (1.2–2.1)	1.5 (1.0–2.1)	
		Cigarettes/day			
		1–19	1.6 (0.96–2.6)	1.4 (0.8–2.3)	
		20–39	1.5 (1.1–2.0)	1.4 (0.9–2.2)	
		≥ 40	1.9 (1.2–3.2)	1.9 (0.9–4.2)	
		Lifetime exposure (no. of cigs)			
		< 117 000	1.3 (0.96–1.7)	1.1 (0.8–1.6)	
		117 000–283 000	1.3 (0.96–1.7)	1.2 (0.8–1.8)	
		≥ 283 000	1.7 (1.3–2.2)	1.4 (0.9–2.2)	
		Years since quitting			
		≥ 20	1.2 (0.9–1.6)	1.2 (0.7–2.0)	
		10–19	1.3 (0.9–1.8)	1.2 (0.7–2.0)	
		1–9	1.6 (1.2–2.3)	0.9 (0.6–1.4)	

CI, confidence interval

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2.1.4 *Upper aerodigestive tract*

Evidence relating to cancers of the upper aerodigestive tract obtained from relevant cohort and case–control studies on specific sites is described in Sections 2.1.4.a to 2.1.4.f, whereas studies that looked at several subsites combined are described in Section 2.1.4.g.

Most of the cohorts in which these studies were conducted have been described in the introduction to Section 2 and Table 2.1. In addition, in 1975, Tomita *et al.* (1991) established a cohort of 38 621 men, aged 20–55 years, who worked for the East Japan Railway Company. The response rate was 98% and after exclusions and loss to follow-up, 37 645 men were included in the analysis. The health status of the subjects was followed until 1985 using records of medical examinations, mutual-aid pensions and notices of deaths.

The major confounders for the relationship between smoking and several cancers of the upper aerodigestive tract are alcohol consumption and use of any form of smokeless tobacco. In general, the studies examined in the Working Group had adjusted for these two confounders when appropriate.

Some studies also adjusted for dietary intake, especially of fruits and vegetables, although few reported stratified relative risks.

(*a*) *Oral cancer*

Tobacco smoking was shown to be causally related to oral cancer by the previous *IARC Monograph* on tobacco smoking (IARC, 1986) and even earlier by other agencies. Since 1986, many more studies have been reported on the relationship between oral cancer and cigarette smoking. New studies include three cohort studies (Table 2.1.4.1), 16 case–control studies (Tables 2.1.4.2–2.1.4.5), and two case-series reports (Table 2.1.4.6).

(i) *Intensity and duration of smoking*

Intensity of smoking was measured in almost all cohort and case–control studies (Tables 2.1.4.1 and 2.1.4.3, respectively). In addition to the number of cigarettes or amount of tobacco smoked daily, cumulative exposure to cigarette smoke was also measured in terms of pack–years, tobacco–years or lifetime tobacco consumption. The link between duration of cigarette consumption and oral cancer was examined in eight case–control studies. Five case–control studies also considered age at starting smoking.

McLaughlin *et al*. (1995) in the US Veterans' Study divided the number of cigarettes smoked per day into four categories and reported a positive, statistically significant trend.

Eleven case–control studies also reported a dose-dependent increase in risk with increasing number of cigarettes smoked daily or increasing daily tobacco consumption (Franceschi *et al.*, 1990; Nandakumar *et al.*, 1990; Zheng *et al.*, 1990; Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Franceschi *et al.*, 1992; Bundgaard *et al.*, 1995; Zheng *et al.*, 1997; De Stefani *et al.*, 1998; Franceschi *et al.*, 1999; Hayes *et al.*, 1999). Whenever analysed, the trend was always statistically significant (Franceschi *et al.*, 1990; Oreggia *et al.*, 1991; Franceschi *et al.*, 1992; Bundgaard *et al.*, 1995; Hayes *et al.*, 1999).

Several case–control studies have reported exposure to tobacco in other ways. Bundgaard *et al.* (1995) used lifetime tobacco consumption divided into four categories and reported a positive, significant trend after adjustment for life-time consumption of alcohol and other risk factors. A positive trend was also found in all studies that have analysed consumption in pack–years or tobacco–years (Zheng *et al.*, 1990; Maier *et al.*, 1992a; Macfarlane *et al.*, 1995; Hung *et al.*, 1997; Zheng *et al.*, 1997; De Stefani *et al.*, 1998).

Eight studies (Franceschi *et al.*, 1990; Nandakumar *et al.*, 1990; Zheng *et al.*, 1990; Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Franceschi *et al.*, 1992; Zheng *et al.*, 1997; De Stefani *et al.*, 1998) classified the duration of smoking in up to four categories, and all but one study (Nandakumar *et al.*, 1990) reported increased relative risks and a positive trend.

Two out of five studies (Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Franceschi *et al.*, 1990, 1992; Zheng *et al.*, 1997) reported a statistically significant trend of increasing risk with decreasing age at starting smoking (Franceschi *et al.*, 1990, 1992).

(ii) *Cessation of smoking*

One cohort study (McLaughlin *et al.*, 1995; Table 2.1.4.1) and eight case–control studies (Zheng *et al.*, 1990; Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Franceschi *et al.*, 1992; Ko *et al.*, 1995; Zheng *et al.*, 1997; De Stefani *et al.*, 1998; Schildt *et al.*, 1998; Table 2.1.4.3) provided point estimates for former smokers. Relative risks among former smokers were always lower than those for current smokers and in half of these studies almost reached unity (Zheng *et al.*, 1990; Choi & Kahyo, 1991; Zheng *et al.*, 1997; Schildt *et al.*, 1998). Seven case–control studies examined the relative risk by years since quitting and all reported a negative trend (Table 2.1.4.4). The risk for oral cancer declines rather rapidly following cessation of smoking, with relative risks compared with those in non-smokers decreasing to near unity after 10 or more years (Franceschi *et al.*, 1990, 1992; De Stefani *et al.*, 1998). When calculated, the trend was always statistically significant (Franceschi *et al.*, 1990; Oreggia *et al.*, 1991; Franceschi *et al.*, 1992).

(iii) *Type of cigarette*

The effect of the type of cigarette smoked was examined in several case–control studies. The characteristics of the cigarettes included the presence of a filter, the type of tobacco, the tar content and whether the product was manufactured or hand-rolled (Table 2.1.4.5). Two studies reported a statistically significantly higher relative risk for black than for blond tobacco (Oreggia *et al.*, 1991; De Stefani *et al.*, 1998). Similarly, a much higher relative risk was found for hand-rolled cigarettes than for manufactured cigarettes, and plain cigarettes had a much higher relative risk than filter-tipped cigarettes (De Stefani *et al.*, 1998). The differences between black and blond tobacco and between hand-rolled and manufactured cigarettes persisted after stratification by duration of smoking (De Stefani *et al.*, 1998). Also smoking cigarettes with a high-tar content led to higher relative risks than smoking cigarettes with a low-tar content (Franceschi *et al.*, 1992).

(iv) *Sex*

Sex-specific effects were examined in two case–control studies (Zheng *et al.*, 1990; Hayes *et al.*, 1999; Table 2.1.4.3). In both studies, the relative risks for all categories of intensity, duration of smoking and pack–years were higher for women than for men.

(v) *Case-series reports*

Case-series reports are the only data available from Jordan and Myanmar; the results are given in Table 2.1.4.6. These data are of limited value in assessing causality, but have been included for the sake of completeness.

(*b*) *Sinonasal cancer*

The Life Span Study in Japan (Akiba, 1994) examined the association of tobacco use with sinonasal cancer (see introduction to Section 2 for cohort description). A total of 26 cases of sinonasal cancer were identified among 61 505 adults during follow-up. Relative risks, adjusted for sex, location, population group, atomic bomb exposure, year of birth and attained age, increased to 2.9 (95% CI, 0.5–) and 4.0 (95% CI, 1.2–) for former and current smokers, respectively, when compared with nonsmokers [upper confidence limits could not be obtained].

A total of nine case–control studies were examined: the study designs and results are presented in Tables 2.1.4.7 and 2.1.4.8, respectively. When histological types were combined, all studies found an increased relative risk associated with cigarette smoking, but only one was statistically significant (Caplan *et al.*, 2000).

Seven studies analysed the dose–response in terms of intensity of smoking (cigarettes/day), duration of smoking or pack–years. A positive significant trend was found in five studies (Brinton *et al.*, 1984; Hayes *et al.*, 1987; Fukuda & Shibata, 1990; Zheng *et al.*, 1993; Caplan *et al.*, 2000) and was suggested in the other two (Strader *et al.*, 1988; Zheng *et al.*, 1992a).

One study (Zheng *et al.*, 1993) examined the residual risk after cessation of smoking and found a significant decrease in risk for sinonasal cancer associated with increasing number of years since cessation. In a previous study, the same authors had found a negative, non-significant association (Zheng *et al.*, 1992a).

Five studies analysed squamous-cell carcinomas and adenocarcinomas separately (Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Zheng *et al.*, 1992b; ‘t Mannetje *et al.*, 1999). In all studies, there was clearly a significantly increased relative risk for squamous-cell carcinomas, whereas the relative risk was generally not increased for adenocarcinomas.

The evidence of an association between tobacco smoking and sinonasal cancer is based on the results from case–control studies, each of which may be subject to different sources of bias. However, several arguments support the existence of a causal association. These are: presence of a dose–response relationship in most studies; the decrease in relative risk associated with time since quitting; the consistently higher relative risks for squamous-cell carcinoma than for adenocarcinoma; and the lack of potential confounders.

(*c*) *Nasopharyngeal carcinoma*

(i) *Cohort studies*

The risk for nasopharyngeal carcinoma was examined in relation to tobacco use in two cohort studies (Table 2.1.4.9). One study, conducted in a low-risk area (Chow *et al.*, 1993), reported a significant increase in risk among smokers and suggested positive dose–response relationships by duration of smoking and age at starting smoking. The other study, conducted in China, Province of Taiwan, an area in which nasopharyngeal cancer area is endemic, reported a similarly increased risk, but it was not statistically significant (Liaw & Chen, 1998).

(ii) *Case–control studies*

The study designs and the results of the case–control studies on the association of nasopharyngeal carcinoma with cigarette smoking are given in Tables 2.1.4.10 and 2.1.4.11, respectively.

The results of nine informative case–control studies were available (Lin *et al.*, 1973; Yu *et al.*, 1990; Nam *et al.*, 1992; West *et al.*, 1993; Ye *et al.*, 1995; Zhu *et al.*, 1995; Vaughan *et al.*, 1996; Cao *et al.*, 2000; Yuan *et al.*, 2000). In all these studies, the risk for nasopharyngeal carcinoma was higher in smokers than in nonsmokers.

In the three studies conducted in the USA, where the incidence rate for nasopharyngeal carcinoma is low (Nam *et al.*, 1992; Zhu *et al.*, 1995; Vaughan *et al.*, 1996), the relative risks for current smokers ranged between 2 and 4. In a study conducted in Shanghai, an area of China in which nasopharyngeal carcinoma is not endemic (Yuan *et al.*, 2000), the relative risk was just below 2. One study from the Philippines reported a sevenfold increase in risk after more than 30 years of smoking (West *et al.*, 1993). The four studies (Lin *et al.*, 1973; Yu *et al.*, 1990; Ye *et al.*, 1995; Cao *et al.*, 2000 [small sample size]) conducted in areas of China in which nasopharyngeal carcinoma is endemic (Taiwan, Guangzhou and Sihui) found relative risks for ever smoking ranging between 2 and 5.

A statistically significant dose–response relationship was detected in six studies that reported the effects of daily or cumulative exposure to tobacco smoke (Yu *et al.*, 1990; Nam *et al.*, 1992; Zhu *et al.*, 1995; Vaughan *et al.*, 1996; Cao *et al.*, 2000; Yuan *et al.*, 2000) and suggested in two others (Lin *et al.*, 1973; West *et al.*, 1993). Two studies investigated the effect of quitting smoking and found that the risk of nasopharyngeal carcinoma decreased with increasing time since quitting (Nam *et al.*, 1992; Vaughan *et al.*, 1996).

In the remaining studies, five from areas in which nasopharyngeal carcinoma is endemic (Ng, 1986; Yu *et al.*, 1986; Sriamporn *et al.*, 1992; Zheng *et al.*, 1994 [small sample size]; Cheng *et al.*, 1999) and five from areas in which it was not endemic (Henderson *et al.*, 1976; Lanier *et al.*, 1980; Mabuchi *et al.*, 1985; Ning *et al.*, 1990; Armstrong *et al.*, 2000), the relative risks for nasopharyngeal carcinoma for ever smoking were not significantly increased (Lanier *et al.*, 1980; Mabuchi *et al.*, 1985; Cheng *et al.*, 1999; Armstrong *et al.*, 2000) or were similar to those of nonsmokers (Henderson *et al.*, 1976; Ng, 1986; Yu *et al.*, 1986; Ning *et al.*, 1990; Sriamporn *et al.*, 1992; Zheng *et al.*, 1994).

In the two studies that distinguished between different histological types, relative risks were higher for keratinized (squamous-cell) carcinoma than for unkeratinized carcinoma (Zhu *et al*., 1995; Vaughan *et al*., 1996).

In the three studies in which men and women were analysed separately, the relative risks were found to increase similarly in both sexes (Lin *et al.,* 1973; Nam *et al*., 1992; Yuan *et al.,* 2000).

Although the interpretation of the results is complicated by small sample sizes, the different criteria used for the selection of controls and the problem of control groups with smoking-related diseases, the combined evidence shows an association between tobacco smoking and nasopharyngeal carcinoma in both endemic and non-endemic areas. Infection with Epstein–Barr virus (human herpesvirus 4), a major cause of nasopharyngeal carcinoma worldwide (IARC, 1997), has not been controlled for in any of the available studies. However, it is unlikely that confounding by infection with Epstein–Barr virus would explain the observed association between tobacco smoking and risk for nasopharyngeal carcinoma. On the other hand, most studies have adjusted for other known and suspected causes of nasopharyngeal carcinoma including intake of Chinese-style salted fish, other dietary factors, alcohol drinking and family history of nasopharyngeal carcinoma, suggesting only a limited confounding effect of these factors.

(*d*) *Cancer of the pharynx*

Tobacco smoking was considered to be an important cause of oropharyngeal and hypopharyngeal cancers in the previous *IARC Monograph* on tobacco smoking (IARC, 1986). Since then more epidemiological studies have yielded results that lend further support for the association. Many studies, however, combine cancers of the oral cavity and of the pharynx (see Section 2.1.4.g). This section summarizes the evidence from three cohort studies (Table 2.1.4.12) and 12 case–control studies (Tables 2.1.4.13 and 2.1.4.14) that reported results specifically on oropharyngeal and hypopharyngeal cancer, or on pharyngeal cancer in general; the latter may include data on nasopharyngeal cancer.

The risk for pharyngeal cancer was significantly increased in smokers in one cohort study (McLaughlin *et al*., 1995; Table 2.1.4.12) and all but one of the case–control studies (Rao *et al*., 1999; Table 2.1.4.14). The trend of increasing risk associated with increasing daily or cumulative consumption of cigarettes was evident from all these studies, particularly those from Europe (Brugere *et al*., 1986; Tuyns *et al*., 1988; Franceschi *et al*., 1990; Maier *et al*., 1994; Franceschi *et al*., 1999), Uruguay (De Stefani *et al*., 1998) and the USA (McLaughlin *et al*., 1995), and less strongly so in studies from Canada (Elwood *et al*., 1984) and the Republic of Korea (Choi & Kahyo, 1991).

Two case–control studies showed that the risk increased with decreasing age at starting smoking (Table 2.1.4.14; Franceschi *et al*., 1990; Choi & Kahyo, 1991), but duration and intensity of smoking were not adjusted for.

The influence of cessation of smoking is also evident in all studies where this aspect has been investigated. Former smokers had consistently lower relative risks than did current smokers in both cohort (McLaughlin *et al*., 1995) and case–control studies (Choi

& Kahyo, 1991; De Stefani *et al.*, 1998). In comparison with nonsmokers, the relative risks for former smokers who had quit smoking for more than 10 years were between 2 and 4 (Franceschi *et al.*, 1990; De Stefani *et al.*, 1998; La Vecchia *et al.*, 1999a), whereas the relative risks for current smokers in these studies were 10–14. In one study in Brazil (Schlecht *et al.*, 1999), relative risks for former smokers who had stopped smoking for more than 10 years approached 1, whereas that for current smokers was just below 6.

Consumption of black tobacco, hand-rolled cigarettes or plain cigarettes (Table 2.1.4.14) resulted in a higher risk for pharyngeal cancer than consumption of blond tobacco, manufactured cigarettes or filter-tipped cigarettes (De Stefani *et al.*, 1998).

(*e*) *Cancer of the oesophagus*

Early studies on the association of tobacco smoking and oesophageal cancer usually examined the risk for cancer of the oesophagus without further specification; sometimes studies reported on cancer of the oesophagus and gastric cardia combined, or specifically on squamous-cell carcinoma of the oesophagus, which was at that time the predominant histological type of oesophageal cancer. Consequently, the results of the early investigations are mainly applicable to squamous-cell carcinoma of the oesophagus. In the previous *IARC Monograph* on tobacco smoking (IARC, 1986), oesophageal cancer was considered to be causally related to cigarette smoking. Many more epidemiological studies have since been conducted, and results of these studies further support this conclusion.

(i) *Squamous-cell carcinoma and unspecified cancer of the oesophagus*

The 19 cohort and 35 case–control studies summarized in this section are described in Tables 2.1.4.15 and 2.1.4.16–2.1.4.19, respectively. All but two cohort studies (Doll *et al.*, 1980; Liaw & Chen, 1998), and all case–control studies, conducted in China, Iceland, Japan, Sweden, the United Kingdom and the USA (Table 2.1.4.17), showed that the risk for oesophageal cancer was associated with cigarette smoking. In one study (Li *et al.*, 1989), the elevated risk was observed only in an area with a relatively low incidence rate of oesophageal cancer. However, two later studies in the same area, Lin County, China, found a twofold increase in risk for oesophageal cancer among smokers (Gao *et al.*, 1994; Lu *et al.*, 2000).

In most positive cohort studies and in most case–control studies with relatively large sample sizes, the risk for oesophageal cancer was shown to increase with increasing duration of smoking (one cohort and 12 case–control studies) or number of cigarettes smoked daily (11 cohort and 21 case–control studies), and to decrease with increasing age at starting smoking (six case–control studies; Tables 2.1.4.15 and 2.1.4.17). In comparison with pharyngeal and laryngeal cancers, relative risks for oesophageal cancer estimated by duration and by intensity of smoking were somewhat lower (see Sections 2.1.4.d and 2.1.4.f, respectively).

One cohort (Guo *et al.*, 1994; Table 2.1.4.15) and 10 case–control studies (Table 2.1.4.18) investigated the effect of cessation of smoking on risk for oesophageal cancer. Although not all studies analysed the trend, all found a decreasing risk with increasing number of years since quitting. In some studies, the risk first started to decrease after 10 years of cessation (Brown *et al.*, 1988; Rolón *et al.*, 1995; Gammon *et al.*, 1997; Castellsagué *et al.*, 1999).

Consumption of black tobacco (Table 2.1.4.19) resulted in a higher risk for oesophageal cancer than did consumption of blond tobacco (De Stefani *et al.*, 1990; Rolón *et al.*, 1995; Castellsagué *et al.*, 1999). Similarly, smoking untipped cigarettes generally resulted in a higher risk for oesophageal cancer than smoking filter-tipped cigarettes (Vaughan *et al.*, 1995; Gammon *et al.*, 1997; Castellsagué *et al.*, 1999).

One study from the USA reported relative risks separately for blacks and whites (Brown *et al.*, 1994a). Relative risks adjusted for alcohol consumption, age and income were very similar for former and current smokers and for the number of cigarettes smoked per day and duration of smoking (Table 2.1.4.17).

(ii) *Adenocarcinoma of the oesophagus*

During recent decades incidence rates for adenocarcinoma of the oesophagus and gastric cardia have increased steadily in the USA, whereas the incidence rate for squamous-cell carcinoma of the oesophagus has remained relatively stable (Blot *et al.*, 1991). An increase in the incidence of adenocarcinoma of the distal oesophagus and cardia has also been noted in the United Kingdom (Powell & McConkey, 1990). Since 1990, a number of studies have focused on the risk factors for adenocarcinoma of the oesophagus.

Confounding

The study designs and results of 10 case–control studies on the association of cigarette smoking and adenocarcinoma of the oesophagus are presented in Tables 2.1.4.20 and 2.1.4.21, respectively.

With the exception of two studies (Levi *et al.*, 1990; Wu *et al.*, 2001), all studies adjusted for alcohol intake as a potential confounder. Most of these studies were conducted in the USA (Kabat *et al.*, 1993; Brown *et al.*, 1994b; Vaughan *et al.*, 1995; Zhang *et al.*, 1996; Gammon *et al.*, 1997) or in the Netherlands (Menke-Pluymers *et al.*, 1993), where chewing of betel quid with tobacco or use of other forms of smokeless tobacco are probably not strong confounders. One study conducted in Sweden was adjusted for snuff use (Lagergren *et al.*, 2000).

Intensity and duration of smoking

Six studies, three that included only cases of adenocarcinoma of the oesophagus (Menke-Pluymers *et al.*, 1993; Gammon *et al.*, 1997; Wu *et al.*, 2001) and three that included cases of adenocarcinoma of the oesophagus, gastro-oesophageal junction and gastric cardia combined (Kabat *et al.*, 1993; Brown *et al.*, 1994b; Vaughan *et al.*, 1995), showed a significant positive association of adenocarcinoma of the oesophagus with cigarette smoking; the relative risks were somewhat lower than those for squamous cell carcinoma of the oesophagus. Three studies, one in China (Gao *et al.*, 1994), one in Sweden (Lagergren *et al.*, 2000) and one in the USA (Zhang *et al.*, 1996), reported similarly elevated relative risks, but these risks were not statistically significant; in some studies this was probably because of the relatively small number of cases involved.

Of those studies that reported risks adjusted for alcohol consumption, a positive, significant dose–response relationship (Table 2.1.4.21) was found with intensity of smoking (Kabat *et al.*, 1993; Brown *et al.*, 1994b; Gammon *et al.*, 1997), duration of smoking (Gammon *et al.*, 1997) and/or pack–years (Vaughan *et al.*, 1995; Zhang *et al.*, 1996; Gammon *et al.*, 1997).

Cessation of smoking

Six studies provided point estimates for former smokers (Table 2.1.4.21). In five studies, relative risks were lower in former smokers than in current smokers, although they remained elevated (Kabat *et al.*, 1993; Gao *et al.*, 1994; Vaughan *et al.*, 1995; Gammon *et al.*, 1997; Wu *et al.*, 2001), and were increased in the sixth study (Lagergren *et al.*, 2000). The decrease in relative risk associated with years since cessation was weak, but a significant trend was found in two out of four studies (Gammon *et al.*, 1997; Wu *et al.*, 2001).

Sex

Kabat *et al.* (1993) examined risks for men and women separately and observed similar patterns in both sexes, although risks among current smokers and heavy smokers were somewhat higher for women than for men.

Overall, several well-conducted case–control studies, many from the USA, reported a statistically significantly higher risk for adenocarcinoma of the oesophagus in smokers than in nonsmokers. Positive dose–response relationships obtained using various indicators of amount smoked support a causal association, which is further corroborated by the findings of decreasing risks after smoking cessation. Several of these studies reported relative risks adjusted for alcohol consumption and other potential confounders. Further risk factors, such as chewing betel quid with tobacco or use of other forms of smokeless tobacco, have not been considered, but are not likely to be strong confounders. Studies from China and Europe also found increased risks for smokers.

(*f*) *Cancer of the larynx*

In the previous *IARC Monograph* on tobacco smoking (IARC, 1986), laryngeal cancer was one of the cancers strongly associated with cigarette smoking. Since then, more epidemiological evidence has become available to strengthen the conclusion.

(i) *Potential confounders*

Other causes of laryngeal cancer include alcohol consumption, some occupational exposures (e.g. sulfuric acid; IARC, 1992) and possibly some dietary habits. In investigating associations between smoking and laryngeal cancer, potential confounding by alcohol consumption is a concern. However, the risks associated with smoking are also modified by alcohol consumption (see Section 2.3). Consequently, the risk should be examined within strata of alcohol consumption and the joint effects of smoking and alcohol should be evaluated.

(ii) *Intensity and duration of smoking*

In all the cohort studies and case–control studies analysed (Tables 2.1.4.22–2.1.4.24) that were carried out in Asia, Europe and North and South America, the risk for laryngeal cancer was consistently higher in smokers, and a positive significant trend was observed with increasing duration and intensity of smoking.

In most case–control studies, the relative risks for laryngeal cancer were near to or greater than 10 for smokers who had smoked for longer than 40 years (Falk *et al.*, 1989; Zheng *et al.*, 1992c) or had smoked more than 20 cigarettes per day (Tuyns *et al.*, 1988; Falk *et al.*, 1989; Choi & Kahyo, 1991; Zatonski *et al.*, 1991; Muscat & Wynder, 1992; Zheng *et al.*, 1992c; Hedberg *et al.*, 1994; Sokic *et al.*, 1994). Cancer of the larynx in nonsmokers is so rare that several studies used light smokers as the reference category (Herity *et al.*, 1982; Olsen *et al.*, 1985; De Stefani *et al.*, 1987; Zatonski *et al.*, 1991; López-Abente *et al.*, 1992; Maier & Tisch, 1997). Consequently, relative risks were lower in these studies, although the increases were still statistically significant.

Two case–control studies reported odds ratios for cancer of the larynx that increased with decreasing age of starting smoking (Franceschi *et al.*, 1990; Zatonski *et al.*, 1991; Table 2.1.4.24).

(iii) *Cessation of smoking*

The risk for cancer of the larynx declines rather rapidly after cessation of smoking (Table 2.1.4.25). No detectable elevation compared with never-smokers was seen among subjects who had quit smoking for at least 10 years (Franceschi *et al.*, 1990; Ahrens *et al.*, 1991; Schlecht *et al.*, 1999).

(iv) *Type of cigarette*

Some investigators considered the role of type of tobacco (Table 2.1.4.26) and reported a 2.5-fold higher risk in smokers of black tobacco than in smokers of blond tobacco (Tuyns *et al.*, 1988; López-Abente *et al.*, 1992; De Stefani *et al.*, 1987). Smoking untipped cigarettes also led to a higher risk than smoking filter-tipped cigarettes (Wynder & Stellman, 1979; Tuyns *et al.*, 1988; Falk *et al.*, 1989).

(v) *Subsites*

Five studies investigated the risk for glottic and supraglottic cancer separately (Olsen *et al.*, 1985; Tuyns *et al.*, 1988; López-Abente *et al.*, 1992; Maier *et al.*, 1992b; Muscat

& Wynder, 1992). The cancer risk increased with increasing amount smoked per day and with cumulative exposure for both subsites (Table 2.1.4.24). In addition, the observed relative risks were up to 10-fold higher for supraglottic cancer than for glottic cancer (Maier *et al.*, 1992b).

(vi) *Sex*

Few studies investigated sex-specific effects. One cohort study (Raitiola & Pukander, 1997) reported similar risks for both men and women (Table 2.1.4.22), whereas in two case–control studies (Zheng *et al.*, 1992c; Tavani *et al.*, 1994), the relative risks for women were up to 10-fold higher than for the corresponding categories in men, perhaps because of the small number of cases involved (Table 2.1.4.24).

(*g*) *Cancer of the upper aerodigestive tract*

Cancers of the upper aerodigestive tract traditionally comprise cancers of the oral cavity, pharynx, larynx and oesophagus. In epidemiological studies, especially in cohort studies in which there are few cases at some sites, investigators often combine several cancer sites and term these 'cancer of the upper aerodigestive tract'. This section summarizes the data from 16 cohort studies (Table 2.1.4.27), 26 case–control studies (Tables 2.1.4.28–2.1.4.31) and one case-series report (Table 2.1.4.32).

(i) *Intensity and duration of smoking*

The results from the cohort studies are presented in Table 2.1.4.27. In all but two cohort studies, both from Japan (Kono *et al.*, 1987; Akiba, 1994), the risk for cancer of the upper aerodigestive tract was strongly associated with cigarette smoking. Relative risks increased with increasing daily cigarette consumption (Hammond & Horn, 1958; Doll *et al.*, 1980; Akiba & Hirayama, 1990; Kuller *et al.*, 1991; Doll *et al.*, 1994; Chyou *et al.*, 1995; Engeland *et al.*, 1996; Murata *et al.*, 1996; Yuan *et al.*, 1996; Kjaerheim *et al.*, 1998; Liaw & Chen, 1998), duration of smoking (Chyou *et al.*, 1995) or pack–years (Liaw & Chen, 1998).

Details of the case–control studies are presented in Table 2.1.4.28 and their results in Table 2.1.4.29. Intensity of smoking was measured in most of these studies. In addition to, or instead of, the number of cigarettes or grams of tobacco smoked per day, exposure to tobacco smoke was also measured in terms of pack–years, lifetime consumption or cumulative tar. The link between duration of smoking and cancer of the upper aerodigestive tract was examined in 10 case–control studies (Blot *et al.*, 1988; Merletti *et al.*, 1989; Barra *et al.*, 1991; De Stefani *et al.*, 1992; Franceschi *et al.*, 1992; Day *et al.*, 1993; Mashberg *et al.*, 1993; Kabat *et al.*, 1994; Lewin *et al.*, 1998; Bosetti *et al.*, 2000). Six case–control studies also considered age at starting smoking (Blot *et al.*, 1988; Merletti *et al.*, 1989; Barra *et al.*, 1991; Franceschi *et al.*, 1992; Day *et al.*, 1993; Lewin *et al.*, 1998).

All but one study (Rao *et al.*, 1999) reported an increase in risk for cancer of the upper aerodigestive tract associated with cigarette smoking. A clear dose–response relationship was seen with increasing daily tobacco consumption and duration of smoking as well as with decreasing age at starting smoking in most of the studies examined.

(ii) *Cessation of smoking*

Eight cohort studies (Doll *et al.*, 1980; Tomita *et al.*, 1991; Akiba, 1994; Doll *et al.*, 1994; Chyou *et al.*, 1995; Engeland *et al.*, 1996; Nordlund *et al.*, 1997; Kjaerheim *et al.*, 1998) provided point estimates for former smokers (Table 2.1.4.27). The relative risks for former smokers were always lower than those for current smokers.

Nine case–control studies examined the relative risk by years since quitting and generally reported a negative trend, which was statistically significant whenever analysed (Table 2.1.4.30).

(iii) *Type of cigarette*

The type of cigarette was examined in several case–control studies: characteristics studied included the use of a filter, the type of tobacco, the tar content and whether the product was manufactured or hand-rolled (Table 2.1.4.31). Consumption of black tobacco, untipped cigarettes, hand-rolled cigarettes, or cigarettes with a high-tar yield led to a higher risk than consumption of blond tobacco (Merletti *et al.*, 1989), filter-tipped cigarettes (Merletti *et al.*, 1989; Mashberg *et al.*, 1993; Kabat *et al.*, 1994), manufactured cigarettes (De Stefani *et al.*, 1992) or low-tar cigarettes (Franceschi *et al.*, 1992), respectively, except in one multivariate analysis (Merletti *et al.*, 1989).

(iv) *Sex*

Sex-specific effects were analysed in two cohort studies (Hammond & Seidman, 1980; Akiba & Hirayama, 1990; Table 2.1.4.27) and four case–control studies (Table 2.1.4.29). Both cohort studies reported a higher relative risk for male smokers than for female smokers. One case–control study (Merletti *et al*., 1989) also reported higher relative risks for men than for women (Table 2.1.4.31), and the trends were generally in the same direction for both men and women in all categories. An exception to the pattern was that for women the relative risk for smoking filter-tipped cigarettes was higher than that for smoking untipped cigarettes.

Three case–control studies (Blot *et al.*, 1988; Kabat *et al.*, 1994; Muscat *et al.*, 1996) found that the relative risks were higher for women than for men in all categories of intensity of smoking (number of cigarettes per day), cumulative exposure (cumulative tar consumption, pack–years, duration of smoking) and age at starting smoking, as well as for former smokers. However, the trends were always in the same direction and of the same order of magnitude.

Overall, the strength of association was generally similar, especially when taking into account the fact that women generally under-report levels of smoking and that most studies included many fewer women than men.

(v) *Ethnicity*

Relative risks were reported separately for blacks and whites in a large case–control study from the USA (Day *et al.*, 1993; Table 2.1.4.29). Relative risks adjusted for alcohol consumption, sex and other relevant variables were very similar for the number of cigarettes smoked per day, years of cigarette smoking, age at starting smoking and number of years since stopping smoking.

(vi) *Case-series report*

One case-series report from Saudi Arabia, from where no other information was available, is presented in Table 2.1.4.32. The data are of limited value in assessing causality, but have been included for the sake of completeness.

(vii) *Second primary tumours*

The occurrence of second primary tumours was investigated in three studies (Day *et al.*, 1994; Barbone *et al.*, 1996; Cianfriglia *et al.*, 1999) and their results are presented in Table 2.1.4.33. All these studies showed an increased risk of second upper aerodigestive tract cancer after a previous cancer in the same organs.

The similarity in the association observed between tobacco smoking and cancers of various upper aerodigestive organs is consistent with the concept of field cancerization, i.e. the concomitant occurrence of carcinogenic alterations in different areas of the mucosa of the upper aerodigestive tract.

Table 2.1.4.1. Cohort studies on tobacco smoking and cancer of the oral cavity

Reference Country and years of study	Subjects	Cancer site ICD code	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Weir & Dunn (1970) 1954–62	Californian Study 68 153 men	Oral cavity ICD: 141 tongue 143 gum 144 floor of mouth		19			Nonsmokers include cigar and/or pipe only smokers.
			Ever smoker		2.8		
			Cigarettes/day				
			1–14		3.7		
			15–25		1.2		
			> 25		5.5		
McLaughlin *et al.* (1995) USA 1954–80	US Veterans' Study 248 046 men	Oral cavity ICD-7: 140 lip 141 tongue 142 salivary glands 143 gum 144 floor of mouth		189			Adjusted for attained age and calendar-year time-period at death
			Former smoker		1.5	0.9–2.4	
			Ever-smoker		2.6	1.8–3.9	
			Current smoker		3.4	2.3–5.0	
			Cigarettes/day				
			1–9		0.6	0.2–2.1	
			10–20		2.5	1.6–4.0	
			31–39		5.4	3.5–8.4	
			≥ 40		8.6	4.7–15.7	*p* for trend < 0.01
Nordlund *et al.* (1997) Sweden 1964–89	Swedish Census Study 26 032 women	Oral cavity ICD-7: 140 lip 141 tongue 142 salivary glands 143 gum 144 floor of mouth		46			Adjusted for age and place of residence
			Current smoker		1.6	0.7–3.5	

CI, confidence interval

Table 2.1.4.2. Case–control studies on tobacco smoking and oral cancer: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Franceschi *et al.* (1990) Italy 1986–89	Men: 157 cases and 1272 controls	Hospital-based study Cases of cancer of the oral cavity, histologically confirmed, aged < 75 years; 98% response rate Controls were inpatients with acute conditions unrelated to tobacco or alcohol consumption, without malignant tumours, chosen on the basis of area of residence and age (± 5-year categories); 97% response rate
Nandakumar *et al.* (1990) India 1982–84	Men: 115 cases and 115 controls; women: 233 cases and 233 controls	Hospital-based study 93% cases histologically confirmed Controls: patients attending the same hospital during the same period, with no diagnosis of cancer, individually matched on sex, age and residence
Zheng *et al.* (1990) China 1988–89	Men: 248 cases and 248 controls; women: 156 cases and 156 controls	Hospital-based study in seven hospitals from the Beijing area Cases histologically confirmed, mainly squamous-cell carcinoma Controls randomly selected from non-cancer patients diagnosed within 1 year of interview, individually matched on age and sex
Choi & Kahyo (1991) Republic of Korea 1986–89	Men: 113 casess and 339 controls; women: 44 cases and 132 controls	Based on several studies within the Korea Cancer Centre Hospital Some cases histologically confirmed Controls selected from patients excluding individuals with cancers at other sites or tobacco- and alcohol-related diseases, matched 3:1 on age, sex and admission date
Oreggia *et al.* (1991) Uruguay 1987–89	Men: 57 cases and 353 controls	Hospital-based study in the university hospital at Montevideo Cases histologically confirmed as squamous-cell carcinoma Controls selected from patients with conditions unrelated to tobacco or alcohol consumption

Table 2.1.4.2 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Franceschi *et al.* (1992) Italy 1986–90	Men: 102 cases and 726 controls	Hospital-based study in the Pordenone province and the greater Milan area (Lombardy region) Cases histologically confirmed Non-cancer controls admitted to the same hospitals for acute illnesses unrelated to tobacco or alcohol consumption
Maier *et al.* (1992a) Germany 1987–88	Men: 200 cases and 800 controls	Hospital-based study in two university clinics in Giessen and Heidelberg Cases histologically confirmed as squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx Non-cancer controls, matched 4:1 on age and residential area
Bundgaard *et al.* (1995) Denmark 1986–90	Men: 97 cases and 250 controls; women: 64 cases and 150 controls	Population-based study Cases histologically confirmed as primary squamous-cell carcinoma and verrucous carcinoma Controls drawn from the Danish Central Population Register, matched on sex and age
Ko *et al.* (1995) China, Province of Taiwan 1992–93	Men: 104 cases and 194 controls; women: 3 cases and 6 controls	Hospital-based study in a dentistry department Cases histologically confirmed Controls: non-carcinoma patients treated in the hospital's ophthalmology and physical check-up departments, matched on sex and age
Macfarlane *et al.* (1995) China, 1988–89 Italy, 1975–83 USA, 1982–84	Men: 549 cases and 834 controls; women, 286 cases and 466 controls	Meta-analysis of three studies in Beijing, Turin and New York Cases histologically confirmed Population and hospital controls

Table 2.1.4.2 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Hung *et al.* (1997) China, Province of Taiwan 1996	Men: 41 cases and 123 controls	Population-based study Cases histologically confirmed Controls randomly selected from household registration offices in Taipei, matched 3:1 on age and ethnicity
Zheng *et al.* (1997) China 1988–89	Men: 65 cases and 65 controls; women: 46 cases and 46 controls	Hospital-based study in seven hospitals from the Beijing area Cases histologically confirmed Controls randomly selected from non-cancer patients attending the same hospital for conditions unrelated to smoking or alcohol consumption, matched on age and sex
De Stefani *et al.* (1998) Uruguay 1992–96	Men: 206 cases and 437 controls	Hospital-based study Cases histologically confirmed as squamous-cell carcinoma of the oral cavity Controls with diseases unrelated to smoking or alcohol consumption, without non-neoplastic lesions of the oral cavity and pharynx, selected from the same hospital, frequency-matched by age (10-year periods), residence and urban/rural status
Schildt *et al.* (1998) Sweden 1980–89	Men: 237 cases and 237 controls; women: 117 cases and 117 controls	Population-based study Histologically confirmed cases of squamous-cell oral cancer reported to Cancer Registry Living controls drawn from the National Population Registry, deceased controls from the National Registry for Causes of Death; all controls matched on age, sex, residence and year of death (for deceased controls)

Table 2.1.4.2 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Franceschi *et al.* (1999) Italy and Switzerland 1992–97	Men: 274 cases and 1254 controls	Multicentre hospital-based study Cases histologically confirmed Controls admitted for acute non-neoplastic conditions unrelated to alcohol abuse or tobacco smoking, frequency-matched by age and area of residence
Hayes *et al.* (1999) Puerto Rico 1992–95	Men: 298 cases and 417 controls; women: 69 cases and 104 controls	Population-based study Cases histologically confirmed, reported to the Central Cancer Registry Controls younger than 65 years selected from residents of the neighbourhood; controls aged 65 years and over selected from the rosters of the Health Care Financing Administration

Table 2.1.4.3. Case–control studies on tobacco smoking and oral cancer: intensity, duration and age at starting smoking

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Franceschi	Oral cavity:	147	967	Current smoker	11.1	3.4–34.8	Adjusted for age, area of
et al. (1990)	ICD-9:			Cigarettes/day			residence, education,
Italy	140 lip	26	313	≤ 14	5.3	1.5–17.6	occupation and alcohol intake
1986–89	141 tongue	79	396	15–24	14.3	4.4–46.7	
	143 gum	42	258	≥ 25	14.3	4.2–48.0	*p* for trend < 0.01
	144 floor of mouth			Duration (years)			
	145 other parts of	34	414	1–29	5.9	1.8–18.7	
	mouth	49	255	30–39	14.3	4.3–47.7	
		69	300	≥ 40	18.0	5.4–60.4	*p* for trend < 0.01
				Age at starting (years)			
		23	224	≥ 25	9.2	2.7–31.7	
		74	498	17–24	10.0	3.1–32.5	
		54	247	< 17	13.6	4.1–44.9	*p* for trend < 0.01
Nandakumar	Oral cavity:			Cigarette smoker	3.5	1.5–8.2	
et al. (1990)	lip, anterior tongue,			Cigarettes/day			
India	alveolus and mouth	17	23	1–10	1.2	0.6–2.7	
1982–84		37	24	11–20	2.5	1.2–5.4	
		32	25	> 20	2.1	1.0–4.4	
				Duration (years)			
		10	6	1–5	2.6	0.8–8.6	
		9	14	6–15	0.9	0.3–2.7	
		18	18	16–25	1.5	0.6–3.5	
		49	34	> 25	2.2	1.1–4.3	

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Zheng *et al.*	Oral cavity:	Men	Men				Adjusted for age, alcohol
(1990)	ICD-9:	22	36	Former smoker	1.1	0.6–2.1	consumption and education
China	141 tongue	190	143	Ever-smoker	2.1	1.3–3.3	
1988–89	143 gum	168	107	Current smoker	2.4	1.5–4.0	
	144 floor of mouth			Cigarettes/day			
	145 other parts of	64	30	< 10	1.2	0.6–2.4	
	mouth	61	49	10–19	2.0	1.2–3.6	
		61	46	20	2.2	1.1–4.1	
		44	18	> 20	3.7	1.8–7.9	
				Duration (years)			
		44	48	< 26	1.4	0.8–2.5	
		42	36	26–32	1.9	1.0–3.7	
		49	31	33–41	2.3	1.1–4.6	
		55	28	> 41	4.5	2.1–9.6	
				Pack–years			
		35	49	< 15	1.2	0.7–2.3	
		44	35	15–24	2.0	1.1–3.6	
		49	28	25–34	3.2	1.6–6.7	
		62	31	> 34	3.7	1.8–7.4	

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Zheng *et al.*		Women	Women				
(1990)		52	16	Ever-smoker	2.8	1.5–5.4	
(contd)				Current smoker			
				Cigarettes/day			
		17	7	< 10	2.1	0.8–5.7	
		22	7	10–19	2.9	1.1–7.4	
		13	2	> 19	5.9	1.1–31.7	
				Duration (years)			
		10	4	< 25	2.0	0.6–0.09 [sic]	
		19	4	25–34	4.7	1.5–15.3	
		23	8	> 34	2.3	0.9–6.2	
				Pack–years			
		15	7	< 13	2.9	0.7–4.7	
		17	6	13–23	3.8	1.1–13.4	
		20	3	> 23	9.0	1.5–27.3	

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Choi & Kahyo (1991) Republic of Korea 1986–89	Oral cavity ICD-9: 140 lip 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth	7	48	Former smoker	0.9	0.4–2.2	Analysis for men only; adjusted for alcohol use Cases in women (44) included 42 nonsmokers and 2 current smokers. Female controls (131) included 112 nonsmokers, 18 current smokers and 1 former smoker.
		91	201	Current smoker	2.5	1.3–4.5	
				Cigarettes/day			
		69	196	1–20	1.9	1.02–3.3	
		27	50	21–40	3.1	1.5–6.5	
		2	3	≥ 41	6.1	1.01–37.0	
				Duration (years)			
		16	53	1–19	1.9	0.8–4.3	
		45	128	20–39	2.0	1.01–4.0	
		37	68	≥ 40	3.0	1.6–5.8	
				Age at starting (years)			
		12	44	≥ 25	1.8	0.7–4.2	
		75	170	18–24	2.4	1.3–4.4	
		11	35	≤ 17	1.9	0.8–4.7	
Oreggia *et al.* (1991) Uruguay 1987–89	Tongue	11	92	Former smoker	11.8	1.4–100.4	Adjusted for age, county, total alcohol consumption, variables analysed and type of tobacco
		45	154	Current smoker	29.4	3.7–234.2	
				Cigarettes/day			
		8	201	≤ 10	1.0	–	
		9	61	11–20	1.9	0.6–5.4	
		13	42	21–30	3.6	1.3–10.2	
		27	49	≥ 31	5.2	2.0–13.3	p for trend < 0.001

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Oreggia *et al.* (1991) (contd)				Duration (years)			
		6	144	≤ 29	1.0	–	
		10	67	30–39	1.5	0.5–5.0	
		23	83	40–49	3.1	1.1–9.1	
		18	59	≥ 50	3.6	1.0–12.5	p for trend < 0.01
				Age at starting (years)			
		25	71	≤ 14	1.0	–	
		23	97	15–19	1.1	0.5–2.3	
		8	78	≥ 20	0.5	0.2–1.3	p for trend = 0.25
Franceschi *et al.* (1992) Italy 1986–90	Tongue ICD-9: 141	15	260	Former smoker	2.1	0.6–7.7	Adjusted for age, area of residence, occupation and alcohol habits
		83	306	Current smoker	10.5	3.2–34.1	
				Cigarettes/day			
		15	206	≤ 14	2.9	0.8–10.2	
		52	229	15–24	9.0	2.7–29.8	
		29	125	≥ 25	9.8	2.8–33.6	p for trend ≤ 0.01
				Duration (years)			
		24	229	≤ 29	3.7	1.1–12.8	
		29	157	30–39	7.7	2.3–26.2	
		43	174	≥ 40	12.4	3.6–43.3	p for trend ≤ 0.01
				Age at starting (years)			
		45	280	≥ 20	6.3	1.9–20.9	
		54	282	≤ 19	7.6	2.3–25.0	p for trend ≤ 0.01

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Maier *et al.* (1992a) Germany 1987–88	Oral cavity	47	188	Pack–years			Adjusted for alcohol consumption
				< 5	1.0	–	
				5–50	17.1	3.4–85.3	Study included cigar and pipe smokers (1 pack = 20 cigarettes or 4 cigars or 5 pipes).
				> 50	77.5	11.0–545.6	p for trend = 0.0001
Bundgaard *et al.* (1995) Denmark 1986–90	Intra-oral sites: buccal mucosa, upper alveolus and gingiva, lower alveolus and gingiva, hard palate, tongue, retromolar area, floor of mouth	58	128	Daily tobacco consumption (g)			Adjusted for alcohol consumption
		52	41	1–20	2.1	1.3–3.5	1g tobacco equals one cigarette
				≥ 21	5.8	3.1–10.9	p for trend < 0.001
				Lifetime tobacco consumption (kg)			
		30	116	1–135	1.7	0.9–3.2	
		32	76	136–235	2.5	1.3–5.0	
		73	68	≥ 236	6.3	3.1–12.9	p for trend < 0.001
				Lifetime tobacco consumption (kg)			Adjusted for lifetime consumption of alcohol, marital status, residence and no. of teeth
				1–135	1.7	0.9–3.4	
				136–235	2.2	1.1–4.5	
				≥ 236	6.1	2.8–13.0	p for trend < 0.001

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Ko *et al.* (1995) China, Province of Taiwan 1992–93	Oral cavity ICD: 140 lip 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth	11 85	30 98	Former smoker Current smoker	3.6 4.6	0.9–14.6 1.5–14.0	Adjusted for betel quid chewing, alcohol consumption, education and occupation
Macfarlane *et al.* (1995) China, Italy, USA 1975–89	Oral cavity ICD-9: 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth			Men			Adjusted for age, study centre, education, alcohol consumption, alcohol–study centre interaction. No cases of floor-of-mouth cancer were found among male nonsmokers.
				1–33 pack–years			
				Tongue	1.6	0.9–2.8	
				Gum	1.5	0.8–2.7	
				Floor of mouth	–	–	
				Other/unspec. mouth	1.6	0.8–2.9	
				> 33 pack–years			
				Tongue	2.9	1.5–5.6	
				Gum	1.7	0.8–3.8	
				Floor of mouth	–	–	
				Other/unspec. mouth	3.1	1.5–6.3	

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Macfarlane *et al.* (1995) (contd)				Women			
				1–33 pack–years			
				Tongue	2.5	1.1–5.3	
				Gum	0.5	0.1–2.3	
				Floor of mouth	8.4	1.6–44.7	
				Other/unspec. mouth	3.6	1.6–8.2	
				> 33 pack–years			
				Tongue	4.9	2.1–11.4	
				Gum	3.8	1.0–14.0	
				Floor of mouth	14.2	2.4–84.3	
				Other/unspec. mouth	7.5	3.2–18.1	
				Pack–years			Analysis restricted to abstainers from alcohol
		88 men		1–33	1.1	0.6–2.2	
				> 33	1.3	0.6–3.1	
		153 women		1–18	2.6	1.2–5.6	
				> 18	4.6	1.9–10.9	
Hung *et al.* (1997) China, Province of Taiwan 1996	Oral cavity ICD-9: 140 lip 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth	37	81	Ever-smoker	5.0	1.7–15.1	Adjusted for age and ethnicity; 30 cases and 15 controls chewed betel quid, all of whom smoked cigarettes. p for trend = 0.027
				Pack–years			
		14	41	< 22.5	4.0	1.2–13.5	
		23	40	≥ 22.5	5.9	1.9–18.5	

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Zheng *et al.* (1997) China 1988–89	Tongue	3	10	Former smoker	0.5	0.1–2.2	Adjusted for alcohol consumption and education
		63	43	Ever-smoker	2.2	1.1–4.6	
		60	33	Current smoker	2.7	1.3–5.2	
				Cigarette equivalents/day			
		30	22	≤ 15	1.9	0.9–4.2	
		33	21	> 15	2.9	1.2–7.2	
				Duration (years)			
		25	18	< 30	2.1	0.9–4.9	
		38	25	≥ 30	2.4	1.0–5.9	
				Pack–years			
		23	23	≤ 20	1.3	0.6–3.0	
		40	30	> 20	5.1	1.8–14.5	
				Age at starting (years)			
		29	18	≥ 21	2.6	1.1–6.0	
		24	25	< 21	1.9	0.9–4.5	

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
De Stefani *et al.* (1998) Uruguay 1992–96	Oral cavity: mucosal surface of the lip, tongue, other parts of mouth	36	105	Former smoker	2.2	1.2–3.9	Adjusted for age, residence, urban/rural status, birthplace, education and total alcohol consumption
		182	287	Ever-moker	4.2	2.6–6.8	
		146	172	Current smoker	5.7	3.4–9.5	
				Cigarettes/day			
		27	91	1–14	1.9	1.0–3.5	
		76	106	15–24	5.1	2.9–8.7	
		79	80	≥ 25	6.1	3.5–10.8	
				Duration (years)			
		51	99	1–39	3.5	1.8–6.5	
		68	98	40–49	4.3	2.5–7.5	
		63	80	≥ 50	4.5	2.5–7.9	
				Pack–years			
		34	100	1–28	2.2	1.2–4.1	
		52	61	29–47	5.5	3.1–9.9	
		47	70	48–76	4.4	2.7–7.9	
		49	46	≥ 77	5.7	3.1–10.6	
Schildt *et al.* (1998) Sweden 1980–89	Oral cavity ICD-9: 140 lip 141 tongue 143 gum	80	95	Former smoker	1.0	0.6–1.6	Adjusted for alcohol consumption, oral snuff and chewing tobacco Never snuff-users only
		202	183	Ever-moker	1.3	0.9–1.9	
		122	88	Current smoker	1.8	1.1–2.7	
				Lifetime consumption (kg)			
	144 floor of mouth	48	52	≤ 124.8	1.2	0.7–1.9	
	145 other parts of mouth	79	58	> 124.8	1.2	1.1–2.9	

Table 2.1.4.3 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Franceschi *et al.* (1999)	Oral cavity (lip and salivary glands excluded)			Current smoker			Adjusted for alcohol consumption
Italy and Switzerland				Cigarettes/day			
1992–97		27		1–14	3.3	1.5–7.2	
		98		15–24	7.7	3.8–15.4	
		72		≥ 25	10.7	5.0–22.8	
Hayes *et al.* (1999)	Oral cavity	Men	Men				Adjusted for age and alcohol use
Puerto Rico	ICD-9:	259	270	Ever-smoker	3.9	2.1–7.1	
1992–95	141 tongue			Cigarettes/day			
	143 gum	9	61	1–9	0.9	0.4–2.4	
	144 floor of mouth	30	53	10–19	2.8	1.3–6.0	
	145 other parts of mouth	118	89	20–39	6.0	3.1–11.4	
		101	65	≥ 40	4.9	2.5–9.7	*p* for trend < 0.0001
		Women	Women				
		36	30	Ever-smoker	4.9	2.0–11.6	
				Cigarettes/day			
		5	9	1–9	2.2	0.6–8.4	
		6	7	10–19	4.3	1.1–16.1	
		19	12	20–39	6.4	2.1–19.6	
		6	2	≥ 40	28.2	3.7–216.0	*p* for trend = 0.0001

CI, confidence interval; unspec., unspecified

Table 2.1.4.4. Case–control studies on tobacco smoking and oral cancer: smoking cessation

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Years since quitting	Relative risk	95% CI	Comments
Franceschi *et al.* (1990) Italy 1986–89	Oral cavity ICD-9: 140 lip 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth	147 20 5	967 203 197	Current smoker < 10 ≥ 10	11.1 5.7 1.1	3.4–34.8 1.6–20.8 0.3–5.1	Adjusted for age, area of residence, education, occupation and alcohol intake p for trend < 0.01
Choi & Kahyo (1991) Republic of Korea 1986–89	Oral cavity ICD-9: 140 lip 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth	91 2 3 2	201 4 15 29	Current smoker 1–4 5–9 ≥ 10	1.0 0.7 0.6 0.2	– 0.1–3.9 0.2–2.2 0.1–0.7	Analysis for men only; adjusted for alcohol use
Oreggia *et al.* (1991) Uruguay 1987–89	Tongue	45 5 2 4	154 28 23 41	Current smoker 1–4 5–9 ≥ 10	1.0 0.4 0.3 0.2	– 0.1–1.2 0.1–1.4 0.0–0.6	Adjusted for age, county, total alcohol intake, intensity and duration of smoking, age at starting smoking and type of tobacco p for trend < 0.001

Table 2.1.4.4 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Years since quitting	Relative risk	95% CI	Comments
Franceschi *et al.* (1992) Italy 1986–90	Tongue ICD-9: 141	83	306	Current smoker	10.5	3.2–34.1	Adjusted for age, area of residence, occupation and alcohol habits
		12	122	< 10	3.8	1.0–14.5	*p* for trend < 0.01
		3	138	≥ 10	0.7	0.1–3.8	
Macfarlane *et al.* (1995) China, Italy, USA 1975–89	Oral cavity ICD-9: 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth			Current smoker	1.0	–	Adjusted for age, sex, study centre, education, alcohol consumption, previous tobacco use and interaction terms for study centre/education and study centre–alcohol use
				< 1	1.2	0.7–1.8	
				1–9	0.7	0.5–1.1	
				≥ 9	0.5	0.3–0.7	
De Stefani *et al.* (1998) Uruguay 1992–96	Oral cavity: mucosal surface of the lip, tongue, other parts of mouth	146	172	Current smoker	5.8	3.5–9.6	Adjusted for age, residence, urban/rural status, birthplace, education and total alcohol consumption
		20	40	1–4	3.2	1.6–6.5	
		12	28	5–9	2.7	1.2–6.1	
		4	37	≥ 10	0.7	0.2–2.1	
Hayes *et al.* (1999) Puerto Rico 1992–95	Oral cavity ICD-9: 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth	Men	Men				Adjusted for age and alcohol use
		259	270	Current smoker	3.9	2.1–7.1	
		183	103	< 2	7.5	3.9–14.4	
		37	38	2–9	4.1	1.8–8.9	
		20	56	10–19	2.0	0.9–4.5	
		18	73	≥ 20	1.2	0.5–2.7	
		Women	Women				
		36	30	Current smoker	4.9	2.0–11.6	
		23	10	< 2	14.1	4.2–47.2	
		8	5	2–9	8.7	2.2–35.2	
		2	4	10–19	2.1	0.3–13.9	
		2	10	≥ 20	0.8	0.1–4.2	

CI, confidence interval

Table 2.1.4.5. Case–control studies on tobacco smoking and oral cancer: type of tobacco and/or cigarette

Reference (country and years of study)	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Oreggia *et al.* (1991) Uruguay 1987–89	Tongue			Type of tobacco			Adjusted for age, county, total alcohol consumption, smoking intensity and duration, age at starting smoking p for trend < 0.25
		10	106	Blond	1.0	–	
		6	23	Mixed	1.8	0.5–6.8	
		40	117	Black	4.0	1.7–9.6	
Franceschi *et al.* (1992) Italy 1986–90	Tongue ICD-9: 141			Tar yield			Adjusted for age, area of residence, occupation and alcohol habits p for trend < 0.01
		49	364	Low tar (< 22 mg)	5.8	1.8–19.1	
		45	185	High tar (≥ 22 mg)	9.8	2.9–33.1	
De Stefani *et al.* (1998) Uruguay 1992–96	Oral cavity, mucosal surface of the lip, tongue, other parts of mouth			Type of tobacco			Adjusted for age, residence, urban/rural status, birthplace, education and total alcohol consumption
		91	222	Mainly blond	2.4	1.5–4.1	
		91	55	Mainly black	9.4	5.4–16.3	
				Duration by tobacco type			
		32	85	Blond 1–39 years	2.3	1.2–4.5	
		59	137	Blond ≥ 40 years	2.5	1.4–4.3	
		19	13	Black 1–39 years	8.3	3.5–19.7	
		72	42	Black ≥ 40 years	9.7	5.4–17.3	
				Hand-rolling			
		45	107	Lifelong manufactured	2.9	1.6–5.2	
		31	69	Mixed	2.6	1.4–4.9	
		106	101	Lifelong hand-rolled	6.1	3.6–10.2	
				Duration by hand-rolling			
		17	49	Manufactured 1–39 years	2.6	1.2–5.6	
		28	58	Manufactured ≥ 40 years	3.2	1.7–6.1	
		34	49	Rolled 1–39 years	4.2	2.1–8.2	
		103	121	Rolled ≥ 40 years	4.8	2.9–8.1	

Table 2.1.4.5 (contd)

Reference (country and years of study)	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
De Stefani *et al.* (1998) (contd)				Filter use			
		6	25	Lifelong filter	1.7	0.6–4.8	
		48	129	Mixed	2.3	1.3–4.1	
		128	123	Lifelong plain	6.0	3.6–10.0	
				Smoking pattern			
		28	96	Blond + manufactured	1.9	0.9–3.5	
		63	126	Blond + hand-rolled	2.8	1.6–4.8	
		17	11	Black + manufactured	10.3	4.2–25.1	
		74	44	Black + hand-rolled	9.2	5.1–16.3	
Hayes *et al.* (1999) Puerto Rico 1992–95	Oral cavity ICD-9: 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth	Men	Men				Adjusted for age and alcohol use
		259	270	Cigarettes	3.9	2.1–7.1	
		11	7	Other tobacco only	7.6	2.1–27.7	
		Women	Women				
		36	30	Cigarettes + other tobacco	4.9	2.0–11.6	
		6	3	Other tobacco only	7.1	1.4–34.6	

CI, confidence interval

Table 2.1.4.6. Case-series on smoking and oral cancer

Reference[a] Country and years of study	Cancer subsite	%	No. of cases	Age	Histological types	Exposures		Comments
Sein *et al.* (1992)	Alveolar ridge	61	35 men	15–85 years	85.7% squamous-	*Smoking habit*	*%*	Incident cases
Myanmar	Buccal mucosa	15	35 women		cell carcinoma	Nonsmoker	32.9	only
1985–88						Occasional	1.4	
						Regular 65.7		
Ma'aita (2000)	Tongue	23	89 men	35–90 years;	96% squamous-cell	*Smoking habit*	*%*	
Jordan	Buccal mucosa		29 women	mean age,	carcinoma	Nonsmoker	24	
1989–98	and sulcus	5		62.5 years		Cigarette smoker	55	
	Gingiva	6				Pipe/cigar	21	
	Lower alveolar							
	ridge	19						
	Upper alveolar							
	ridge	9						
	Floor of mouth	34						
	Palate	4						

[a] Studies from regions where no other analytical epidemiological data are available

Table 2.1.4.7. Case–control studies on tobacco smoking and sinonasal cancer: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility
Brinton *et al.* (1984) USA 1970–80	Men: 93 cases and 183 controls; women, 67 cases and 1076 controls	Hospital-based study in four hospitals in two states Cases diagnosed as cancer of the nasal cavity (61), maxillary sinus (71) or other sinuses (28), histologically confirmed as squamous-cell carcinomas (54%), adenocarcinomas (15%) or others (31%), aged ≥ 18 years; response rate, 83% Controls (178 hospital controls for living cases and 112 death certificate controls for deceased cases), matched on hospital, admission year, age, sex, race and residence; response rate, 78%; cancers and other conditions of upper aerodigestive tract were excluded.
Ng (1986) Hong Kong SAR 1974–81	Men: 157 cases and 158 controls; women: 68 cases and 68 controls	Hospital-based study at the Institute of Radiology and Oncology Cases of cancers of the nasal fossa (82), maxillary sinus (110) and other sinuses (33), aged ≥ 18 years Controls with all other malignancies except nasopharyngeal cancer, randomly selected and individually matched on admission year, age (± 5 years), sex, race and resident status
Hayes *et al.* (1987) The Netherlands 1978–81	Men: 92 cases and 195 controls	Population-based study Cases of cancers of the nasal cavity and sinuses, including 28 deceased cases, histologically confirmed as squamous-cell carcinomas (54%) or adenocarcinomas (26%), aged 35–79 years; response rate, 79% Controls included a random sample of residents in the country and of persons deceased during 1980; response rate, 75%
Strader *et al.* (1988) USA 1979–83	Men: 33 cases and 327 controls; women: 20 cases and 225 controls	Population-based study in Washington Cases identified by the population-based cancer registry, histologically confirmed as squamous-cell carcinomas (51%), adenocarcinomas (11%) or other types (38%), aged 20–74 years; response rate, 72% Controls selected by random-digit dialling and matched by age and sex; 83% of eligible controls participated
Fukuda & Shibata (1990) Japan 1982–86	Men: 125 cases and 250 controls; women: 44 cases and 88 controls	Population-based study in Hokkaido Incident cases of squamous-cell carcinoma of the maxillary sinus, aged 40–79 years; response rate, 96.6% Controls matched by sex, age and area of residence; response rate, 93.4%

Table 2.1.4.7 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility
Zheng *et al.* (1992b) China 1988–90	Men: 39 cases and 269 controls; women: 21 cases and 145 controls	Population-based study conducted in Shanghai Cases of cancers of the nasal cavity, paranasal sinuses and middle ear, including 40% of squamous-cell carcinomas, aged 20–75 years; response rate, 95.2% Controls frequency matched on sex and age; response rate, 89.6%
Zheng *et al.* (1993) USA 1986	White men: 147 cases and 449 controls	Data from the 1986 US National Mortality Followback Survey Deaths from cancer of the maxillary sinus (76), nasal cavity (11), other sinuses (56) and auditory tube and middle ear (4), aged ≥ 45 years; response rate, 88% Controls aged ≥ 45 years who died from causes unrelated to smoking or alcohol consumption
't Mannetje *et al.* (1999) France, Germany, Italy, Netherlands and Sweden 1979–90	Men: 451 cases and 1464 controls; women: 104 cases and 241 controls	Pooled analysis of eight studies conducted in five European countries Cases of sinonasal cancer, histologically confirmed as squamous-cell carcinomas (43%), adenocarcinomas (29%), other types (26%) and of unknown histology (1%)
Caplan *et al.* (2000) USA 1984–88	Men: 70 cases and 1910 controls	Population-based study (Selected Cancers Study) Cases identified from the registries, histologically confirmed as carcinomas (74%) or non-carcinomas (26%), aged 35–60 years; response rate, 78% of all cases Controls selected by random-digit dialling, frequency-matched to another case group by geographical area and age (5-year groups)

Table 2.1.4.8. Case–control studies on tobacco smoking and cancer of the nasal cavity and sinuses

Reference Country and years of study	Cancer subsite ICD code	Exposure categories	Relative risk	95% CI	Comments
Brinton *et al.* (1984) USA 1970–80	Nasal cavity, sinuses ICD-8: 160.0; 160.2–5; 160.8–9	Squamous-cell carcinomas (*n* = 86)			Adjusted for sex
		Current smoker	1.8		
		Duration (years)			
		< 30	1.7		
		30–39	1.9		
		40–49	1.9		
		≥ 50	3.0		
		Adenocarcinomas (*n* = 24)			
		Current smoker	0.6		
		Duration (years)			
		< 30	1.5		
		30–39	0.4		
		40–49	0.8		
		≥ 50	1.4		
Ng (1986) Hong Kong SAR 1974–81	Nasal cavity, sinuses ICD-8: 160.0, 160.2–5; 160.8–160.9	Current smoker	1.4	0.9–2.3	Referent group included large proportions of smoking-associated malignancies; inconsistent trend with duration or intensity of smoking; relative risk was not reduced after adjusting for confounders.
Hayes *et al.* (1987) The Netherlands 1978–81	Nasal cavity, accessory sinuses ICD-9: 160.0; 160.2–160.5	Squamous-cell carcinomas (*n* = 48)			Adjusted for age; small sample size
		Ever-smoker	3.0	0.9–20.8	
		Current smoker	3.1	1.2–9.9	
		Cigarettes/day			
		1–9	1.7		
		10–19	2.6		
		20–34	1.8		
		≥ 35	5.1		*p* for trend < 0.005

Table 2.1.4.8 (contd)

Reference Country and years of study	Cancer subsite ICD code	Exposure categories	Relative risk	95% CI	Comments
Hayes *et al*. (1987) (contd)		Adenocarcinomas (*n* = 23)			
		Ever-smoker	3.0	0.5–65.5	
		Current smoker	1.4	0.5–5.5	
		Cigarettes/day			
		1–9	1.8		
		10–19	1.3		
		20–34	1.5		
		≥ 35	0.8		*p* for trend > 0.005
Strader *et al*. (1988) USA 1979–83	Nasal cavity, sinuses ICD-O (1976): 160.0–160.9	≥ 40 pack–years vs ≤ 1 pack–year			Referent group may not be appropriate. Increased relative risk with increasing levels of smoking
		All types (*n* = 53)	1.7	0.8–3.9	
		Squamous-cell (*n* = 27)	6.6	1.7–29.6	
Fukuda & Shibata (1990) Japan 1982–86	Maxillary sinuses ICD-9: 160.2	Cigarettes/day			Analysis for men only; study included only squamous-cell carcinomas.
		< 10	2.7		
		10–19	2.5		
		20–39	2.9		
		> 39	4.6		
		Pack–years			
		< 25	2.1		
		25–50	2.9		
		> 50	4.1		

Table 2.1.4.8 (contd)

Reference Country and years of study	Cancer subsite ICD code	Exposure categories	Relative risk	95% CI	Comments
Zheng *et al.* (1992b) China 1988–90	Nasal cavity, paranasal sinuses, middle ear ICD-9: 160	All types (*n* = 60)			Adjusted for age (< 63 vs ≥ 63 years)
		Ever-smoker	0.7	0.4–1.2	
		Cigarettes/day			
		< 20	0.7	0.4–1.2	
		≥ 20	0.7	0.3–1.9	
		Duration (years)			
		< 30	0.6	0.3–1.3	
		≥ 30	0.7	0.4–1.5	
		Squamous-cell carcinomas (*n* = 24)			
		Ever-smoker	1.7	0.7–3.8	
		Cigarettes/day			
		< 20	1.7	0.7–4.1	
		≥ 20	1.5	0.4–5.6	
		Duration (years)			
		< 30	1.5	0.5–4.1	
		≥ 30	1.8	0.7–4.9	
Zheng *et al.* (1993) USA 1986	Nasal cavity, paranasal sinuses, middle ear ICD-9: 160	Ever-smoker	1.2	0.7–1.9	
		Cigarettes/day			
		< 15 or occasional	0.6	0.3–1.2	
		15–34	1.1	0.7–1.9	
		> 34	2.0	1.1–3.6	*p* for trend = 0.01
		Duration (years)			
		≤ 25	0.8	0.4–1.4	
		26–40	1.2	0.7–2.2	
		> 40	1.9	1.1–3.5	*p* for trend = 0.01
		Years since quitting			
		Current smoker	1.0	–	
		< 5	1.3	0.7–2.2	
		5–9	1.2	0.5–2.8	
		> 10	0.4	0.2–0.7	*p* for trend < 0.01

Table 2.1.4.8 (contd)

Reference Country and years of study	Cancer subsite ICD code	Exposure categories	Relative risk	95% CI	Comments
‘t Mannetje *et al.* (1999) France, Germany, Italy, Netherlands and Sweden 1979–90	Nasal cavity and sinuses	All			Adjusted for age (10-year categories), sex, study centre and smoking status
		Former smoker	1.3	1.0–1.8	
		Current smoker	1.2	0.9–1.6	
		Women			
		Former smoker	1.5	0.6–3.4	
		Current smoker	0.8	0.3–1.8	
		Men			
		Former smoker	1.4	1.03–2.0	
		Current smoker	1.3	0.97–1.9	
		Squamous-cell carcinomas (*n* = 241)			
		Former smoker	1.2	0.8–1.8	
		Current smoker	1.7	1.2–2.6	
		Adenocarcinomas (*n* = 160)			
		Former smoker	1.3	0.8–2.2	
		Current smoker	0.7	0.4–1.2	
Caplan *et al.* (2000) USA 1984–88	Nasal cavity	Ever-smoker	2.4	1.1–5.2	Adjusted for age, registry area, living or working on a farm, several other occupations, and household income
		Cigarettes/day			
		1–19	1.5	0.6–3.9	
		20–39	2.1	1.0–4.7	
		≥ 40	3.1	1.3–7.4	
		Pack–years			
		< 15	1.3	0.5–3.3	
		15–29.9	1.6	0.7–3.9	
		30–44.9	2.4	1.0–5.7	
		≥ 45	3.3	1.3–7.4	
		Duration (years)			
		< 15	1.4	0.5–3.6	
		15–24.9	1.9	0.8–4.5	
		25–34.9	3.1	1.3–7.1	
		≥ 35	3.1	1.2–8.2	

CI, confidence interval

Table 2.1.4.9. Cohort studies on tobacco smoking and nasopharyngeal cancer

Reference Country and years of study	Subjects	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Chow *et al.* (1993) USA 1954–80	US Veterans' Study 248 046 men		48			Adjusted for age and calendar year
		Former smoker		1.5	0.4–5.1	
		Current smoker		3.9	1.5–10.3	
		Duration (years)				
		< 30		1.5	0.2–10.6	
		30–39		1.8	0.3–10.3	
		≥ 40		1.8	0.3–10.2	
		Age at starting (years)				
		> 24		1.4	0.2–9.2	
		20–24		1.7	0.3–9.8	
		15–19		1.8	0.3–9.7	
		< 15		2.5	0.3–18.0	
Liaw & Chen (1998) China, Province of Taiwan 1982–94	Taiwanese Study 11 096 men, 3301 women		16			Adjusted for age
		Current smoker		3.9	0.9–17.0	
		Cigarettes/day				
		≤ 10		3.6	0.8–16.3	
		11–20		3.3	0.8–14.0	
		> 20		3.1	0.3–31.5	
		Duration (years)				
		≤ 20		4.4	0.8–23.5	
		21–30		2.6	0.5–14.4	
		> 30		3.5	0.8–15.1	
		Pack–years				
		< 20		3.2	0.7–14.5	
		20–40		3.9	0.9–16.7	
		> 40		2.8	0.4–18.9	
		Age at starting (years)				
		> 24		3.3	0.8–14.1	
		21–24		4.8	1.0–23.5	
		≤ 20		2.8	0.5–14.8	

CI, confidence interval

Table 2.1.4.10. Case–control studies on tobacco smoking and nasopharyngeal cancer: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Lin *et al.* (1973) China, Province of Taiwan 1969–71	Men and women: 343 cases and 1017 controls	Population-based study in eight cities and counties Cases reported by all the medical facilities in the study areas; 93% histologically confirmed; response rate, 79.4% Controls from neighbourhood individually matched by age (± 5 years) and sex; response rate, 85%
Henderson *et al.* (1976) USA 1960–74	Men: 105 cases and 179 controls; women: 51 cases and 88 controls	Population-based study in California Cases: 88 identified by the Los Angeles Cancer Surveillance Program in 1971–74, 27 by the California Tumor Registry in 1960–70, and 41 incident cases in 1972–74; mean age, 51.4 years Controls were in- and outpatients, individually matched on sex, age, race, area and socioeconomic class; mean age, 52.4 years
Lanier *et al.* (1980) USA 1966–76	Men and women: 13 cases and 13 controls	Population-based study among natives in Alaska Cases identified from pathology files and tumour registries of the Alaska Native Medical Center, aged 32–80 years Controls were apparently healthy, individually matched (1:1) by sex, age (± 2.5 years), race and area of residence
Mabuchi *et al.* (1985) USA 4 years	Men and women: 39 cases and 39 controls	Hospital-based study in five metropolitan areas Cases histologically confirmed; response rate, 64% Controls randomly selected from admissions, matched on age (± 3 years), sex, race, marital status, hospital and admission period
Ng (1986) Hong Kong SAR 1974–81	Men: 159 cases and 158 controls; women: 65 cases and 68 controls	Hospital-based study at the Institute of Radiology and Oncology, among Chinese Cases aged ≥ 18 years; mean age, 57 years Controls with all other malignancies except cancer of the nasal cavity and sinuses, selected in random order from patient's register, matched on admission year, age (± 5 years), sex, race and resident status; mean age, 57 years
Yu *et al.* (1986) Hong Kong SAR 1981	Men: 160 cases and 160 controls; women: 90 cases and 90 controls	Population-based study in 4 hospitals, among Chinese Incident cases histologically confirmed, aged ≤ 35 years; response rate, 94% Controls were friends, individually matched by age and sex
Ning *et al.* (1990) China 1981	Men: 68 cases and 204 controls; women: 32 cases and 96 controls	Population-based study in Tianjin city Cases identified from the population-based cancer registry histologically confirmed, aged ≤ 64 years; response rate, 61.3% Controls individually matched (3:1) on age, sex and race (Han); 97% first chosen controls participated
Yu *et al.* (1990) China 1983–85	Men: 209 cases and 209 controls; women: 97 cases and 97 controls	Population-based study in Guangzhou city Incident cases identified at the Tumor Hospital, histologically confirmed, aged < 50 years; response rate, 93% Controls individually matched by age (± 5 years) and sex

Table 2.1.4.10 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Nam *et al.* (1992) USA 1986	Men: 141 cases and 282 controls; women: 63 cases and 126 controls	Population-based mortality study among white Americans Cases taken from a random sample of all deaths in 1986, aged ≥ 25 years; response rate, 89% Controls had died from diseases unrelated to smoking or alcohol drinking, aged ≤ 65 years, randomly selected from the sex and age strata, individually matched (2:1)
Sriamporn *et al.* (1992) Thailand 1987–90	Men: 80 cases and 80 controls: women: 40 cases and 40 controls	Hospital-based study in north-eastern Thailand Cases diagnosed and attending radiation therapy at the hospital Controls admitted for other diseases excluding any cancers and respiratory diseases, matched by sex and age (± 5 years)
West *et al.* (1993) Philippines	Men: 76 cases; women: 28 cases; 205 controls	Hospital- and population-based study Incident cases recruited from Philippine General Hospital, histologically confirmed, < 10% ethnically Chinese, aged 11–83 years; response rate, 100% Controls: 104 hospital controls matched for sex, age and ward type; response rate, 100%; 101 community controls matched for sex, age and neighbourhood; response rate, 77%
Zheng *et al.* (1994) China 1986	Men: 64 cases and 128 controls; women: 24 cases and 48 controls	Population-based study in Wuzhou and Zangwu Incident cases, histologically confirmed; mean age, 41.6 years; response rate, 98% Controls from neighbourhood, individually matched (2:1) on sex, age (± 4 years) and place of residence
Ye *et al.* (1995) China	Men: 114 cases and 114 controls; women: 21 cases and 21 controls	Hospital-based study in teaching hospital Incident cases, histologically confirmed, 82% poorly differentiated Controls from the surgical and orthopaedic departments with non-cancer, non-respiratory diseases, individually matched on sex, age, admission date and residence or ethnicity
Zhu *et al.* (1995, 1997) USA 1984–88	Men: 113 cases and 1910 controls	Population-based study in eight cancer registries (Selected Cancers Study) Cases histologically confirmed including 73% of squamous-cell carcinomas, aged 15–39 years in 1968; response rate, 86.3% Controls selected by random digit dialling, frequency-matched to another case group; 83.1% of eligible controls
Vaughan *et al.* (1996) USA 1987–93	Men and women: 231 cases and 244 controls	Population-based study Cases identified by five population-based cancer registries, histologically confirmed as differentiated squamous-cell carcinomas (60%) or undifferentiated and nonkeratinizing carcinomas (28%); aged 18–74 years; response rate, 82% Controls selected by random-digit dialling and frequency-matched on sex and age (± 5 years); response rate, 70%

Table 2.1.4.10 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Cheng *et al.* (1999) China, Province of Taiwan 1991–94	Men: 114 cases and 104 controls; women: 260 cases and 223 controls	Population-based study in Taipei Incident cases identified in two hospitals, histologically confirmed, aged ≤ 75 years; 99% response rate Controls with no history of nasopharyngeal cancer, randomly selected using the National Household Registration System, individually matched on sex, age (± 5 years) and area of residence; response rate, 88%
Armstrong *et al.* (2000) Malaysia 1987–92	Men: 195 cases and 195 controls; women: 87 cases and 87 controls	Population-based study among Malaysian Chinese Cases (119 prevalent and 163 incident) diagnosed at four study centres, histologically confirmed, aged 19–74 years; response rate, 53% Controls with no history of cancer of the head, neck or respiratory system, randomly selected and pair-matched by age (± 3 years) and sex; response rate, 90%
Cao *et al.* (2000) China 1998–99	Men and women: 57 cases and 327 controls	Population-based study in Sihui city Incident cases identified in a highly endemic area Controls were family members of the spouse of case; no matching
Yuan *et al.* (2000) China 1987–91	Men: 668 cases and 699 controls; women: 267 cases and 333 controls	Population-based study Incident cases identified by the Shanghai cancer registry, aged 15–74 years; response rate, 84% Controls randomly selected from general population and frequency matched by sex and age (5 year groups); response rate, 96.4%

Table 2.1.4.11. Case–control studies on tobacco smoking and nasopharyngeal cancer

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Lin *et al.* (1973) China, Province of Taiwan 1969–71	Men			Adjusted for age and area of residence
	Former smoker	0.8		
	Cigarettes/day			
	< 10	0.6		
	10–19	1.1		
	20–29	3.2		
	≥ 30	3.5		
	Women			
	Former smoker	6.6		
	Cigarettes/day			
	< 10	1.1		
	10–19	5.0		
	20–29	7.5		
Henderson *et al.* (1976) USA 1960–74		1.0	$p = 0.50$	Two-sided *p* value
Lanier *et al.* (1980) USA 1966–76		Discrepant pairs:		Very small sample size; no detailed results in the text
		Case/control	Yes/No 3	
		Case/control	No/Yes 1	
Mabuchi *et al.* (1985) USA 4 years	Ever-smoker	1.9	0.6–5.6	Matched-pair analysis Smokers for > 1 year
	Cigarettes/day			
	1–20	1.4	0.4–4.5	
	21–39	2.8	0.7–12.0	
	≥ 40	2.8	0.6–13.0	

Table 2.1.4.11 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Ng (1986) Hong Kong SAR 1974–81	Ever-smoker	0.9	0.6–1.4	Adjusted for sex The control group included a large proportion of smoking-related cancers.
Yu *et al.* (1986) Hong Kong SAR 1981	Similar cigarette smoking habits between cases and controls			Matched-pair analysis
Ning *et al.* (1990) China 1981	Similar use of cigarettes between cases and controls		$p = 0.88$	Matched-pair analysis
Yu *et al.* (1990) China 1983–85	Ever-smoker	1.3		Adjusted for intake of salted fish, mouldy bean curd, preserved plum and tomato intake at age 10 years
	Cigarettes/day			
	1–9	1.3		
	10–19	1.0		
	20–29	1.7	$p < 0.05$	
	≥ 30	4.3	$p < 0.05$	
	Pack–years			
	–14	1.2		
	15–29	1.6		
	≥ 30	2.9	$p < 0.05$	
Nam *et al.* (1992) USA 1986	Men			Adjusted for sex and alcohol intake
	Pack–years			
	≤ 30	0.9	0.5–1.7	
	31–59	1.8	1.0–3.5	
	≥ 60	3.1	1.6–6.1	*p* for trend < 0.001

Table 2.1.4.11 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Nam *et al.* (1992) (contd)	Years since quitting			
	Current smoker	1.0	–	
	< 5	1.2	0.7–2.2	
	≥ 5	0.6	0.3–1.1	
	Women			
	Pack–years			
	≤ 30	1.3	0.6–2.8	
	31–59	3.5	1.3–9.2	
	≥ 60	4.9	1.2–20.9	*p* for trend < 0.001
	Years since quitting			
	Current smoker	1.0	–	
	< 5	1.3	0.5–3.4	
	≥ 5	0.3	0.1–1.3	
Sriamporn *et al.* (1992) Thailand 1987–90	Manufactured cigarette	0.8	0.3–2.1	Adjusted for education, area of residence, intake of alcohol and salted fish
	Hand-made cigarette	0.9	0.3–2.5	
West *et al.* (1993) Philippines	All controls			Adjusted for education, occupational exposure, intake of fresh fish and processed meats, use of anti-mosquito coils and herbal medicines Hospital controls included patients with smoking-related diseases.
	Duration (years)			
	1–20	0.5	0.2–1.5	
	21–30	0.9	0.3–3.0	
	≥ 31	2.3	0.7–7.3	
	Community controls			
	Duration (years)			
	1–20	0.8	0.1–4.4	
	21–30	2.9	0.5–18.2	
	≥ 31	7.2	1.5–34.4	

Table 2.1.4.11 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Zheng *et al.* (1994) China 1986				No significant association between cigarette smoking and nasopharyngeal cancer
Ye *et al.* (1995) China	Cigarettes/month			Adjusted for exposure to fumes during cooking, intake of various vegetables and salted fish, family history of cancer and passive smoking during childhood and adulthood Smoking index 1: duration (years) × intensity (cigarettes/month)/age at starting smoking Smoking index 2: duration (years)/age at starting smoking
	> 5 vs ≤ 5	1.9	1.1–3.4	
	Duration (years)			
	> 10 vs ≤ 10	1.8	1.01–3.2	
	Smoking index 1			
	> 25 vs ≤ 25	2.1	1.3–3.5	
	Smoking index 2			
	> 0.5 vs ≤ 0.5	1.9	1.1–3.3	
Zhu *et al.* (1995, 1997) USA 1984–88	Former smoker	2.3	1.3–4.0	Adjusted for year of birth, cancer registry, existence of home phone, education, ethnic background, growing up in urban/suburban environment, medical history, exposure to asbestos or woodwork, and alcohol consumption. The association was stronger for squamous-cell carcinoma.
	Current smoker	1.4	0.8–2.6	
	Cigarettes/day			
	1–19	1.3	0.7–2.6	
	20–39	1.8	1.0–3.3	
	≥ 40	3.8	2.0–7.3	
	Duration (years)			
	≤ 14	1.7	0.9–3.2	
	15–24	1.5	0.8–2.8	
	25–34	3.0	1.6–5.6	
	≥ 35	2.3	1.0–5.1	
	Pack–years			
	< 15	1.3	0.7–2.5	
	15–29.9	1.8	0.9–3.4	
	30–44.9	2.5	1.3–5.0	
	≥ 45	3.9	2.0–7.8	

Table 2.1.4.11 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Zhu *et al.* (1995, 1997) (contd)	Age at starting smoking (years)			Further adjusted for pack–years
	≥ 22	1.0	–	
	18–21	0.4	0.2–0.9	
	≤ 17	0.8	0.4–1.5	
Vaughan *et al.* (1996) USA 1987–93	Former smoker	1.3	0.7–2.2	Adjusted for age, sex, registry, education and alcohol use. The association was much stronger for differentiated squamous-cell carcinoma.
	Current smoker	2.6	1.4–4.6	
	Pack–years			
	1–34	1.9	0.9–4.0	
	35–59	3.0	1.3–6.8	
	≥ 60	4.3	1.5–13.4	*p* for trend < 0.001
	Years since quitting			The association was much stronger for differentiated squamous-cell carcinoma.
	Current smoker	1.0	–	
	< 5	0.1	0.0–0.6	
	5–14	0.2	0.1–0.7	
	≥ 15	0.2	0.0–0.8	*p* for trend = 0.003
Cheng *et al.* (1999) China, Province of Taiwan 1991–94	Former smoker	1.1	0.6–2.1	Adjusted for age, sex, race, education, family history of nasopharyngeal carcinoma and alcohol use
	Current smoker	1.4	0.9–2.1	
	Cigarettes/day			
	< 20	1.4	0.9–2.1	
	≥ 20	1.4	0.9–2.2	*p* for trend = 0.2
	Duration (years)			
	< 25	1.1	0.7–1.8	
	≥ 25	1.7	1.1–2.9	*p* for trend = 0.03
	Pack–years			
	< 20	1.3	0.8–2.0	
	≥ 20	1.5	0.9–2.4	*p* for trend = 0.1

Table 2.1.4.11 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Cheng *et al.* (1999) (contd)	Age at starting smoking (years)			
	≥ 20	1.4	0.9–2.2	
	< 20	1.3	0.8–2.0	*p* for trend = 0.1
Armstrong *et al.* (2000) Malaysia 1987–92	Ever-smoker (> 6 months)	1.8	0.8–4.2	Adjusted for parental smoking and dietary index. Response rate for cases was too low; control group might be biased.
Cao *et al.* (2000) China 1998–99	Current smoker	5.6	3.3–9.6	No mention of adjustment for age and sex; adjusted for family history of nasopharyngeal carcinoma and separate kitchen
	Cigarettes/day			
	≤ 10	1.0	–	
	> 10	6.4	3.8–10.5	
Yuan *et al.* (2000) China 1987–91	Men			Adjusted for age, education, intake of preserved foods and oranges/tangerines, exposure to smoke from heated rapeseed oil and burning coal during cooking, occupational exposure to chemical fumes, history of chronic ear and nose condition and family history of nasopharyngeal carcinoma
	Former smoker	1.2	0.8–1.8	
	Ever-smoker	1.3	1.01–1.6	
	Current smoker	1.3	1.01–1.7	
	Cigarettes/day			
	< 10	1.1	0.8–1.7	
	10–19	1.2	0.8–1.6	
	20–29	1.4	1.1–2.0	
	≥ 30	1.8	1.1–3.2	
	Pack–years			
	< 20	1.2	0.9–1.6	
	20–39	1.3	0.96–1.8	
	≥ 40	1.6	1.03–2.6	

Table 2.1.4.11 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Yuan *et al.* (2000) (contd)	Women			
	Former smoker	1.2	0.4–3.5	
	Ever-smoker	1.3	0.7–2.5	
	Current smoker	1.4	0.6–2.8	
	Cigarettes/day			
	< 10	1.4	0.5–3.8	
	10–19	2.3	0.5–11.7	
	20–29	0.5	0.1–3.0	
	≥ 30	2.9	0.2–47.8	
	Pack–years			
	< 20	1.3	0.7–2.7	
	20–39	0.9	0.2–4.2	
	≥ 40	2.2	0.1–38.2	

CI, confidence interval

Table 2.1.4.12. Cohort studies on tobacco smoking and pharyngeal cancer

Reference Country and years of study	Subjects	Organ subsite ICD code	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Weir & Dunn (1970) USA 1954–62	Californian Study 68 153 men	Pharynx ICD: 145–148		13			Nonsmokers include cigar and/or pipe only smokers.
			Ever-smoker		0.8		
			Cigarettes/day				
			1–14		–		
			15–25		1.2		
			> 25		0.5		
McLaughlin *et al.* (1995) USA 1954–80	US Veterans' Study 248 046 men	Pharynx (ICD-1957)		143			Adjusted for attained age and calendar-year time-period at death
			Former smoker		2.6	1.1–6.2	
			Ever-smoker		9.5	4.6–19.4	
			Current smoker		14.1	6.9–28.9	
			Cigarettes/day				
			1–9		5.2	1.8–15.0	
			10–20		12.6	6.0–26.6	
			31–39 [sic]		18.1	8.5–38.7	
			≥ 40		37.3	15.9–87.5	*p* for trend < 0.01
Nordlund *et al.* (1997) Sweden 1963–89	Swedish Census Study 26 032 women	Pharynx ICD-7: 145–148		17			Adjusted for age and place of residence
			Current smoker		2.9	0.9–9.7	

CI, confidence interval

Table 2.1.4.13. Case–control studies on tobacco smoking and pharyngeal cancer: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Jussawalla & Deshpande (1971) India 1968	Men and women: 223 cases and 1647 controls	Retrospective study at the Cancer Registry in Mumbai Cases of the oropharynx (185) and hypopharynx (38), histologically confirmed Controls selected among residents from the registered voters' list, matched for age, sex and religion
Elwood *et al.* (1984) Canada 1977–80	Men: 68 cases and 68 controls; women: 19 cases and 19 controls	Hospital-based study at a cancer referral centre in Vancouver Incident cases of pharyngeal cancer; 95% of identified cases participated. Controls were patients with cancers unrelated to smoking, alcohol use or occupational exposure, individually matched on date of diagnosis, sex and age (± 2 years).
Brugere *et al.* (1986) France 1975–82	Men: 1000 cases	Population-based study in Paris Cases of oropharyngeal (634) and hypopharyngeal (366) cancer admitted to the head and neck department of the Institut Curie; non-squamous carcinomas and secondary cancers excluded Controls were a random subsample from a large national survey stratified by age.
Tuyns *et al.* (1988) France, Italy, Spain and Switzerland 1973–80	Men: 281 cases and 3057 controls	Population-based study in six study areas Cases of cancer of the hypopharynx, histologically confirmed; oropharynx excluded; response rate > 80% Controls drawn from the general population within a sample stratified by age and sex; response rate, 56–75%
Franceschi *et al.* (1990) Italy 1986–89	Men: 134 cases and 1272 controls	Hospital-based study Cases of pharyngeal cancer, including the junction between hypopharynx and larynx, histologically confirmed, aged < 75 years; response rate, 98% Controls were inpatients with acute conditions unrelated to tobacco or alcohol consumption, without malignant tumours, chosen on the basis of area of residence and age (± 5-year categories); response rate, 97%
Choi & Kahyo (1991) Republic of Korea 1986–89	Men: 133 cases and 399 controls; women: 19 cases and 57 controls	Hospital-based study at the Cancer Center Hospital in Seoul Cases of pharyngeal cancer, confirmed histologically or cytologically Controls excluded patients with other cancers or tobacco- and alcohol-related diseases, individually matched (3:1) on year of birth (± 5 years) and admission date (± 3 months).
Maier *et al.* (1994) Germany 1990–91	Men: 105 cases and 420 controls	Hospital-based study at the Department of Otorhinolaryngology, Head and Neck Surgery of the University of Heidelberg Cases of squamous-cell carcinoma of the oropharynx (40), hypopharynx (44) or both (21), histologically confirmed Controls were outpatients without known cancer, individually matched (4:1) for age and residential area.

Table 2.1.4.13 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
De Stefani *et al.* (1998) Uruguay 1992–96	Men: 219 cases and 427 controls	Hospital-based study in four hospitals of Montevideo Cases of squamous-cell carcinoma of the oropharynx (111), hypopharynx (97) or unspecified (11), aged 25–84 years; response rate, 93.8% Controls without diseases related to tobacco and alcohol use or non-neoplastic lesions of the oral cavity and pharynx, aged 25–84 years; frequency-matched on age, area of residence and urban/rural status; response rate, 91.0%
Franceschi *et al.* (1999) Italy & Switzerland 1992–97	Men: 364 cases and 1254 controls	Hospital-based study in major hospitals in three areas Cases of oro- or hypopharyngeal cancer, histologically confirmed, aged 32–74 years Controls were patients with acute non-cancerous illnesses unrelated to tobacco smoking or alcohol abuse, frequency-matched by age and area of residence.
La Vecchia *et al.* (1999a) Italy & Switzerland 1984–97	Men and women: 642 cases; men: 3068 controls; women: 1111 controls	Hospital-based study in a network of hospitals in the study areas Incident cases of pharyngeal cancer, aged < 75 years, histologically confirmed Controls with acute, non-neoplastic conditions unrelated to alcohol or tobacco consumption
Rao *et al.* (1999) India 1980–84	Men: 593 cases and 635 controls	Hospital-based study in Mumbai Cases of cancer of the hypopharynx Controls with infectious diseases and benign tumours, free from cancer, admitted during the same period as controls; no matching
Schlecht *et al.* (1999) Brazil 1986–89	Men and women: 217 cases and 1578 controls	Hospital-based study in three metropolitan areas Incident cases of pharyngeal cancer, histologically confirmed Controls without diagnosis of cancer or mental disorder, individually matched for sex, age and trimester of admission

Table 2.1.4.14. Case–control studies on tobacco smoking and pharyngeal cancer

Reference Country and years of study	Cancer subsite ICD code	Smoking categories	Relative risk	95% CI	Comments
Jussawalla & Deshpande (1971) India 1968	Oro- and hypopharynx	Current smoker			
		Oropharynx	2.3	$p < 0.001$	
		Hypopharynx	0.4	$p > 0.05$	
Elwood *et al.* (1984) Canada 1977–80	Oro- and hypopharynx ICD-O: 146, 148, 149	Cigarettes/day			Adjusted for alcohol, socio-economic group, marital status, dental care and history of tuberculosis
		1–9	0.5		
		10–19	1.2		
		20–29	1.3		
		≥ 30	1.5		p for trend > 0.05
Brugere *et al.* (1986) France 1975–82	Oro- and hypopharynx ICD-8: 146, 148	Oropharynx Tobacco/day (g)			Adjusted for alcohol use Light smokers were included in reference group.
		0–9	1.0	–	
		10–19	4.0	2.4–6.5	
		20–29	7.6	4.8–12.1	
		≥ 30	15.2	9.3–24.9	
		Hypopharynx Tobacco/day (g)			
		0–9	1.0	–	
		10–19	7.1	3.1–15.8	
		20–29	12.6	5.8–27.4	
		≥ 30	35.1	16.2–75.9	
Tuyns *et al.* (1988) France, Italy, Spain and Switzerland 1973–80	Hypopharynx ICD-9: 148.0, 148.1, 148.3, 149.8	Cigarettes/day			Adjusted for age, place, age/place interaction and alcohol use
		1–7	5.5	2.0–15.1	
		8–15	13.7	5.4–34.5	
		16–25	18.0	7.2–44.8	
		≥ 26	20.0	7.9–51.0	

Table 2.1.4.14 (contd)

Reference Country and years of study	Cancer subsite ICD code	Smoking categories	Relative risk	95% CI	Comments
Franceschi *et al.* (1990) Italy 1986–89	Pharynx, junction between hypopharynx and larynx ICD-9: 146, 148, 161.1	Current smoker	12.9	3.1–52.9	Adjusted for age, area of residence, years of education, occupation and alcohol use
		Cigarettes/day			
		≤ 14	8.0	1.9–34.5	
		15–24	14.2	3.4–59.3	
		≥ 25	17.6	4.1–74.7	*p* for trend < 0.01
		Duration (years)			
		1–29	6.4	1.5–27.4	
		30–39	15.5	3.6–66.7	
		≥ 40	25.5	6.0–109.9	*p* for trend < 0.01
		Age at starting smoking (years)			
		≥ 25	7.9	1.7–36.1	
		17–24	12.8	3.1–53.2	
		< 17	16.0	3.8–67.5	*p* for trend < 0.01
		Years since quitting			
		< 10	11.3	2.6–49.4	
		≥ 10	3.7	0.8–18.0	*p* for trend < 0.01
Choi & Kahyo (1991) Republic of Korea 1986–89	Pharynx ICD-O: 146–149	Men			Adjusted for alcohol use
		Former smoker	0.9	0.3–2.1	
		Current smoker	1.6	0.9–3.1	
		Cigarettes/day			
		1–20	1.3	0.7–2.5	
		21–40	2.4	1.1–4.9	
		≥ 41	2.9	1.0–9.3	
		Duration (years)			
		1–19	1.2	0.5–2.7	
		20–39	1.2	0.8–2.8	
		≥ 40	2.4	1.2–4.8	

Table 2.1.4.14 (contd)

Reference Country and years of study	Cancer subsite ICD code	Smoking categories	Relative risk	95% CI	Comments
Choi & Kahyo (1991) (contd)		Age at starting smoking (years)			
		≥ 25	1.03	0.5–2.4	
		18–24	1.7	0.9–3.1	
		≤ 17	2.6	1.2–5.9	
		Years since quitting			
		Current smoker	1.0	–	
		1–4	0.1	0.0–0.7	
		5–9	1.1	0.4–2.9	
		≥ 10	0.5	0.1–1.6	
		Women			
		Current smoker	0.98	0.2–4.1	
		Cigarettes/day			
		1–20	1.2	0.3–5.0	
		21–40	0.7	0.1–7.9	
		Duration (years)			
		1–19	0.9	0.2–5.3	
		20–39	0.9	0.1–6.1	
		Age at starting smoking (years)			
		≥ 25	0.98	0.2–4.1	
Maier *et al.* (1994) Germany 1990–91	Oro- and hypopharynx	Tobacco–years			Adjusted for alcohol use
		< 5	1.0		Daily consumption of 20 cigarettes or
		5–< 20	4.5	1.2–17.3	4 cigars or 5 pipes for 1 year
		20–< 40	6.1	1.9–18.7	
		40–60	9.5	2.5–35.4	p for trend = 0.0001

Table 2.1.4.14 (contd)

Reference Country and years of study	Cancer subsite ICD code	Smoking categories	Relative risk	95% CI	Comments
De Stefani *et al.* (1998) Uruguay 1992–96	Oro- and hypopharynx, pharynx unspecified	Former smoker	4.3	2.2–8.3	Adjusted for age, residence, urban/rural status, birthplace, education and total alcohol consumption
		Ever-smoker	7.5	4.1–13.6	
		Current smoker	10.2	5.5–18.8	
		Cigarettes/day			
		1–14	3.6	1.8–7.1	
		15–24	7.8	4.1–14.9	
		≥ 25	12.2	6.4–23.3	
		Duration (years)			
		1–39	6.2	2.9–12.8	
		40–49	8.3	4.3–15.9	
		≥ 50	7.5	3.9–14.4	
		Pack–years			
		1–28	3.5	1.7–7.0	
		29–47	8.9	4.5–17.6	
		48–76	6.7	3.4–13.2	
		≥ 77	13.3	6.7–26.2	
		Years since quitting			
		1–4	5.9	2.7–12.8	
		5–9	5.1	2.2–12.0	
		≥ 10	2.1	0.8–5.5	
		Type of tobacco			
		Mainly blond	4.4	2.4–8.1	
		Mainly black	17.8	9.2–34.1	
		Hand-rolling			
		Only manufactured	4.3	2.2–8.5	
		Mixed	2.7	1.3–5.8	
		Only rolled	13.7	7.3–25.5	

Table 2.1.4.14 (contd)

Reference Country and years of study	Cancer subsite ICD code	Smoking categories	Relative risk	95% CI	Comments
De Stefani *et al.* (1998) (contd)		Filter use			
		Only filter	1.3	0.3–5.2	
		Mixed	4.0	2.1–7.8	
		Only plain	11.3	6.1–20.8	
		Smoking pattern			
		Blond + manufactured	3.4	1.7–6.8	
		Blond + hand-rolled	5.1	2.7–9.6	
		Black + manufactured	9.2	3.4–25.0	
		Black + hand-rolled	20.6	10.5–40.6	
Franceschi *et al.* (1999) Italy & Switzerland 1992–97	Pharynx	Cigarettes/day			Adjusted for area of residence, interviewer, age, education, vegetable and fruit intake, total energy intake and alcohol drinking †Smokers of cigars and/or pipes were included.
		1–14	7.3	3.3–16.3	
		15–24	14.7	7.0–30.8	
		≥ 25†	19.3	8.8–42.4	
La Vecchia *et al.* (1999a) Italy & Switzerland 1984–97	Pharynx	Current smoker	13.5	9.1–19.8	Adjusted for age, sex, study centre, education and alcohol drinking
		Years since quitting			
		1–2	9.9	5.6–17.5	
		3–5	6.3	3.6–11.0	
		6–9	4.8	2.7–8.4	
		10–14	3.2	1.8–5.7	
		≥ 15	2.9	1.7–4.8	

Table 2.1.4.14 (contd)

Reference Country and years of study	Cancer subsite ICD code	Smoking categories	Relative risk	95% CI	Comments
Rao *et al.* (1999) India 1980–84	Hypopharynx ICD-9: 148.0, 148.1, 148.9	Cigarette smoker	0.8	0.5–1.4	Adjusted for age and residence In the study area, cigarette smoking is not as common as bidi smoking.
Schlecht *et al.* (1999) Brazil 1986–89	Pharynx ICD-9: 146–149	Current smoker	5.9	2.2–15.3	Adjusted for sex, study location, admission period and alcohol consumption
		Pack–years			
		1–20	5.4	1.9–15.5	
		21–40	5.7	1.9–16.9	
		> 40	7.5	2.4–23.6	
		Years since quitting			
		≤ 5	2.6	0.8–8.5	
		6–10	1.2	0.2–7.0	
		11–15	1.4	0.2–9.8	
		> 15	0.9	0.1–5.5	

CI, confidence interval

Table 2.1.4.15. Cohort studies on tobacco smoking and oesophageal cancer (unspecified)

Reference Country and years of study	Subjects	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Weir & Dunn	Californian Study		32			Nonsmokers include cigar
(1970)	68153 men	Ever-smoker		1.8		and/or pipe only smokers.
USA		Cigarettes/day				
1954–62		1–14		1.3		
		15–25		1.7		
		> 25		1.8		
Doll *et al.*	British Doctors' Study		2	Mortality rate		Annual mortality rate for
(1980)	6194 women	Nonsmoker		0		100 000 women
UK		Former smoker		8		
1951–73		Cigarettes/day				
(see also Doll		1–14		4		
et al., 1994)		15–24		0		
		≥ 25		0		
Hammond &	Cancer Prevention			Mortality ratio		
Seidman	Study I	Regular smoker		4.0		
(1980)	1 051 038 adults					
USA						
1959–72						
Kono *et al.*	Japanese Physicians	Cigarettes/day				Adjusted for age and
(1987)	Study	1–19		0.5	0.1–3.2	alcohol drinking
Japan	5477 men	≥ 20		2.1	0.5–9.2	
1965–83						

Table 2.1.4.15 (contd)

Reference Country and years of study	Subjects	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Akiba & Hirayama (1990) Japan 1965–81 (see Kinjo *et al.*, 1998)	Six-prefecture Study 265 118 (122 261 men and 142 857 women)	Current smoker	314	2.2	1.6–3.0	Data stratified by prefecture, occupation, attained age and observation period
		Cigarettes/day				
		1–4	3	0.9	0.2–2.5	
		5–14	127	2.0	1.4–2.8	
		15–24	164	2.4	1.7–3.3	
		25–34	13	2.1	1.1–3.8	
		≥ 35	7	2.5	1.0–5.2	
Kuller *et al.* (1991) USA 1975–85	MRFIT Study 12 866 men			Mortality rate		Annual mortality rate per 10 000 men Relative risk adjusted for age, diastolic blood pressure, serum cholesterol level, race (black/non-black)
		Non- and former smoker	73	3.1		
		Cigarettes/day				
		1–15	15	5.6		
		16–25	29	6.7		
		26–35	17	6.3		
		36–45	18	8.2		
		≥ 46	12	15.9		
				Relative risk		
		Current smoker		2.4	$p < 0.0001$	
Tomita *et al.* (1991) Japan 1975–85	37 646 men			Mortality rate		Annual mortality rate per 100 000 men. The authors did not state whether the mortality rates had been adjusted for age.
		Nonsmoker	1	0.2		
		Cigarettes/day				
		1–14	1	0.5		
		15–24	10	1.1		
		25–34	4	1.1		

Table 2.1.4.15 (contd)

Reference Country and years of study	Subjects	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Akiba (1994)	Life Span Study		103			†[Upper limit could not be
Japan	61 505 survivors	Former smoker		2.8	1.3–6.3	obtained.]
1968–87		Current smoker		3.3	1.7–†	
Doll *et al.*	British Doctors' Study		172	Mortality rate		Annual mortality rate for
(1994)	30 440 men	Nonsmoker		4		100 000 men
UK		Former smoker		19		
1951–91		Current smoker		30		
(see also Doll		Cigarettes/day				
et al., 1980)		1–14		17		
		15–24		33		
		≥ 25		45		
Guo *et al.*	Linxian Intervention	Ever-smoker	150	1.6	1.2–2.2	Adjusted for cancer history
(1994)	Trial Study	Cigarettes/day†				in first-degree relatives
China	29 584 residents	< 10	85	1.8	1.3–2.6	†Tobacco smoked in pipe
1985–91		10–19	96	1.8	1.3–2.5	was converted to cigarette
		≥ 20	60	1.9	1.3–2.8	equivalent (1 g tobacco =
		Duration (years)				0.8 cigarette).
		< 20	24	1.2	0.7–2.0	
		20–39	145	1.8	1.3–2.5	
		≥ 40	73	2.1	1.4–3.1	*p* for trend < 0.01
		Pack–years†				
		< 10	54	1.5	1.0–2.2	
		10–19	84	2.1	1.5–3.1	
		20–29	43	1.6	1.0–2.4	
		≥ 30	60	2.0	1.4–3.0	

Table 2.1.4.15 (contd)

Reference Country and years of study	Subjects	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Guo *et al.* (1994) (contd)		Years since quitting				
		Current smoker		1.0	–	
		< 3		1.1	0.6–2.2	
		≥ 3		0.5	0.2–1.2	
McLaughlin *et al.* (1995) USA 1954–80	US Veterans' Study 248 046 men		318			Adjusted for attained age and calendar-year time-period at death
		Former smoker		1.5	1.0–2.2	
		Ever-smoker		3.0	2.3–4.1	
		Current smoker		4.1	3.0–5.6	
		Cigarettes/day				
		1–9		1.4	0.7–2.7	
		10–20		3.3	2.4–4.7	
		31–39 [sic]		6.7	4.7–9.4	
		≥ 40		6.1	3.5–10.7	p for trend < 0.01
Yuan *et al.* (1996) China 1986–96	Shanghai Men's Study 18 244 men	Ever-smoker	24	1.4	$p > 0.05$	Adjusted for age and alcohol consumption
		Cigarettes/day				
		< 20		1.0	$p > 0.05$	
		≥ 20		1.7	$p > 0.05$	
Chen *et al.* (1997) China 1972–93	Shanghai Factory Study 6494 men		29			Adjusted for age, systolic blood pressure, serum cholesterol level and regular alcohol drinking (yes/no)
		Ever-smoker		3.6	$p < 0.05$	
		Cigarettes/day				
		1–19		2.8	$p > 0.05$	
		≥ 20		4.6	$p < 0.01$	p for trend = 0.009

Table 2.1.4.15 (contd)

Reference Country and years of study	Subjects	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Lam *et al.* (1997) China 1976–96	Xi'an Factory Study 1124 men	Ever-smoker	12	4.3	0.9–19.9	Adjusted for age, marital status, occupation, education, diastolic blood pressure and triglyceride and total cholesterol levels
Nordlund *et al.* (1997) Sweden 1963–89	Swedish Census Study 26 032 women		25			Adjusted for age and place of residence
		Former smoker		3.6	0.8–16.0	
		Current smoker		1.7	0.5–5.3	
Tulinius *et al.* (1997) Iceland 1968–95	Reykjavík Study 11 366 men	Former smoker		2.0	0.6–6.6	Adjusted for age
		Cigarettes/day				
		1–14		3.6	1.01–12.8	
		15–24		4.1	1.2–14.1	
		≥ 25		1.5	0.2–13.2	
Kinjo *et al.* (1998) Japan 1966–81 (see also Akiba & Hirayama, 1990)	Six-prefecture Study 220 272 adults (100 840 men and 119 432 women)	Men	328			Adjusted for age, area of residence and occupation
		Former smoker	12	1.9	0.9–3.6	
		Cigarettes/day				
		1–14	117	2.3	1.5–3.3	
		≥ 15	163	2.7	1.8–3.8	*p* for trend < 0.001
		Women	112			
		1–14 cigarettes/day	19	1.8	1.1–3.0	
		Men and women				Further adjusted for sex, green and yellow vegetable intake, consumption of hot tea and alcohol
		Former smoker		1.5	0.8–2.8	
		Cigarettes/day				
		1–14		1.8	1.3–2.5	
		≥ 15		1.9	1.4–2.7	

Table 2.1.4.15 (contd)

Reference Country and years of study	Subjects	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Liaw & Chen	Taiwanese Study		26			Adjusted for age and
(1998)	11 096 men,	Current smoker		1.0	0.4–2.6	alcohol drinking
China,	3301 women	Duration (years)				
Province of		21–30		2.4	0.7–8.9	
Taiwan		> 30		1.3	0.5–3.4	
1982–94		Pack–years				
		< 20		0.4	0.1–2.1	
		20–40		2.1	0.8–5.9	
		> 40		1.2	0.4–4.1	
		Age at starting smoking (years)				
		> 24		1.1	0.3–4.0	
		21–24		1.5	0.4–5.3	
		≤ 20		1.3	0.5–3.6	
Gao *et al.*	Shanghai Residential	Ever-smoker				Adjusted for age
(1999)	Study	Urban men		2.6[†,‡]	$p < 0.05$	Significant linear trend
China	213 800 residents	Suburban men		3.3[†]	$p < 0.05$	($p < 0.05$) for:
1983–94		Rural men		1.8[†,‡]	$p < 0.05$	[†], intensity of smoking
		Urban women		1.9	$p > 0.05$	[‡], age at starting smoking

CI, confidence interval

Table 2.1.4.16. Case–control studies on tobacco smoking and oesophageal cancer (unspecified) or squamous-cell carcinoma of the oesophagus: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Victora *et al.* (1987) Brazil 1985–86	Men: 135 cases and 270 controls; women: 36 cases and 72 controls	Hospital-based study in eight main hospitals in southern Brazil Cases of histologically confirmed squamous-cell carcinoma of the oesophagus aged < 80 years; 90% of eligible cases Controls without disease related to alcohol or tobacco use, or upper gastrointestinal tract diseases, individually matched (2:1) by hospital, age (± 5 years) and sex
Brown *et al.* (1988) USA 1977–84	Men: 74 cases and 157 controls	Hospital-based incidence study combined with mortality study Incident cases of oesophageal cancer (NOS) identified at four hospitals in Charleston (85% squamous-cell carcinoma), aged ≤ 79 years; 85% of eligible cases participated Controls individually matched (2:1) on race, age (± 5 years), hospital and admission period; response rate, 95%; only controls without alcohol- or diet-related conditions or diagnosis of mental disorder were included.
	Men: 133 deaths and 265 controls	Mortality series: deaths from oesophageal cancer (NOS) at age ≤ 79 years Controls randomly selected and individually matched (2:1) by race, age, area of residence and year of death Cases with diagnoses and deaths with causes related to alcohol and/or diet excluded; response rate for deaths and controls combined, 94%
Nakachi *et al.* (1988) Japan 1973–85	Men: 257 cases and 257 controls; women: 86 cases and 86 controls	Population-based study in the Saitama prefecture using interviews Cases were deaths from oesophageal cancer (NOS); participation rate, 54% Controls selected from electoral roll and individually matched on sex, age (± 2 years) and neighbourhood; about 60% of first chosen controls participated.
Yu *et al.* (1988) USA 1975–81	Men: 187 cases and 187 controls; women: 88 cases and 88 controls	Population-based study in Los Angeles County Incident cases of histologically confirmed oesophageal cancer (88% squamous-cell carcinoma), identified through the local Cancer Surveillance Program, aged 20–64 years, mean, 56.5 years; 56% of eligible cases Neighbourhood controls individually matched on sex, age and race; 87% of controls were the first or the second eligible neighbour.
Ferraroni *et al.* (1989) Italy 1983–88	Men: 162 cases and 1334 controls; women: 47 cases and 610 controls	Hospital-based study in four hospitals in Milan Cases of oesophageal cancer (NOS), confirmed histologically, aged ≤ 75 years Controls with traumatic, non-traumatic orthopaedic and acute surgical conditions and ear, nose, throat, skin and dental disorders; malignant tumours, digestive tract disorders or coffee-, alcohol- or tobacco-related conditions were excluded; median age, 56 years
Li *et al.* (1989) China 1984–85	Men: 758 cases and 789 controls; women: 486 cases and 525 controls	Population-based study among residents of Linxian County using interviews Cases of cancer of the oesophageal–gastric junction (mostly squamous-cell carcinoma) or gastric cardia (mostly adenocarcinoma), aged 35–64 years, identified from all hospitals in the county; 98% of eligible cases Controls without cancer, randomly selected from population and roughly matched on age and sex; aged 35–64 years; participation rate, 100%

Table 2.1.4.16 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Rao *et al.* (1989) India 1980–84	Men: 503 cases and 634 controls	Hospital-based study at the Tata Memorial Hospital Cases with oesophageal cancer (NOS) Controls without cancer or infectious diseases
De Stefani *et al.* (1990) Uruguay 1985–88	Men: 199 cases and 398 controls; women: 62 cases and 124 controls	Hospital-based study in four main hospitals in Montevideo Cases of squamous-cell carcinoma of the oesophagus; response rate, 92% Controls without diagnosis of tobacco and/or alcohol-related diseases and individually matched (2:1) by age (± 5 years), sex and hospital
Franceschi *et al.* (1990) Italy 1986–89	Men: 288 cases and 1272 controls	Hospital-based study in two areas of northern Italy Cases of histologically confirmed oesophageal cancer (NOS), aged < 75 years; response rate, 98% Controls with traumatic or non-traumatic orthopaedic conditions, acute conditions, eye disorders and other illnesses unrelated to tobacco and alcohol consumption, matched by area of residence, hospital and age; response rate, 97%
Sankaranarayanan *et al.* (1991) India 1983–84	267 cases (207 men and 60 women) and 895 controls (546 men and 349 women)	Hospital-based study at the Regional Cancer Centre of Trivandrum Cases of oesophageal cancer (NOS) confirmed by histology (67%) or radiology (33%); 100% of eligible cases participated. Controls included 271 patients diagnosed with conditions other than cancer or precancerous lesions and 624 patients selected from those attending a teaching hospital with diagnoses of acute respiratory, gastrointestinal and genitourinary infections [no matching]
Cheng *et al.* (1992) Hong Kong SAR 1989–90	Men: 345 cases and 1378 controls; women: 55 cases and 220 controls	Hospital-based study in four general hospitals in Hong Kong using interviews Cases of histologically confirmed oesophageal cancer (85% squamous-cell carcinoma); 86.8% of all cases participated. Controls individually matched (4:1) by sex and age: 2 controls admitted to the same surgical departments; patients with tobacco- or alcohol-related cancers were excluded; 2 controls selected from private or general practice clinics in the area where case was originally referred to the physician; response rate, 95%
Negri *et al.* (1992) Italy 1984–90	Men: 244 cases and 901 controls; women: 56 cases and 302 controls	Hospital-based study in several major hospitals in the greater Milan area Cases of histologically confirmed oesophageal cancer (NOS), aged 29–74 years; median, 60 years Controls admitted for traumatic or non-traumatic orthopaedic conditions, acute surgical diseases and various other diseases; patients with cancer or digestive diseases, and diseases related to alcohol or tobacco consumption excluded; aged 25–74 years; median, 55 years
Wang *et al.* (1992) China 1988–89	Men: 204 cases and 241 controls; women: 122 cases and 155 controls	Population-based study in two major cancer hospitals in two areas Cases of oesophageal cancer (mostly squamous-cell carcinomas), aged 30–87 years (15–20% of all cases); response rate > 90% Controls selected from the population and frequency-matched on gender, age (5-year categories) and residence; response rate > 90%

Table 2.1.4.16 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Kabat *et al.* (1993) USA 1981–90	Men: 136 cases and 4544 controls; women: 78 cases and 2228 controls	Hospital-based study in 28 hospitals in 8 US cities Cases of histologically confirmed squamous-cell carcinoma of the oesophagus Controls included patients with cancers of breast, endometrium, ovary, prostate and skin, leukaemias, lymphomas and sarcomas and non-cancer diagnosis, individually matched on age (± 5 years), sex, race and hospital
Brown *et al.* (1994a) USA 1986–89	Men: 124 white and 249 black cases, and 750 white and 614 black controls	Population-based study in three areas Cases of histologically confirmed squamous-cell carcinoma of the oesophagus, aged 30–79 years; response rate, 68% Controls selected by random digit dialling and random sampling from Medicare recipients, frequency-matched on race and age; response rates, 78% and 82% for whites and blacks, respectively
Gao *et al.* (1994) China 1990–93	Men: 624 cases; women: 278 cases; 1552 controls	Population-based study in permanent residents of urban Shanghai Cases of oesophageal cancer (NOS), aged 30–74 years Controls randomly selected from the general population and frequency-matched on sex and age (5-year categories) within a larger case–control study
Hanaoka *et al.* (1994) Japan 1989–91	Men: 141 cases and 141 controls	Hospital-based study in seven university clinics Cases of histologically confirmed oesophageal cancer (NOS), aged < 85 years Controls selected from patients with diseases supposedly unrelated to alcohol or tobacco use; 54% cancer of the stomach, colon or rectum, and 18% benign gastrointestinal conditions, individually matched (1:1) by age (± 3 years), sex, hospital and area of residence
Hu *et al.* (1994) China 1985–89	Men: 170 cases and 340 controls; women: 26 cases and 52 controls	Hospital-based study at five major hospitals in north-eastern China Cases of histologically confirmed oesophageal cancer (NOS); 100% of eligible cases Controls without cancer or oesophageal diseases, individually matched (2:1) by sex, age (± 5 years), hospital and area of residence
Chen *et al.* (1995) China 1990–92	Men: 117 cases and 234 controls; women: 31 cases and 62 controls	Population-based study in Shichuan Province Incident cases of oesophageal cancer (NOS) registered in Jintang county, aged 26–88 years (mean, 61.5 years) Healthy controls from neighbourhood, individually matched (2:1) by age (± 5 years), sex and residence
Cheng *et al.* (1995) Hong Kong SAR 1989–90	Men: 30 cases and 279 controls; women: 23 cases and 128 controls	Hospital-based study in four general hospitals; cases and controls were abstainers from alcohol. Cases of histologically confirmed oesophageal cancer (NOS) Controls not matched to cases; patients with diabetes mellitus and alcohol- and tobacco-related conditions excluded
Rolón *et al.* (1995) Paraguay 1988–91	Men: 110 cases and 318 controls; women: 21 cases and 63 controls	Hospital-based study in all medical facilities of Asunción Cases of oesophageal cancer (NOS) diagnosed by cytology, histology and radiology, aged < 75 years; 100% of eligible cases Controls with cancers thought not to be associated with smoking or alcohol (skin, prostate, leukaemia, lymphomas) and benign conditions, individually matched (3:1) by sex and age (± 5 years), hospital and admission period; 97% participation rate

Table 2.1.4.16 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Siemiatycki *et al.* (1995) Canada 1979–85	Men: 99 cases and 2238 controls	Hospital- and population-based study in Montreal Cases of cancers of the oesophagus (NOS), confirmed histologically, aged 35–70 years Controls: 533 population-based, selected from electoral list stratified by age; participation rate, 72%; 1705 patients with all other cancers
Vaughan *et al.* (1995) USA 1983–90	Men: 64 cases and 506 controls; women: 42 cases and 218 controls	Population-based study in western Washington State Cases of histologically confirmed squamous-cell carcinoma of the oesophagus, identified by the local Cancer Surveillance System; response rate, 83% Controls identified by random-digit dialling and frequency-matched on age and sex; response rate, 80%
Vizcaino *et al.* (1995) Zimbabwe 1963–77	Men: 826 cases and 3007 controls; women: 55 cases and 2231 controls	Hospital-based study in Bulawayo using interviews Incident cases of oesophageal cancer registered by the local cancer registry; 86% confirmed histologically, of whom 90% had squamous-cell carcinoma; mean age, 55.7 years; 73% of all cases participated. Controls with all other cancers unrelated to alcohol or tobacco consumption; response rate, 71%
Tavani *et al.* (1996) Italy 1984–92	Men: 22 cases and 79 controls; women: 18 cases and 72 controls	Hospital-based study in major hospitals in Milan, restricted to abstainers from alcohol Incident cases of oesophageal cancer (NOS), aged 26–74 years; 97% of eligible cases Controls without malignant, digestive or metabolic diseases or diseases known or suspected to be related to alcohol or tobacco consumption; 97% of eligible controls
Gammon *et al.* (1997) USA 1993–95	Men: 176 cases and 555 controls; women: 45 cases and 140 controls	Population-based study in three areas Cases of histologically confirmed squamous-cell carcinoma of the oesophagus, identified through population-based tumour registries, aged 30–79 years; 74% of eligible cases Controls identified by random-digit dialling or random sampling of Health Care Financing Administration rosters, frequency matched by area, age, sex and/or race, depending on study centre; response rate, 70%
Launoy *et al.* (1997) France 1991–94	Men: 208 cases and 399 controls	Hospital-based study in three university hospitals Cases of histologically confirmed squamous-cell carcinoma of the oesophagus, aged < 85 years Controls with osteoarthritis, lumbago, sciatica or eye conditions; trauma patients excluded; matched on age and hospital
Castellsagué & Muñoz (1999) Argentina, Brazil, Paraguay & Uruguay 1985–92	Men (76–84%) and women: 179 cases and 776 controls	Pooled analysis of five hospital-based studies in over 30 hospitals and clinics; study restricted to abstainers from alcohol Cases of squamous-cell carcinoma of the oesophagus; response rates, 90–99% Controls with diseases unrelated to alcohol or tobacco use, individually matched (2:1 or 3:1) on age (± 5 years), sex, hospital and residence

Table 2.1.4.16 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Castellsagué *et al.* (1999) Argentina, Brazil, Paraguay, Uruguay 1985–92	Men (76–84%) and women: 830 cases and 1779 controls	Pooled analysis of five hospital-based studies in over 30 hospitals and clinics Cases of squamous-cell carcinoma of the oesophagus; response rates, 90–99% Controls with diseases unrelated to alcohol or tobacco, individually matched (2:1 or 3:1) by age (± 5 years), sex, hospital, admission period and residence
La Vecchia *et al.* (1999b) Italy 1984–92	Men: 22 cases and 79 controls; women: 18 cases and 72 controls	Pooled analysis of two hospital-based studies in two regions in northern Italy; study restricted to abstainers from alcohol Incident cases of histologically confirmed oesophageal cancer (NOS) Controls with acute, non-neoplastic conditions; diseases related to tobacco use or alcohol abuse excluded
Shen *et al.* (1999) China 1994–95	Men: 307 cases and 307 controls; women: 242 cases and 242 controls	Population-based study Incident cases of oesophageal cancer (NOS) confirmed by X-rays or computerized tomography scan (53%) or by histology (47%); 71% of squamous-cell carcinomas; aged 30–74 years; response rate, 90.3% Controls with no history of digestive cancer, individually matched on age (± 3 years), sex and village
Lagergren *et al.* (2000) Sweden 1995–97	Men: 120 cases; women: 47 cases; 820 controls	Population-based study in the entire population of Sweden using interviews Cases of squamous-cell carcinoma of the oesophagus, born in Sweden on even dates; median age, 67 years; response rate, 73% Controls randomly selected and frequency-matched to total cases of squamous-cell carcinoma and adenocarcinoma of the oesophagus, and adenocarcinoma of the gastric cardia; participation rate, 73%
Lu *et al.* (2000) China 1995–96	Men: 198 cases and 198 controls; women: 154 cases and 154 controls	Population-based study in Lin County Cases of oesophageal cancer (NOS), confirmed by histology or cytology (87%) or X-rays or surgery (13%) Neighbourhood controls individually matched (1:1) on age (± 3 years) and sex
Zambon *et al.* (2000) Italy 1992–97	Men: 275 cases and 593 controls	Hospital-based study in three areas of northern Italy using interviews Incident cases of histologically confirmed squamous-cell carcinoma of the oesophagus, aged 39–79 years; 95% of eligible cases Controls admitted for acute illnesses unrelated to tobacco and alcohol use to major hospitals in the same areas, frequency-matched by age (± 5 years) and area of residence; malignant lesions excluded; 95% of eligible controls participated.
Pacella-Norman *et al.* (2002) South Africa 1995–99	Men: 267 cases and 804 controls; women: 138 cases and 1370 controls	Hospital-based study at 3 major hospitals in greater Johannesburg Incident cases of oesophageal cancer (NOS), 90% confirmed by histology, haematology or cytology, aged 18–74 years Controls with cancers thought to be unrelated to tobacco and alcohol use: breast, prostate, leukaemia, lymphoma, myelomas, ovary, endometrium, vulva, skin, colon, penis and others; aged 18–74 years

Table 2.1.4.17. Case–control studies on tobacco smoking and oesophageal cancer (unspecified) or squamous-cell carcinoma of the oesophagus

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Victora *et al.* (1987) Brazil 1985–86	Squamous-cell carcinoma	Former smoker	1.3	0.6–2.7	Adjusted for cachaça (local beverage) consumption, place of residence, intake of fruit and meat
		Current smoker	3.9	1.9–8.0	
Brown *et al.* (1988) USA 1977–84	Oesophagus (unspecified)	Current smoker	1.8	1.0–3.0	Cases and controls from the incidence and mortality series were combined for the analysis. Adjusted for study series (incidence or mortality), use of local beverage and other alcoholic beverages
		Cigarettes/day			
		1–19	0.8	0.4–1.5	
		20–29	2.0	1.1–3.4	
		≥ 30	2.6	1.4–4.7	
		Duration (years)			
		1–24	1.4	0.6–2.9	
		25–44	1.6	1.0–2.8	
		≥ 45	1.8	1.0–3.3	
Nakachi *et al.* (1988) Japan 1973–85	Oesophagus (unspecified)	Men			Participation rates for both cases and controls were low. Relevant factors were not fully adjusted for except variables for matching.
		> 400 000 vs < 400 000 cigarettes smoked	2.4	0.99–5.7	
		Women			
		Ever-smoker vs never	2.3	1.02–5.2	
Yu *et al.* (1988) USA 1975–81	Oesophagus (unspecified)	Packs/day			Analysis restricted to directly interviewed pairs (*n* = 129); relevant factors were not adjusted for except variables for matching (age, sex and race).
		≤ 1	6.6	2.3–19.3	
		2	9.1	2.9–29.0	
		≥ 3	5.1	1.5–16.9	

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Ferraroni *et al.* (1989) Italy 1983–88	Oesophagus (unspecified)	Former smoker	2.9		Adjusted for age, sex, education, social class, marital status, smoking, coffee and alcohol consumption $p < 0.01$ for all current smokers combined
		Cigarettes/day			
		< 15	4.2		
		15–24	4.2		
		≥ 25	7.2		
Li *et al.* (1989) China 1984–85	Oesophagus (unspecified)	High-risk area			Analysis included only men because of the very small number of women who smoked; cancers of the oesophagus and gastric cardia were combined in the analysis; adjusted for age
		Current smoker	0.9	0.6–1.2	
		Cigarettes/day			
		1–9	1.0	0.6–1.6	
		10–19	0.8	0.5–1.2	
		≥ 20	0.9	0.6–1.4	
		Age at starting smoking (years)			
		≥ 35	1.0	0.6–1.7	
		25–34	1.1	0.7–1.7	
		20–24	0.8	0.5–1.3	
		< 20	0.7	0.4–1.1	
		Low-risk area			
		Current smoker	1.5	1.1–2.0	
		Cigarettes/day			
		1–9	1.4	0.4–2.1	
		10–19	1.3	0.9–2.0	
		≥ 20	1.7	1.2–2.6	

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Li *et al.* (1989) (contd)		Age at starting smoking (years)			
		≥ 35	1.3	0.7–2.3	
		25–34	2.2	1.5–3.4	
		20–24	2.1	1.3–3.3	
		< 20	0.8	0.5–1.2	
Rao *et al.* (1989) India 1980–84	Oesophagus (unspecified)	Smoker			Adjusted for age and residence. Both bidi and cigarette smokers were included as smokers.
		All	1.7	1.1–2.7	
		Vegetarian	1.2	0.4–3.7	
		Non-vegetarian	2.3	1.3–4.0	
De Stefani *et al.* (1990) Uruguay 1985–88	Squamous-cell carcinoma	Men			Adjusted for age, residence and alcohol intake
		Cigarettes/day			
		1–7	1.9	0.7–5.4	
		8–14	2.7	1.1–6.8	
		15–24	4.3	1.7–10.4	
		≥ 24	4.6	1.9–11.1	
		Women			
		Cigarettes/day			
		1–7	2.3	0.9–6.0	
		≥ 8	3.2	1.1–9.3	
Franceschi *et al.* (1990) Italy 1986–89	Oesophagus (unspecified)	Cigarette smoker	3.8	2.2–6.6	Adjusted for age, residence, education, occupation and alcohol intake
		Cigarettes/day			
		≤ 14	3.0	1.7–5.5	
		15–24	3.8	2.1–6.7	
		≥ 25	4.7	2.6–8.4	p for trend < 0.01

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Franceschi *et al.* (1990) (contd)		Duration (years)			
		1–29	2.4	1.3–4.4	
		30–39	4.0	2.2–7.2	
		≥ 40	5.6	3.1–10.0	*p* for trend < 0.01
		Age at starting smoking (years)			
		≥ 25	3.7	2.0–6.8	
		17–24	4.5	2.5–7.8	
		< 17	2.5	1.4–4.8	*p* for trend < 0.01
Sankaranarayanan *et al.* (1991) India 1983–84	Oesophagus (unspecified)	Cigarette smoker	0.6	0.3–1.2	Only 9 cases were cigarette smokers.
		Duration (years)			
		≤ 20	0.5	0.1–2.1	
		> 21	0.6	0.3–1.4	*p* for trend > 0.05
Cheng *et al.* (1992) Hong Kong SAR 1989–90	Oesophagus (unspecified)	Tobacco/day (g)			Adjusted for age, education, birthplace, alcohol use, consumption of pickled vegetables, green leafy vegetables and citrus fruits, preference for hot drinks or soups, meals taken at home or eaten out
		< 5	1.7	0.8–3.9	
		5–< 10	1.8	1.0–3.2	
		10–< 15	2.2	1.3–3.6	
		15–< 20	1.8	1.1–3.1	
		20–< 25	2.5	1.5–4.1	
		25–< 30	2.3	1.0–5.7	
		30–< 40	3.9	1.9–7.8	
		≥ 40	1.7	0.6–5.1	

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Negri *et al.* (1992) Italy 1984–90	Oesophagus (unspecified)	Men			Adjusted for age, education, alcohol use and β-carotene intake
		Former smoker and < 15 cigarettes/day	3.5	1.9–6.3	
		≥ 15 cigarettes/day	5.1	2.9–9.0	p for trend < 0.001
		Women			
		Former smoker and < 15 cigarettes/day	1.8	0.8–4.0	
		≥ 15 cigarettes/day	4.8	2.1–10.7	p for trend < 0.001
Wang *et al.* (1992) China 1988–89	Oesophagus (unspecified)	High-risk area			Analysis for men only; adjusted for age and occupation; alcohol consumption was a significant risk factor in the high-risk area but was not adjusted for; amount of tobacco consumption too low to show a clear result
		Ever-smoker	0.6	0.3–1.2	
		> 20 cigarettes/month	3.2	0.8–12.6	
		Low-risk area			
		Ever-smoker	1.5	0.7–3.4	
		> 20 cigarettes/month	2.2	0.6–7.6	
Kabat *et al.* (1993) USA 1981–90	Squamous-cell carcinoma	Men			Adjusted for age, education, hospital, time period and alcohol use
		Former smoker	1.3	0.7–2.4	
		Current smoker	4.5	2.5–8.1	
		Cigarettes/day			
		1–20	1.9	1.1–3.5	
		21–30	2.7	1.3–5.4	
		≥ 31	2.7	1.5–5.0	

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Kabat *et al.* (1993) (contd)		Women			
		Former smoker	2.2	1.1–4.3	
		Current smoker	6.8	3.7–12.1	
		Cigarettes/day			
		1–20	3.7	2.0–6.7	
		≥ 21	4.8	2.4–9.5	
Brown *et al.* (1994a) USA 1986–89	Squamous-cell carcinoma	Whites			Adjusted for age, geographical area, alcohol consumption and income
		Former smoker	2.4	0.9–6.5	
		Ever-smoker	3.7	1.4–9.7	
		Current smoker	5.5	2.0–14.9	
		Cigarettes/day			
		1–19	2.9	0.9–8.8	
		20–39	3.8	1.4–10.4	
		≥ 40	3.9	1.4–11.2	p for trend = 0.078
		Duration (years)			
		1–29	2.0	0.7–6.0	
		30–39	3.6	1.3–10.6	
		≥ 40	5.9	2.1–16.3	p for trend < 0.001
		Blacks			
		Former smoker	1.5	0.7–3.6	
		Ever-smoker	3.2	1.5–7.0	
		Current smoker	4.2	1.9–9.2	
		Cigarettes/day			
		1–19	2.2	0.9–4.9	
		20–39	4.0	1.8–8.9	
		≥ 40	3.4	1.3–8.5	p for trend < 0.001

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Brown *et al.* (1994a) (contd)		Duration (years)			
		1–29	1.7	0.7–4.1	
		30–39	3.0	1.3–6.9	
		≥ 40	5.1	2.3–11.6	p for trend < 0.001
Gao *et al.* (1994) China 1990–93	Oesophagus (unspecified)	Men			Adjusted for age, education, birth place, tea drinking, dietary factors and alcohol intake (for men only)
		Former smoker	1.7	1.1–2.6	
		Current smoker	2.1	1.6–3.0	
		Cigarettes/day			
		1–9	1.4	0.8–2.3	
		10–19	1.7	1.1–2.6	
		20–29	2.5	1.7–3.6	
		≥ 30	6.0	3.2–11.1	p for trend < 0.001
		Duration (years)			
		0.5–19	1.0	0.5–1.8	
		20–29	1.1	0.7–2.0	
		30–39	2.3	1.5–3.6	
		≥ 40	2.9	2.0–4.2	p for trend < 0.001
		Pack–years			
		< 15	1.0	0.6–1.7	
		15–34	1.8	1.2–2.7	
		≥ 35	3.8	2.5–5.6	p for trend < 0.001
		Age at starting smoking (years)			
		≥ 30	1.3	0.8–2.1	
		20–29	2.6	1.8–3.7	
		< 20	2.5	1.6–3.9	p for trend < 0.001

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Gao *et al.* (1994)		Women			
(contd)		Former smoker	4.0	1.9–8.3	
		Current smoker	1.6	1.0–2.4	
		Cigarettes/day			
		1–9	1.1	0.5–2.2	
		10–19	2.1	1.1–4.0	
		≥ 20	1.9	0.8–4.6	*p* for trend < 0.05
		Duration (years)			
		0.5–19	0.5	0.2–1.5	
		20–29	2.4	1.1–5.2	
		30–39	1.2	0.5–3.0	
		≥ 40	2.4	1.2–4.9	*p* for trend < 0.01
		Pack–years			
		< 10	0.8	0.4–1.7	
		≥ 10	2.4	1.4–4.1	*p* for trend < 0.01
		Age at starting smoking (years)			
		≥ 25	1.4	0.8–2.3	
		< 25	2.4	1.1–5.2	*p* for trend < 0.05
Hanaoka *et al.* (1994) Japan 1989–91	Oesophagus (unspecified)	Cigarettes/day			Adjusted for alcohol intake; controls include patients with tobacco-related diseases. [†]Also includes former smokers
		1–4	1.2[†]	0.6–2.6[†]	
		5–14	1.4	0.6–3.2	
		15–24	1.5	0.8–3.0	
		≥ 25	1.0	0.5–2.2	*p* for trend = 0.55

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Hu *et al.* (1994) China 1985–89	Oesophagus (unspecified)	Cigarettes/day[†]			Adjusted for consumption of spirits [†]Former smokers were included in corresponding categories.
		1–10	1.7	1.0–2.9	
		11–20	2.2	1.3–3.7	
		21–30	1.7	0.8–3.7	
		≥ 31	3.3	1.5–7.4	*p* for trend = 0.005
		Duration (years)			
		1–10	1.5	0.5–5.2	
		11–20	2.1	1.1–4.3	
		21–30	2.8	1.6–5.0	
		≥ 31	3.3	2.0–5.3	*p* for trend < 0.0001
		Age at starting smoking (years)			
		≥ 31	2.5	1.3–5.1	
		26–30	2.1	1.1–4.3	
		21–25	2.7	1.5–4.8	
		16–20	3.1	1.8–5.3	
		≤ 15	3.4	1.7–6.6	*p* for trend = 0.03
Chen *et al.* (1995) China 1990–92	Oesophagus (unspecified)	Ever-smoker	1.3	0.8–2.1	Adjusted for age, sex, residence, alcohol use, relevant food items and eating habits. Smoking could not enter into the multivariate analysis. The risk was not significantly associated with daily tobacco consumption, years of smoking, age at starting smoking and type of tobacco smoking.

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Cheng *et al.* (1995) Hong Kong SAR 1989–90	Oesophagus (unspecified)	Former smoker	2.4	0.95–6.1	Analysis restricted to abstainers from alcohol; adjusted for sex, age, education, place of birth, preference for hot drinks or soups, consumption of green leafy vegetables, citrus fruits and pickled vegetables
		Current smoker			
		Tobacco/day (g)			
		< 15	3.0	1.1–8.4	
		15–24.99	2.6	0.9–8.1	
		≥ 25	10.3	1.8–57.6	*p* for trend = 0.019
Rolón *et al.* (1995) Paraguay 1988–91	Oesophagus (unspecified)	Former smoker	3.6	1.6–7.9	Adjusted for age, sex, hospital group, lifetime alcohol consumption
		Current smoker	4.5	2.2–9.1	
		Cigarettes/day			
		1–14	3.2	1.6–6.5	
		15–39	8.4	3.6–19.3	
		≥ 40	6.1	1.8–20.8	*p* for trend = 0.01
		Lifetime no. of cigarettes			
		1–49 999	1.8	0.7–4.2	
		50 000–99 999	3.4	1.4–8.5	
		100 000–299 999	9.1	4.0–21.0	
		≥ 300 000	10.0	3.9–25.8	*p* for trend < 0.00001
		Duration (years)			
		1–29	1.5	0.6–3.7	
		30–39	4.4	1.9–10.0	
		≥ 40	7.3	3.3–16.3	*p* for trend = 0.00001

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Siemiatycki *et al.* (1995)	Oesophagus (unspecified)	Ever-smoker	2.4	1.0–5.7	
Canada		Pack–years			
1979–85		≤ 25	1.7	0.6–4.7	
		25–49	2.3	0.9–5.8	
		50–74	3.1	1.2–7.9	
		≥ 75	2.8	1.1–7.6	*p* for trend < 0.01
Vaughan *et al.* (1995)	Squamous-cell carcinoma	Pack–years			Adjusted for alcohol intake, body mass index, age, sex, race and education
USA		1–39	5.2	1.7–16.2	
1983–90		40–79	7.9	2.8–22.1	
		≥ 80	16.9	4.1–69.1	*p* for trend < 0.001
Vizcaino *et al.* (1995)	Oesophagus (unspecified)	Former smoker	3.1	1.7–5.6	Analysis for men only because of low prevalence of women who smoked; adjusted for age, province, occupation and total alcohol consumption
Zimbabwe		Cigarettes/day			
1963–77		< 15	3.1	2.4–4.0	
		≥ 15	4.3	2.8–6.7	*p* for trend < 0.001
Tavani *et al.* (1996)	Oesophagus (unspecified)	Former smoker	0.8	0.2–3.4	Adjusted for age, sex and education
Italy		Current smoker	3.4	1.5–8.1	
1984–92		Cigarettes/day			
		< 20	1.3	0.4–4.2	
		≥ 20	7.5	2.7–20.4	*p* for trend < 0.01
		Duration (years)			
		≤ 30	2.0	0.7–5.3	
		> 30	4.9	1.8–13.6	*p* for trend < 0.01

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Tavani *et al.* (1996) (contd)		Age at starting smoking (years)			
		> 25	1.7	0.6–4.7	
		≤ 25	3.9	1.5–10.5	
Gammon *et al.* (1997) USA 1993–95	Squamous-cell carcinoma	Former smoker	2.8	1.5–4.9	Adjusted for age, sex, area, race, body mass index, income and use of alcohol
		Current smoker	5.1	2.8–9.2	
		Cigarettes/day			
		< 16	2.7	1.4–5.1	
		16–20	3.9	2.1–7.2	
		21–30	5.3	2.6–10.7	
		> 30	3.9	2.0–7.6	*p* for trend < 0.05
		Duration (years)			
		< 20	1.8	0.9–3.7	
		20–31	2.0	1.0–4.0	
		32–42	3.3	1.8–6.1	
		> 42	5.9	3.2–10.7	*p* for trend < 0.05
		Pack–years			
		< 14	2.0	1.0–4.0	
		14–31	2.8	1.4–5.5	
		32–54	4.5	2.4–8.5	
		> 54	5.8	3.1–11.0	*p* for trend < 0.05

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Launoy *et al.* (1997) France 1991–94	Squamous-cell carcinoma	Duration (years)			Nonsmokers and abstainers from alcohol were excluded from the analysis, hence the reference group included smokers who had smoked for 1–14 years; adjusted for interviewer, age, place of residence, occupation, education, lifestyle and weekly alcohol consumption
		1–14	1.0	–	
		15–29	1.7	0.7–4.1	
		30–44	3.3	1.3–8.3	
		≥ 45	3.2	1.1–10.0	*p* for trend < 0.0001
Castellsagué & Muñoz (1999) Argentina, Brazil, Paraguay & Uruguay 1985–92	Squamous-cell carcinoma	Ever-smoker	2.2	1.5–3.4	Adjusted for hospital, age group, sex and years of schooling
		Cigarettes/day			
		1–7	1.5	0.8–2.6	
		8–14	2.6	1.2–5.4	
		15–24	3.4	1.9–6.1	
		≥ 25	2.5	1.2–5.4	*p* for trend < 0.001
Castellsagué *et al.* (1999) Argentina, Brazil, Paraguay & Uruguay 1985–92	Squamous-cell carcinoma	Men			Adjusted for age, hospital, education and alcohol intake
		Former smoker	2.8	1.8–4.3	
		Ever-smoker	4.1	2.7–6.0	
		Current smoker	5.1	3.4–7.6	
		Cigarettes/day			
		1–7	2.2	1.3–3.5	
		8–14	4.1	2.6–6.4	
		15–24	5.3	3.4–8.1	
		≥ 25	5.0	3.2–7.7	*p* for trend < 0.00001

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Castellsagué *et al.* (1999) (contd)		Duration (years)			
		1–29	2.6	1.7–4.2	
		30–39	3.6	2.3–5.6	
		40–49	4.7	3.0–7.2	
		≥ 50	6.0	3.8–9.5	p for trend < 0.00001
		Age at starting smoking (years)			
		≤ 13	1.0	–	
		14–16	0.7	0.5–0.96	
		17–20	0.8	0.6–1.0	
		≥ 21	0.6	0.4–0.9	p for trend = 0.02
		Women			
		Former smoker	1.6	0.8–3.1	
		Ever-smoker	2.4	1.5–3.7	
		Current smoker	3.1	1.8–5.3	
		Cigarettes/day			
		1–14	2.1	1.2–3.7	
		≥ 15	2.8	1.4–5.4	p for trend = 0.0003
		Duration (years)			
		1–29	1.5	0.8–2.9	
		30–39	2.0	0.9–4.4	
		≥ 40	4.4	2.2–9.0	p for trend < 0.00001

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Castellsagué *et al.* (1999) (contd)		Age at starting smoking (years)			
		≤ 13	1.0	–	
		14–16	1.6	0.3–7.5	
		17–20	0.6	0.2–2.4	
		≥ 21	0.2	0.1–0.7	*p* for trend = 0.003
La Vecchia *et al.* (1999b) Italy 1984–92	Oesophagus (unspecified)	Cigarettes/day			Analysis restricted to abstainers from alcohol
		< 20	1.3	0.4–4.2	
		≥ 20	7.5	2.7–20.4	*p* for trend < 0.001
Shen *et al.* (1999) China 1994–95	Oesophagus (unspecified)	Men			Adjusted for age, education, salted food consumption and fruit intake
		Ever-smoker	1.9	0.9–4.0	
		Current smoker	2.5	1.6–3.8	
		Cigarettes/day			
		1–9	1.5	0.8–3.1	
		10–19	1.9	1.1–3.1	
		20–29	2.5	1.6–4.0	
		≥ 30	7.7	2.8–20.8	*p* for trend < 0.001
		Duration (years)			
		0.5–19	1.8	0.9–3.4	
		20–29	2.4	1.4–4.3	
		30–39	2.5	1.5–4.2	
		≥ 40	2.7	1.5–4.9	*p* for trend < 0.001

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Shen *et al.* (1999) (contd)		Pack–years			
		0.5–13	1.3	0.7–2.4	
		14–29	2.1	1.3–3.5	
		> 29	3.3	2.0–5.5	p for trend < 0.001
		Age at starting smoking (years)			
		> 29	2.0	1.2–3.5	
		20–29	2.4	1.5–3.8	
		< 20	2.8	1.6–5.1	p for trend < 0.01
		Women			
		Ever-smoker	3.3	0.6–17.6	
		Current smoker	1.2	0.8–1.8	
		Cigarettes/day			
		1–9	1.8	1.0–3.4	
		10–19	0.9	0.6–1.6	
		≥ 20	1.4	0.7–2.8	p for trend > 0.05
		Duration (years)			
		0.5–19	0.9	0.5–1.5	
		20–29	1.3	0.7–2.4	
		≥ 30	2.4	1.1–5.1	p for trend < 0.05
		Pack–years			
		0.5–13	0.9	0.7–1.6	
		≥ 14	1.9	1.0–3.4	p for trend > 0.05

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Shen *et al.* (1999) (contd)		Age at starting smoking (years)			
		≥ 30	1.1	0.7–1.7	
		< 30	2.1	1.1–4.1	*p* for trend > 0.05
Lagergren *et al.* (2000) Sweden 1995–97	Squamous-cell carcinoma	Former smoker	2.5	1.4–4.7	Adjusted for age, sex, alcohol use, education, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake and physical activity
		Current smoker	9.3	5.1–17.0	
		Cigarettes/day[†]			
		1–9	2.8	1.5–5.2	
		10–19	3.9	2.2–6.9	[†]Also adjusted for pipe smoking and snuff use
		≥ 20	4.9	2.7–9.0	
Lu *et al.* (2000) China 1995–96	Oesophagus (unspecified)	Ever-smoker	2.0	1.1–3.4	Adjusted for age, sex, occupation, body mass index, dietary factors and habits, depression and hyperplasia
Zambon *et al.* (2000) Italy 1992–97	Squamous-cell carcinoma	Cigarettes/day			
		1–14	3.2	1.6–6.4	
		15–24	5.4	2.8–10.1	
		≥ 25	7.0	3.2–15.1	*p* for trend < 0.001
		Duration (years)			
		1–24	1.5	0.4–6.2	
		25–34	2.6	1.2–5.6	
		≥ 35	6.4	3.5–12.0	*p* for trend < 0.001

Table 2.1.4.17 (contd)

Reference Country and years of study	Cancer subsite	Smoking categories	Relative risk	95% CI	Comments
Zambon *et al.* (2000) (contd)		Age at starting smoking (years)			
		≥ 20	4.3	2.2–8.3	
		17–19	3.6	1.8–7.5	
		< 17	6.3	3.3–12.3	p for trend = 0.15
Pacella-Norman *et al.* (2002) South Africa 1995–99	Oesophagus (unspecified)	Men			Adjusted for age, place of birth, education, work category, heating fuel, snuff use and alcohol consumption
		Former smoker	3.8	2.3–6.3	
		Current smoker	3.8	2.3–6.1	
		Tobacco (g/day)			
		1–14	3.3	2.0–5.5	
		≥ 15	6.0	3.2–11.0	
		Women			
		Former smoker	2.6	1.5–4.5	
		Current smoker	3.1	1.7–5.4	
		Tobacco (g/day)			
		1–14	2.8	1.5–5.2	
		≥ 15	6.2	1.9–20.2	

CI, confidence interval

Table 2.1.4.18. Case–control studies on tobacco smoking and oesophageal cancer (unspecified) or squamous-cell carcinoma of the oesophagus: smoking cessation

Reference (country and years of study)	Cancer subsite	Years since quitting	Relative risk	95% CI	Comments
Brown *et al.* (1988) USA 1977–84	Oesophagus (unspecified)	Current smoker	1.8	1.0–3.0	Cases and controls from the incidence and mortality series were combined for the analysis. Adjusted for study series (incidence or mortality), use of local beverage and other alcoholic beverages
		1–9	2.0	1.0–3.7	
		≥ 10	1.0	0.5–2.1	
Yu *et al.* (1988) USA 1975–81	Oesophagus (unspecified)	< 5	4.1	0.6–28.6	Analysis restricted to directly interviewed pairs (*n* = 129); relevant factors were not adjusted for, except variables for matching (age, sex and race).
		5–9	3.3	0.8–12.8	
		10–19	2.0	0.6–7.2	
		≥ 20	1.9	0.5–6.6	
		Nonsmoker	1.0	–	
Franceschi *et al.* (1990) Italy 1986–89	Oesophagus (unspecified)	Current smoker	3.8	2.2–6.6	Adjusted for age, residence, education, occupation and alcohol intake *p* for trend < 0.01
		< 10	2.5	1.3–4.8	
		≥ 10	2.2	1.1–4.3	
Kabat *et al.* (1993) USA 1981–90	Squamous-cell carcinoma	Men			Adjusted for age, education, hospital, time period and alcohol use
		Current smoker	1.0	–	
		1–5	0.5	0.3–1.0	
		6–10	0.4	0.2–0.8	
		11–20	0.3	0.2–0.6	
		≥ 21	0.2	0.1–0.3	
		Women			
		Current smoker	1.0	–	
		1–10	0.4	0.2–0.9	
		≥ 11	0.3	0.1–0.5	

Table 2.1.4.18 (contd)

Reference (country and years of study)	Cancer subsite	Years since quitting	Relative risk	95% CI	Comments
Rolón *et al.* (1995) Paraguay 1988–91	Oesophagus (unspecified)	Current smoker	4.5	2.2–9.1	Adjusted for age, sex, hospital group, lifetime alcohol consumption
		1–7	5.2	2.2–12.4	
		8–19	2.0	0.6–6.7	
		≥ 20	2.0	0.5–7.9	*p* for trend = 0.06
Gammon *et al.* (1997) USA 1993–95	Squamous-cell carcinoma	Current smoker	5.1	2.8–9.2	Adjusted for age, sex, area, race, body mass index, income and use of alcohol
		< 11	5.6	2.9–10.8	
		11–20	2.3	1.1–4.8	
		21–30	1.0	0.4–2.7	
		> 30	1.8	0.8–4.2	*p* for trend < 0.05
Launoy *et al.* (1997) France 1991–94	Squamous-cell carcinoma	Current smoker	1.0	–	Adjusted for interviewer, age, place of residence, occupation, education, lifestyle and weekly alcohol consumption
		1–5	1.4	0.7–2.6	
		6–10	0.9	0.4–1.9	
		≥ 11	0.5	0.3–1.03	*p* for trend = 0.06
Castellsagué *et al.* (1999) Argentina, Brazil, Paraguay & Uruguay 1985–92	Squamous-cell carcinoma	Men			Adjusted for age, hospital, education, alcohol intake
		Current smoker	1.0	–	
		1–4	0.7	0.5–1.0	
		5–9	0.5	0.3–0.8	*p* for trend < 0.00001
		≥ 10	0.5	0.4–0.7	
		Women			
		Current smoker	1.0	–	
		1–9	1.0	0.3–3.1	
		≥ 10	0.4	0.1–1.2	*p* for trend = 0.14

Table 2.1.4.18 (contd)

Reference (country and years of study)	Cancer subsite	Years since quitting	Relative risk	95% CI	Comments
Lagergren *et al.* (2000) Sweden 1995–97	Squamous-cell carcinoma	Current smoker	9.3	5.1–17.0	Adjusted for age, sex, alcohol use, education, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake and physical activity
		< 2	10.3	5.6–19.1	
		3–10	5.2	2.4–11.3	
		11–25	2.1	1.0–4.7	p for trend < 0.0001
		> 25	1.9	0.8–4.0	
Zambon *et al.* (2000) Italy 1992–97	Squamous-cell carcinoma	< 5	7.7	3.2–18.5	
		5–9	4.1	1.8–9.1	
		≥ 10	1.5	0.8–3.0	
		Nonsmoker	1.0	–	p for trend < 0.001

CI, confidence interval

Table 2.1.4.19. Case–control studies on tobacco smoking and oesophageal cancer (unspecified) or squamous-cell carcinoma of the oesophagus: type of tobacco and/or cigarette

Reference (country and years of study)	Cancer subsite	Cigarette exposure	Relative risk	95% CI	Comments
De Stefani *et al.* (1990) Uruguay 1985–88	Squamous-cell carcinoma	Type of tobacco			Adjusted for age, residence, alcohol intake and duration of smoking
		Mainly blond	1.0	–	
		Mainly black	2.6	1.7–3.9	
Rolón *et al.* (1995) Paraguay 1988–91	Oesophagus (unspecified)	Type of tobacco			Adjusted for age, sex, hospital group and lifetime ethanol consumption
		Mainly black	1.0	–	
		Mixed	1.0	0.3–3.4	
		Mainly blond	0.5	0.2–1.1	
Vaughan *et al.* (1995) USA 1983–90	Squamous-cell carcinoma	Type of cigarettes			Adjusted for alcohol intake, body mass index, age, sex, race and education
		Filter	1.0	–	
		Mixed	0.6	0.2–1.9	
		Untipped			
		vs filter only	1.1	0.3–3.5	
		vs filter and mixed	1.6	0.8–3.3	
Gammon *et al.* (1997) USA 1993–95	Squamous-cell carcinoma	Filter status			Adjusted for age, sex, area, race, body mass index, income and use of alcohol
		Filter only	2.9	1.7–5.0	
		Filter + no filter	2.7	1.4–5.6	
		No filter only	3.6	2.0–6.4	

Table 2.1.4.19 (contd)

Reference (country and years of study)	Cancer subsite	Cigarette exposure	Relative risk	95% CI	Comments
Castellsagué *et al.* (1999) Argentina, Brazil, Paraguay & Uruguay 1985–92	Squamous-cell carcinoma	Men			Adjusted for age, hospital, education, alcohol intake
		Type of tobacco			
		Only blond	1.0	–	
		Mixed	1.3	0.8–1.9	
		Only black	2.0	1.5–2.7	p for trend < 0.00001
		Use of filter			
		Never	1.0	–	
		Ever	0.8	0.6–0.98	
		Women			
		Type of tobacco			
		Blond or mixed	1.0	–	
		Only black	3.4	0.9–13.0	
		Use of filter			
		Never	1.0	–	
		Ever	1.5	0.5–4.4	

CI, confidence interval

Table 2.1.4.20. Case–control studies on tobacco smoking and adenocarcinoma of the oesophagus: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Levi *et al.* (1990) Switzerland 1963–85	Men: 21 cases and 85 controls; women: 9 cases and 55 controls	Hospital-based study Cases histologically confirmed as adenocarcinoma in Barrett's oesophagus, aged 37–86 years Controls with Barrett's oesophagus without any malignant features
Kabat *et al.* (1993) USA 1981–90	Men: 173 cases and 4544 controls; women: 21 cases and 2228 controls	Hospital-based study in 28 hospitals in eight cities Cases histologically confirmed as adenocarcinoma of the distal oesophagus, gastro–oesophageal junction or cardia Controls included cancers of the breast, endometrium, ovary, prostate and skin, leukaemia, lymphomas and sarcomas and non-cancer diagnoses; individually matched on age (± 5 years), sex, race and hospital
Menke-Pluymers *et al.* (1993) Netherlands 1978–85	Men: 47 cases and 53 controls; women: 15 cases and 43 controls	Hospital-based study Cases histologically confirmed as adenocarcinoma in Barrett's oesophagus; mean age, 62 years Controls with cancer-free Barrett's oesophagus; mean age, 61 years
Brown *et al.* (1994b) USA 1986–89	Men: 174 cases and 750 controls	Population-based study in three areas Cases histologically confirmed as adenocarcinoma of the oesophagus or gastro–oesophageal junction, identified through cancer registries, aged 30–79 years Controls selected from general population by random-digit dialling and random sampling of Medicare recipients, frequency-matched on age and race
Gao *et al.* (1994) China 1990–93	Men and women: 51 cases and 1552 controls	Population-based study in the urban area of Shanghai Cases histologically confirmed as adenocarcinomas of the oesophagus, identified through Shanghai Cancer Registry, aged 30–74 years Controls randomly selected from Resident Registry, matched on age and sex
Vaughan *et al.* (1995) USA 1983–90	Men and women: 298 cases and 724 controls	Population-based study in western Washington State Cases histologically confirmed as adenocarcinomas of the oesophagus (133) or gastric cardia/gastro–oesophageal junction (165), identified through the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center Controls identified by random-digit dialling, frequency-matched by age and sex

Table 2.1.4.20 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Zhang *et al.* (1996) USA 1992–94	Men: 79 cases and 62 controls; women: 16 cases and 70 controls	Hospital-based study Cases histologically confirmed as adenocarcinomas of the oesophagus (28) or gastro–oesophageal junction and gastric cardia (67) Controls were patients who had undergone gastrointestinal endoscopy.
Gammon *et al.* (1997) USA 1993–95	Men: 245 cases and 555 controls; women: 48 cases and 140 controls	Population-based study in three areas Cases histologically confirmed as adenocarcinomas of the oesophagus, identified through population-based tumour registries, aged 30–79 years; 81% of eligible cases participated. Controls identified by random-digit dialling or random sampling of Health Care Financing Administration rosters, frequency-matched by geographical area, age, sex and/or race, depending on study centre; response rate, 70%
Lagergren *et al.* (2000) Sweden 1995–97	Men: 164 cases and 681 controls; women: 25 cases and 139 controls	Population-based study Cases histologically confirmed as adenocarcinomas of the oesophagus from the entire population of Sweden; median age, 69 years; 87% of eligible cases participated. Controls randomly selected in general population, from age and sex strata (frequency-matched); participation rate, 73%
Wu *et al.* (2001) USA 1992–97	Men: 202 cases and 999 controls; women: 20 cases and 357 controls	Population-based study in Los Angeles County Cases histologically confirmed as adenocarcinomas of the oesophagus, identified by the Los Angeles County Cancer Surveillance Program; 77% of those approached participated. Controls from neighbourhood, matched on gender, race and age (± 5 years); diagnosis of oesophageal or stomach cancer excluded

Table 2.1.4.21. Case–control studies on tobacco smoking and adenocarcinoma of the oesophagus

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Levi *et al.* (1990) Switzerland 1963–85	Cigarettes/day			Adjusted for age and sex; the control group used have been inappropriate.
	< 15	1.0	0.3–4.1	
	15–24	0.6	0.2–1.9	
	≥ 25	0.9	0.3–2.9	
Kabat *et al.* (1993) USA 1981–90	Men			Adjusted for age, education, hospital, time period and alcohol use; adenocarcinomas of the distal oesophagus and gastric cardia were combined.
	Former smoker	1.9	1.2–3.0	
	Current smoker	2.3	1.4–3.9	
	Cigarettes/day			
	1–20	1.8	1.1–2.9	
	21–30	2.1	1.1–3.9	
	≥ 31	2.4	1.5–4.0	
	Years since quitting			
	Current smoker	1.0	–	
	1–5	0.5	0.2–1.1	
	6–10	1.1	0.6–1.9	
	11–20	1.2	0.8–1.9	
	≥ 21	0.5	0.3–0.9	
	Women			
	Former smoker	1.4	0.4–4.4	
	Current smoker	4.8	1.7–14.0	
	Cigarettes/day			
	1–20	1.9	0.7–5.4	
	≥ 21	4.5	1.4–14.2	
	Years since quitting			
	Current smoker	1.0	–	
	1–10	0.3	0.1–1.7	
	≥ 11	0.3	0.1–1.1	

Table 2.1.4.21 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Menke-Pluymers *et al.* (1993) Netherlands 1978–85	Current smoker	2.3	$p < 0.05$	Adjusted for age, sex, alcohol intake and length of Barrett's oesophagus; controls may be inappropriate.
Brown *et al.* (1994b) USA 1986–89	Current smoker	2.1	1.2–3.8	Adjusted for age, area, intake of spirits and income
	Cigarettes/day			
	< 20	1.1	0.5–2.4	
	20–39	2.4	1.3–4.4	
	≥ 40	2.6	1.3–5.0	*p* for trend < 0.01
	Duration (years)			
	< 30	2.5	1.3–4.7	
	30–39	2.5	1.3–4.9	
	≥ 40	1.6	0.8–3.2	*p* for trend > 0.05
	Age at starting smoking (years)			
	≥ 21	2.4	0.5–3.2	
	16–20	1.9	0.9–3.2	
	< 16	2.5	0.9–3.6	*p* for trend > 0.05
	Years since quitting			
	1–9	2.0	1.0–4.1	
	10–19	2.4	1.2–4.9	
	20–29	2.2	1.0–4.7	
	≥ 30	3.1	1.5–6.6	*p* for trend > 0.05

Table 2.1.4.21 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Gao *et al.* (1994) China 1990–93	Former smoker	1.8		Adjusted for age, sex, education, birthplace, tea drinking, dietary factors and alcohol intake (for men only); for separated histological types, odds ratios were not statistically significant at $p < 0.05$ (numbers too small).
	Current smoker	2.1		
	Cigarettes/day			
	1–9	2.0		
	10–19	1.1		
	20–29	2.0		
	≥ 30	3.5		p for trend > 0.05
	Duration (years)			
	0.5–19	1.8		
	20–29	1.0		
	30–39	2.0		
	≥ 40	2.0		p for trend > 0.05
	Pack–years			
	< 15	1.7		
	15–34	1.4		
	≥ 35	2.4		p for trend > 0.05
	Age at starting smoking (years)			
	≥ 30	2.0		
	20–29	1.6		
	< 20	1.8		p for trend > 0.05
Vaughan *et al.* (1995) USA 1983–90	Former smoker	1.5	1.0–2.3	Adjusted for age, gender, race, education, alcohol intake and body mass index; cases of adenocarcinoma of the oesophagus, gastro–oesophageal junction and gastric cardia were combined.
	Pack–years			
	1–39	1.4	0.7–2.7	
	40–79	2.4	1.4–4.1	
	≥ 80	3.4	1.4–8.0	p for trend = 0.03

Table 2.1.4.21 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Vaughan *et al.* (1995) (contd)	Type of cigarette			Among ever smokers, further adjusted for pack–years of smoking
	Filter	1.0	–	
	Mixed	0.8	0.4–1.6	
	Untipped			
	vs filter only	1.4	0.7–3.0	
	vs filter and mixed	1.7	1.1–2.7	
Zhang *et al.* (1996) USA 1992–94	Cigarettes/day			Adjusted for age, sex, race, education, alcohol consumption, body-mass index and daily total calories
	1–20	1.1	0.5–2.4	
	21–40	2.8	1.1–7.2	*p* for trend = 0.07
	> 40	1.3	0.1–11.3	
	Duration (years)			
	1–20	0.9	0.3–2.4	
	21–40	2.2	0.99–4.9	
	> 40	1.3	0.4–3.8	*p* for trend = 0.17
	Pack–years			
	1–29	1.5	0.7–3.4	
	30–59	1.6	0.6–3.9	
	≥ 60	2.4	0.7–7.9	*p* for trend = 0.18
	continuous variable			*p* for trend = 0.034
	Age at starting smoking (years)			
	> 20	1.8	0.7–4.7	
	17–20	2.0	0.8–4.9	
	≤ 16	1.0	0.4–2.5	*p* for trend = 0.79

Table 2.1.4.21 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Gammon *et al.* (1997) USA 1993–95	Former smoker	2.0	1.4–2.9	Adjusted for age, sex, area, race, body-mass index, income and use of alcohol
	Current smoker	2.2	1.4–3.3	
	Cigarettes/day			
	< 16	1.5	1.0–2.4	
	16–20	2.2	1.4–3.4	
	21–30	3.1	1.9–5.1	
	> 30	2.1	1.3–3.3	p for trend < 0.05
	Duration (years)			
	< 20	1.4	0.9–2.2	
	20–31	1.7	1.0–2.8	
	32–42	2.9	1.8–4.4	
	> 42	2.4	1.5–3.7	p for trend < 0.05
	Pack–years			
	< 14	1.4	0.8–2.2	
	14–31	1.6	1.0–2.6	
	32–54	2.9	1.8–4.5	
	> 54	2.8	1.8–4.4	p for trend < 0.05
	Years since quitting			
	< 11	2.7	1.6–4.4	
	11–20	2.3	1.4–3.8	
	21–30	1.9	1.1–3.2	
	> 30	1.2	0.7–2.2	p for trend < 0.05
	Filter status			
	Filter only	2.0	1.4–2.9	
	Filter + no filter	1.7	1.0–3.0	
	No filter only	1.9	1.2–2.9	

Table 2.1.4.21 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Lagergren *et al.* (2000) Sweden 1995–97	Former smoker	1.9	1.2–2.9	Adjusted for age, sex, alcohol use, education, body-mass index, reflux symptoms, intake of fruit and vegetables, energy intake, physical activity, pipe smoking and snuff use
	Current smoker	1.6	0.9–2.7	
	Cigarettes/day			
	1–9	1.2	0.7–2.2	
	10–19	1.7	1.0–2.9	
	> 19	1.1	0.6–2.0	
	Duration (years)[†]			[†]Includes cigar and pipe smoking.
	1–20	1.8	1.1–3.1	
	21–35	1.5	0.9–2.6	
	> 35	2.0	1.2–3.3	
	Years since quitting			
	0–2	1.7	1.0–3.0	
	3–10	2.4	1.2–4.8	
	11–25	1.6	0.9–2.5	
	> 25	1.6	0.9–2.8	*p* for trend = 0.02
Wu *et al.* (2001) USA 1992–97	Former smoker	1.5	1.0–2.2	Adjusted for age, sex, race, birthplace and education
	Current smoker	2.8	1.8–4.3	
	Cigarettes/day			
	1–19	1.6	0.7–3.3	
	20–39	2.9	1.8–4.8	*p* for trend < 0.0001
	≥ 40	4.5	2.3–8.7	
	Duration (years)			
	≤ 20	1.4	0.9–2.2	
	21–40	2.1	1.4–3.1	
	≥ 41	2.2	1.3–3.5	*p* for trend = 0.0001

Table 2.1.4.21 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Wu *et al.* (2001) (contd)	Age at starting smoking (years)			
	≥ 21	1.9	1.2–3.0	
	17–20	1.8	1.2–2.7	
	≤ 16	1.8	1.2–2.8	*p* for trend = 0.003
	Years since quitting			
	1–5	2.2	1.2–3.9	
	6–10	1.1	0.5–2.3	
	11–19	1.7	1.1–2.9	
	≥ 20	1.3	0.8–2.1	*p* for trend = 0.01

CI, confidence interval

Table 2.1.4.22. Cohort studies on tobacco smoking and laryngeal cancer

Reference Country and years of study	Subjects	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Weir & Dunn (1970) USA 1954–62	Californian Study 68 153 men		11			Light smokers were used as the reference group as none of the cases were nonsmokers.
		Cigarettes/day				
		1–14		1.0		
		15–25		6.0		
		> 25		5.8		
Hirayama (1985); Akiba & Hirayama (1990) Japan 1965–81	Six-prefecture Study 265 118 adults (122 261 men and 142 857 women)	Current smoker	72	23.8	5.3–420	Data stratified by prefecture, occupation, attained age and observation period
		Cigarettes/day				
		1–4	1	13.7	0.5–346	
		5–14	23	17.0	3.6–304	
		15–24	35	25.7	5.5–458	
		25–34	9	76.9	14–1427	
		≥ 35	4	73.4	11–1444	
		Cigarettes/day		SMR†		†Standardized mortality ratio
		1–24		31		
		≥ 25		98.5		*p* for trend < 0.0001
Akiba (1994) Japan 1968–87	Life Span Study 61 505 atomic bomb survivors		46			
		Former smoker		> 100		
		Current smoker		> 100		
McLaughlin *et al.* (1995) USA 1954–80	US Veterans' Study 293 958 men		167			
		Former smoker		5.0	2.4–10.5	
		Ever-smoker		10.2	5.2–20.0	
		Current smoker		13.7	7.0–27.1	
Raitiola & Pukander (1997) Finland 1962–91	Data from files of Tampere University Hospital and Finnish Cancer Registry	Current smoker				Adjusted for age No description of collection of information on smoking status among reference population; significantly higher proportion of smokers in supra-glottic than in glottic cases ($p = 0.025$)
		Men	244	15.9	10.0–25.4	
		Women	14	12.4	3.9–39.5	

CI, confidence interval

Table 2.1.4.23. Case–control studies on tobacco smoking and laryngeal cancer: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility
Wynder & Stellman (1979) USA 1969–76	Men: 286 cases and 4835 controls; women, 64 cases and 4712 controls	Retrospective study conducted in six cities Cases histologically confirmed Controls with cancers not related to tobacco consumption, benign neoplasms and other non-neoplastic conditions
Burch *et al.* (1981) Canada 1977–79	Men: 184 cases and 184 controls; women: 20 cases and 20 controls	Population-based study Cases histologically confirmed, ascertained by two Ontario hospitals; response rate, 79% Neighbourhood controls individually matched (1:1) on sex, age (± 5 years) and area of residence; response rate, 78%
Graham *et al.* (1981) USA 1957–65	White men: 374 cases and 381 controls	Hospital-based study in a major cancer institution Cases histologically confirmed Controls without cancer or respiratory or digestive tract diseases, randomly selected by 5-year age groups
Herity *et al.* (1982) Ireland	Men only: 68 cases and 68 controls	Hospital-based study Controls with cancers and premalignant skin conditions considered not to be related to tobacco or alcohol consumption
Olsen *et al.* (1985) Denmark 1980–82	326 cases (276 men and 50 women) and 1134 controls	Population-based study Cases of cancer of the glottis (58%) and supraglottis (34%); aged < 75 years, 91% histologically confirmed; response rate, 96% Controls matched about 4:1 on sex and date of birth; response rate, 78%
Brownson (1987) USA 1984–85	White men: 63 cases and 200 controls	Hospital-based study Cases ascertained through the Missouri Cancer Registry, histologically confirmed Controls with colon cancer, matched about 3:1 by area and admission time period
De Stefani *et al.* (1987) Uruguay 1985–86	Men: 107 cases and 290 controls	Hospital-based study in the University Hospital in Montevideo Cases histologically confirmed, aged 30–89 years Controls with diseases not related to tobacco or alcohol consumption, admitted to the same hospital in the same time period
Tuyns *et al.* (1988) France, Italy, Spain and Switzerland 1973–80	Men: 696 cases and 3057 controls	Population-based study in six areas in four countries Cases of cancer of the endolarynx (61% supraglottic, 39% glottic and subglottic); response rate > 80% Controls drawn from the local population as a stratified sample by sex and 10-year age group; response rate, 56–75%

Table 2.1.4.23 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility
Falk *et al*. (1989) USA 1975–80	Whie men: 151 cases and 235 controls	Population-based study Cases aged 30–79 years, ascertained from 56 hospitals in six counties Controls frequency-matched by area of residence, 5-year age group and ethnicity
Franceschi *et al.* (1990) Italy 1986–89	Men: 162 cases and 1272 controls	Hospital-based study in two hospitals Cases histologically confirmed, aged ≤ 75 years Controls with acute conditions unrelated to tobacco or alcohol consumption from the same hospital, matched by area of residence and age (± 5 years)
Sankaranarayanan *et al*. (1990) India 1983–84	Men: 191 cases and 546 controls	Hospital-based study in two major hospitals Cases histologically confirmed Controls with diagnosis of respiratory, genitourinary and gastrointestinal infections without cancer
Ahrens *et al*. (1991) Germany 1986–87	Men: 85 cases and 100 controls	Hospital-based study in a hospital in Bremen Cases histologically confirmed (55 incident and 30 prevalent) Controls without cancer and with diseases not related to smoking, matched on age
Choi & Kahyo (1991) Republic of Korea 1986–89	Men: 94 cases and 282 controls; women: 6 cases and 18 controls	Hospital-based study in a Cancer Center Hospital in Seoul Cases histologically confirmed Controls without cancer and tobacco- or alcohol-related diseases, matched on sex, year of birth (± 5 years) and admission time period
Zatonski *et al.* (1991) Poland 1986–87	Men: 249 cases and 965 controls	Population-based study Cases identified in Lower Silesia, histologically confirmed, aged < 65 years; response rate, 88% Controls from the same region, aged 25–64 years; response rate, 94%
Freudenheim *et al.* (1992) USA 1975–85	Men: 250 cases and 250 controls	Population-based study in three counties in New York Cases identified from pathology records of the hospitals, Caucasians only; response rate, 30% Neighbourhood controls matched on sex, race and age; response rate, 48%
López-Abente *et al.* (1992) Spain 1982–85	Men: 50 cases and 103 controls	Hospital- and population-based study in Madrid Cases of cancer of the glottis (30%) and supraglottis (54%); aged ≤ 80 years; response rate, 51% Controls matched on sex and age (± 5 years): 45 hospital controls with diseases considered not to be related to tobacco or alcohol consumption, 58 population controls from the general population selected from the electoral roll; response rate, 49%

Table 2.1.4.23 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility
Maier *et al.* (1992b) Germany 1988–89	Men: 164 cases and 656 controls	Hospital-based study in Heidelberg Cases of cancer of the glottis and supraglottis, histologically confirmed; mean age, 58.1 years Controls with no known tumorous diseases, selected randomly from outpatient clinics, matched 4:1 by age and residential area
Muscat & Wynder (1992) USA 1985–90	White men: 194 cases and 184 controls	Hospital-based study in eight hospitals in four states Cases of cancer of the glottis (48%) and supraglottis (47%), histologically confirmed Controls with conditions unrelated to tobacco-induced diseases, individually matched on hospital, age (± 5 years) and year of interview
Zheng *et al.* (1992c) China 1988–90	Men: 177 cases and 269 controls; women: 24 cases and 145 controls	Population-based study among residents of urban Shanghai Cases aged 20–75 years; response rate, 76% Controls randomly selected and frequency-matched by sex and age (5-year groups); response rate, 88%
Hedberg *et al.* (1994) USA 1983–87	Men: 185 cases and 356 controls; women: 50 cases and 191 controls	Population-based study Cases had response rate of 81%. Controls randomly selected from the population of same area by random-digit dialling and frequency-matched on sex and age (5-year groups); response rate, 75%
Sokic *et al.* (1994) Yugoslavia 1991–92	Men: 93 cases and 93 controls; women: 7 cases and 7 controls	Hospital-based study in University Clinical Center in Belgrade Cases histologically confirmed Controls with minor injuries, matched on sex, age (5-year groups) and residence
Tavani *et al.* (1994) Italy 1986–92	Men: 350 cases and 1373 controls; women: 17 cases and 558 controls	Hospital-based study in the greater Milan area Cases histologically confirmed, aged < 80 years Controls without cancer and with diseases or conditions unrelated to smoking, alcohol consumption or long-term dietary modifications, matched by hospital
Dosemeci *et al.* (1997) Turkey 1979–84	Men: 832 cases and 829 controls	Hospital-based study in an oncology treatment centre in Istanbul Cases histologically confirmed Controls with selected cancers not reported to be related to smoking or alcohol drinking (97%) or without cancer (3%)

Table 2.1.4.23 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility
Maier & Tisch (1997) Germany 1988–89	Men: 164 cases and 656 controls	Hospital-based study in two clinical departments of the University of Heidelberg Cases histologically confirmed Controls without cancer, randomly selected from outpatients, individually matched (4:1) on age and residential area
Rao *et al.* (1999) India 1980–84	Men: 427 cases and 635 controls	Hospital-based study in Mumbai Cases histologically confirmed Controls free from cancer, infectious diseases or benign tumours, admitted at the same hospital during the same period
Schlecht *et al.* (1999) Brazil 1986–89	Men and women: 194 cases and 1578 controls	Hospital-based study in three metropolitan areas in southern Brazil Cases histologically confirmed Controls without cancer or mental disorders, selected from the same or nearby hospitals, matched on sex, age (± 5 years) and admission period

Table 2.1.4.24. Case–control studies on tobacco smoking and laryngeal cancer

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Burch *et al.* (1981)	Cigarettes/day			Adjusted for lifetime alcohol consumption
Canada	1–14	3.0	1.4–6.3	
1977–79	15–24	3.4	1.7–6.8	
	≥ 25	4.5	2.2–9.2	
Graham *et al.* (1981)	Cigarettes/day			Adjusted for alcohol consumption. Possible selection bias in controls
USA	1–10	2.1	$p < 0.05$	
1957–65	11–20	4.8	$p < 0.005$	
	21–39	8.8	$p < 0.005$	
	≥ 40	8.5	$p < 0.005$	p for trend < 0.005
Herity *et al.* (1982)	Tobacco consumption			Analysis restricted to abstainers from alcohol and light drinkers. Consumption of tobacco in pipes and cigars converted into the equivalent of cigarettes/day (1 oz tobacco = 25 cigarettes, 1 cigar = 7 cigarettes, 1 cheroot = 2.5 cigarettes). Smokers whose consumption was at or below the median are referred to as light smokers; those above the median consumption as heavy smokers. Possible selection bias in controls
Ireland	None or light	1.0	–	
	Heavy	4.9	2.6–9.0	
Olsen *et al.* (1985)	Tobacco/day (g)			Adjusted for age, sex and alcohol consumption. One cigarette equals 1 g; one cigar, 3 g, and a pipeful, 2.5 g of tobacco. Effects of smoking cigarettes, cigars and pipe could not be separated. The association was similar for the glottis and supraglottis.
Denmark	0–10	1.0		
1980–82	11–20	1.7		
	≥ 21	2.3		
Brownson (1987)	Cigarettes/day			Adjusted for age and alcohol consumption. Former smokers were classified as 1–19 cigarettes/day, cigar and pipe smokers as 20–40 cigarettes/day. Possible selection bias in controls. Effects of cigarette, cigar and pipe smoking could not be separated.
USA	1–19	2.6	1.1–6.1	
1984–85	20–40	3.7	1.5–9.2	
	> 40	7.0	1.3–37.9	p for trend < 0.01

Table 2.1.4.24 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
De Stefani *et al.* (1987) Uruguay 1985–86	Cigarettes/day			Adjusted for age and alcohol consumption. Reference group might not have been appropriate. Controls included patients with diseases possibly related to smoking.
	0–15	1.0		
	≥ 16	10.9		
Tuyns *et al.* (1988) France, Italy, Spain and Switzerland 1973–80	Ever-smoker	9.9	6.4–15.4	Adjusted for alcohol intake, age, place and their interaction. The association was stronger (2–3-fold) for the supraglottis than for the glottis.
	Cigarettes/day			
	1–7	2.4	1.3–4.3	
	8–15	6.7	4.2–10.7	
	16–25	13.7	8.7–21.6	
	≥ 26	16.4	10.1–26.6	
Falk *et al.* (1989) USA 1975–80	Cigarettes/day			Adjusted for age, residence, fruit and vegetable consumption, high-risk occupations and usual alcohol intake
	1–10	5.4	1.1–27.1	
	11–20	7.0	2.8–18.0	
	21–30	6.0	2.0–17.9	
	31–40	20.8	6.3–68.1	
	> 40	19.2	5.0–73.4	p for trend < 0.002
	Duration (years)			
	For < 20 cigarettes/day			
	< 35	3.4	0.9–13.2	
	35–44	7.4	2.4–23.0	
	≥ 45	9.6	3.2–29.1	p for trend < 0.001
	For > 20 cigarettes/day			
	< 35	11.1	3.1–39.2	
	35–44	11.3	3.9–33.3	
	≥ 45	11.3	3.6–35.0	p for trend < 0.001

Table 2.1.4.24 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Franceschi *et al.* (1990) Italy 1986–89	Cigarettes/day			Adjusted for age, area of residence, years of education, occupation and alcohol intake
	≤ 14	2.2	1.0–5.2	
	15–24	4.8	2.3–10.4	
	≥ 25	7.1	3.3–15.4	*p* for trend < 0.01
	Duration (years)			
	1–29	1.9	0.8–4.4	
	30–39	5.2	2.4–11.5	
	≥ 40	7.2	3.3–15.6	*p* for trend < 0.01
	Age at starting smoking (years)			
	≥ 25	2.4	1.0–5.7	
	17–24	5.1	2.4–10.9	
	< 17	6.5	3.3–14.3	*p* for trend < 0.01
Sankaranarayanan *et al.* (1990) India 1983–84	Current smoker	1.4	0.8–2.4	Adjusted for age and religion
	Duration (years)[†]			[†]Further adjusted for duration of alcohol and bidi consumption and daily consumption of cigarettes and bidis
	≤ 20	1.6	0.3–7.7	
	> 20	5.2	2.2–12.0	*p* for trend < 0.005
Ahrens *et al.* (1991) Germany 1986–87	Current smoker	3.8	0.96–14.7	Adjusted for age; possible selection bias; only 3 cases and 9 controls were nonsmokers, 20 cases and 18 controls smoked both cigarettes and pipe/cigars.
	Pack–years[†]			[†]Further adjusted for alcohol intake
	6–29	2.6	1.0–6.6	
	≥ 30	3.0	1.1–7.9	

Table 2.1.4.24 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Choi & Kahyo (1991) Republic of Korea 1986–89	Former smoker	2.2	0.6–8.4	Selection bias could not be excluded.
	Current smoker	5.4	2.1–14.3	
	Cigarettes/day			
	1–20	3.7	1.3–10.0	
	21–40	10.6	3.8–29.9	
	≥ 41	27.3	5.3–141.9	
	Duration (years)			
	1–19	3.8	1.3–23.6	
	20–39	4.8	2.0–15.7	
	≥ 40	5.6	1.8–12.9	
	Age at starting smoking (years)			
	≥ 25	6.6	2.1–21.1	
	18–24	5.2	2.0–13.9	
	≤ 17	3.8	1.2–12.1	
Zatonski *et al.* (1991) Poland 1986–87	Cigarettes/day			Adjusted for age, residence and education
	0–5	1.0	–	
	6–10	8.4	1.5–46.0	
	11–15	18.1	3.9–83.2	
	16–20	29.9	7.0–128.0	
	21–30	33.7	7.6–150.0	
	> 30	59.7	13.0–274.0	
	Age at starting smoking (years)			
	> 22	0.6	0.3–1.2	
	16–22	1.0	–	
	< 16	1.3	0.7–2.23	

Table 2.1.4.24 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Freudenheim *et al.* (1992) USA 1975–85	Pack–years			Adjusted for alcohol consumption and education. Response rates too low; possibility of selection bias
	1–12	2.0	0.7–5.9	
	13–29	2.0	0.8–5.3	
	30–45	5.1	1.9–13.6	
	≥ 46	12.6	5.0–31.5	*p* for trend < 0.001
López-Abente *et al.* (1992) Spain 1982–85	Cigarettes/day			Adjusted for age, alcohol intake and occupation. Low response rates, small sample size; reference groups may have been inappropriate. The association was stronger for the supraglottis than for the glottis.
	0–9	1.0	–	
	10–19	1.9	0.6–6.0	
	20–29	2.2	0.6–8.0	
	≥ 30	4.3	1.2–15.4	*p* for trend = 0.02
	Duration (years)			
	0–20	1.0	–	
	21–40	3.6	0.7–19.6	
	≥ 41	13.7	2.3–82.6	*p* for trend = 0.001
	Pack–years			
	≤ 19	1.0	–	
	> 19–41	3.3	0.98–10.8	
	> 41	4.5	1.4–14.9	*p* for trend = 0.02
Maier *et al.* (1992b) Germany 1988–89	Pack–years			Adjusted for alcohol consumption. Smokers in case and control groups included 3.5% and 9.5% of cigar or pipe smokers, respectively. The association was much stronger (10-fold) for the supraglottis than for the glottis.
	5–50	5.6	2.9–10.9	
	> 50	9.1	4.5–18.7	
Muscat & Wynder (1992) USA 1985–90	Former smoker	4.8	1.7–13.0	Adjusted for age, education, alcohol and Quetelet index. The association was stronger (3–4-fold) for the supraglottis than for the glottis.
	Current smoker	13.8	2.3–27.1	
	Cigarettes/day			
	1–20	10.3	3.6–29.4	
	21–40	38.5	12.1–122	

Table 2.1.4.24 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Zheng *et al.* (1992c)	Men			Adjusted for age and education
China	Ever-smoker	8.7	3.8–19.6	
1988–90	Cigarettes/day			
	< 10	1.6	0.5–4.9	
	10–19	7.1	3.1–16.6	
	20	12.4	4.6–33.2	
	> 20	25.1	9.9–63.2	*p* for trend < 0.01
	Pack–years			
	< 10	1.4	0.4–4.5	
	10–19	2.9	1.1–7.9	
	20–29	3.1	1.1–8.6	
	30–39	15.4	6.0–39.6	
	≥ 40	25.1	10.3–61.2	*p* for trend < 0.01
	Duration (years)			
	< 20	1.4	0.4–4.6	
	20–29	4.1	1.6–11.1	
	30–39	12.0	4.8–30.1	
	≥ 40	13.2	5.6–31.2	*p* for trend < 0.01
	Women			
	Pack–years			
	1–9	9.4	2.4–37.2	
	≥ 10	20.2	5.3–76.9	

Table 2.1.4.24 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Hedberg *et al.* (1994) USA 1983–87	Never-smoker + quit ≥ 15 years	1.0	–	Adjusted for age, sex, alcohol consumption and score in alcoholism screening test
	Former smoker (< 15 years)	2.5	1.4–4.3	
	Cigarettes/day			
	< 20	6.3	3.1–11.8	
	20–39	10.6	6.5–18.7	
	≥ 40	23.1	9.4–52.6	
Sokic *et al.* (1994) Yugoslavia 1991–92	≥ 10 years	5.5	0.6–51.6	Multivariate regression model with 25 variables including coffee, alcohol consumption, dietary factors, working conditions, exposure to secondhand smoke and health status; relatively small sample size; referent group not specified
	≥ 10 cigarettes/day	18.2	2.0–169.8	
Tavani *et al.* (1994) Italy 1986–92	Men			Adjusted for centre, age, education, alcohol intake and β-carotene index. Moderate smokers included former smokers, pipe and/or cigar smokers and current smokers of < 15 cigarettes/day. Estimates in women based on a small number of cases *p* for trend in men < 0.001
	Moderate smoker	3.3	1.9–5.5	
	Heavy smoker	8.8	5.2–14.8	
	Women			
	Current smoker	23.9	5.2–110.9	

Table 2.1.4.24 (contd)

Reference Country and years of study	Smoking categories	Relative risk	95% CI	Comments
Dosemeci *et al.* (1997) Turkey 1979–84	Ever-smoker	3.5	2.6–4.4	Adjusted for age and alcohol
	Cigarettes/day			
	1–10	1.6	0.9–2.6	
	11–20	3.5	2.6–4.8	
	≥ 21	6.6	4.2–10.3	p for trend < 0.001
	Pack–years			
	1–10	1.9	1.3–3.0	
	11–20	4.4	2.9–6.7	
	≥ 21	6.0	3.8–9.5	p for trend < 0.001
	Duration (years)			
	1–10	1.1	0.6–1.9	
	11–20	4.8	3.1–7.4	
	≥ 21	4.1	2.8–6.0	p for trend < 0.001
Maier & Tisch (1997) Germany 1988–89	Tobacco–years			Adjusted for alcohol. Tobacco–year defined as 20 cigarettes or 4 cigars or 5 pipes/day for 1 year. Reference group included light smokers; effects of cigarettes, cigars and pipes could not be separated. The categories of tobacco–years are not continuous and appear surprisingly high.
	< 5	1.0		
	5–19	4.0	1.7–9.2	
	50–74 [sic]	6.3	3.0–13.3	
	75–99	7.8	3.6–16.7	
	≥ 100	9.5	4.6–19.6	
Rao *et al.* (1999) India 1980–84	Current smoker	1.5	0.9–2.4	Adjusted for age and area of residence. Bidi smoking was more common than cigarette smoking in the study area.
Schlecht *et al.* (1999) Brazil 1986–89	Current smoker	11.7	4.4–31.5	Adjusted for age, sex, study location, admission period, alcohol consumption, race, beverage temperature, religion, wood stove use and consumption of spicy food. One pack = 20 manufactured cigarettes = 4 hand-rolled, black tobacco cigarettes = 4 cigars = 5 pipefuls with regular pipe tobacco. Possible selection bias in controls
	Pack–years			
	1–20	8.2	3.0–22.6	
	21–40	9.4	3.3–26.7	
	> 40	16.3	5.3–49.8	

CI, confidence interval

Table 2.1.4.25. Case–control studies on tobacco smoking and laryngeal cancer: smoking cessation

Reference Country and years of study	Subjects	No. of years since quitting	Relative risk	95% CI	Comments
Tuyns *et al.* (1988) France, Italy, Spain and Switzerland 1973–80	Men with cancer of the endolarynx	Current smoker	1.0		Adjusted for alcohol intake, daily cigarette consumption, use of filter, type of tobacco and degree of inhalation
		1–4	1.5	1.2–2.0	
		5–9	0.5	0.3–0.8	
		≥ 10	0.3	0.2–0.4	
Falk *et al.* (1989) USA 1975–80	Men	*3–9 years' cessation*			Adjusted for age, area of residence, fruit and vegetable consumption, high-risk occupations and usual alcohol intake
		Cigarettes/day			
		1–10	3.0	0.2–40.2	
		11–20	3.6	0.8–15.8	
		21–30	4.0	0.6–29.5	
		31–40	7.2	1.0–54.3	
		> 40	10.9	1.8–68.5	*p* for trend < 0.002
		≥ 10 years' cessation			
		Cigarettes/day			
		1–10	2.8	0.7–10.7	
		11–20	1.2	0.4–4.0	
		21–30	1.0	0.2–6.4	
		31–40	3.1	0.4–22.4	
		> 40	3.5	0.6–19.1	*p* for trend = 0.088
Franceschi *et al.* (1990) Italy 1986–89	Men	< 10	4.6	2.0–10.4	Adjusted for age, area of residence, years of education, occupation and alcohol intake
		≥ 10	1.2	0.4–3.3	
		Nonsmoker	1.0	–	

Table 2.1.4.25 (contd)

Reference Country and years of study	Subjects	No. of years since quitting	Relative risk	95% CI	Comments
Ahrens *et al.* (1991)	Men	Current smoker	3.8	0.96–14.7	Adjusted for age; only 3 cases and 9
Germany		1–5	2.4	0.5–12.9	controls were nonsmokers.
1986–87		6–15	1.4	0.3–7.4	
		≥ 16	0.9	0.2–4.3	*p* for trend < 0.001
Choi & Kahyo (1991)	Men	Current smoker	1.0	–	Selection bias could not be excluded.
Republic of Korea		1–4	0.7	0.2–2.2	
1986–89		5–9	0.4	0.1–3.0	
		≥ 10	0.2	0.03–1.02	
Zatonski *et al.* (1991)	Men	Current smoker[†]	1.0	–	Adjusted for age, area of residence and
Poland		5–10	0.8	0.3–1.8	education
1986–87		> 10	0.3	0.1–0.6	[†]including former smokers who had quit
		Nonsmoking period of			within the preceding 4 years
		> 6 months			
		No	1.0	–	
		Yes	0.2	0.1–0.5	
López-Abente *et al.*	Men	Current smoker	1.0	–	Adjusted for age, packs of cigarettes
(1992)		1	1.2	0.3–5.5	smoked over lifetime, alcohol consumption
Spain		2–5	0.7	0.2–2.9	and occupation; low response rate, small
1982–85		6–15	0.8	0.2–3.0	sample size
		> 15	0.5	0.1–3.2	*p* for trend = 0.43
Zheng *et al.* (1992c)	Men	< 2 or current smoker	1.0	–	Adjusted for age and education
China		2–4	1.8	0.6–4.9	
1988–90		5–9	0.6	0.2–1.5	
		≥ 10	0.6	0.3–1.2	
Schlecht *et al.* (1999)	Men	Current smoker	10.2	3.7–27.9	Conditional logistic regression (matching
Brazil		≤ 5	11.8	3.7–38.0	variables: age, sex, location and admission
1986–89		6–10	5.0	1.3–19.1	period) adjusted for alcohol and tobacco
		11–15	6.6	1.0–42.1	consumption
		> 15	1.3	0.3–6.0	

CI, confidence interval

Table 2.1.4.26. Case–control studies on tobacco smoking and laryngeal cancer: type of tobacco and/or cigarette

Reference Country and years of study	Subjects	Type of tobacco	Relative risk	95% CI	Comments
Wynder & Stellman (1979) USA 1969–76		Untipped vs filter			Adjusted for duration, intensity and alcohol consumption
	Men		1.5	1.1–2.1	
	Women		4.0	2.0–7.7	
De Stefani *et al.* (1987) Uruguay 1985–86	Men	Dark tobacco			Adjusted for age; controls included patients with diseases possibly related to smoking.
		All smokers	35.4	20.8–60.3	
		Cigarettes/day			
		1–10	1.0	–	
		11–20	24.6	9.0–67.4	
		≥ 21	59.2	25.5–137.3	
		Age at starting smoking (years)			
		> 15	12.3	4.6–32.4	
		≤ 15	100.1	49.6–202.4	
		Light tobacco			
		All smokers	14.7	7.8–27.6	
		Cigarettes/day			
		1–10	1.0	–	
		11–20	14.5	5.3–39.4	
		≥ 21	24.7	7.8–78.4	
		Age at starting smoking (years)			
		> 15	5.0	1.5–16.2	
		≤ 15	51.4	22.4–117.9	

Table 2.1.4.26 (contd)

Reference Country and years of study	Subjects	Type of tobacco	Relative risk	95% CI	Comments
Tuyns *et al.* (1988) France, Italy, Spain and Switzerland 1973–80	Men	Use of filter			Adjusted for alcohol intake, daily cigarette consumption and variables analysed
		Only plain	1.0	–	
		Plain > filter	0.9	0.7–1.2	
		Plain < filter	1.03	0.8–1.4	
		Only filter	0.5	0.3–0.8	
		Type of tobacco			
		Only blond	1.0	–	
		Blond > black	1.6	0.9–2.7	
		Blond < black	1.7	1.0–2.7	
		Inhaler	1.0	–	
		Non-inhaler	0.7	0.5–0.9	
Falk *et al.* (1989) USA 1975–80	Men	Hand-rolled	20.1	5.4–74.6	Adjusted for age, residence, fruit and vegetable consumption, high-risk occupation and usual alcohol intake
		Filter + untipped	13.9	5.1–38.1	
		Untipped only	9.0	3.2–25.1	
		Filter only	5.9	2.4–14.4	
López-Abente *et al.* (1992) Spain 1982–85	Men	Type of tobacco			Adjusted for age, packs of cigarettes smoked over lifetime, alcohol consumption and occupation, low response rate, small sample size
		Blond	1.0	–	
		Mixed	2.4	0.4–14.9	
		Black	2.6	0.4–15.2	
Schlecht *et al.* (1999) Brazil 1986–89	Men	Never-smoker	1.0	–	Conditional logistic regression (matching variables: age, sex, study location and admission period) adjusted for cumulative alcohol and tobacco consumption, race, beverage temperature, religion, wood stove use and consumption of spicy food
		Filter-tipped cigarettes	8.4	3.1–22.8	
		Untipped cigarettes	12.2	4.1–35.9	
		Black tobacco (pack–years)			
		1–20	7.3	2.4–22.4	
		21–40	8.9	2.9–27.2	
		> 40	8.5	3.0–23.9	

CI, confidence interval

Table 2.1.4.27. Cohort studies on tobacco smoking and cancers of the upper aerodigestive tract

Reference Country and years of study	Subjects	Cancer site ICD code	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Hammond & Horn (1958) USA 1952–55	American Cancer Society Study 187 783 men	Lip, tongue, oral cavity, pharynx, larynx, oesophagus			Mortality ratio		
			Current smoker	84	7.0		
			Cigarettes/day				
			1–9	7	7.8		
			10–20	21	7.0		
			≥ 21	21	10.5		
Doll *et al.* (1980) UK 1951–73	British Doctors' Study 6194 women	Upper respiratory sites		4	Mortality rate		Annual mortality rate per 100 000 women
			Nonsmoker		2		
			Former smoker		3		
			Cigarettes/day				
			1–14		0		
			15–24		8		
			≥ 25		13		p for trend < 0.05
Hammond & Seidman (1980) USA 1967–71	Cancer Prevention Study I 358 422 men and 483 519 women	Oral cavity, pharynx, larynx	Regular smoker		Mortality ratio		
			Men		6.5		
			Women		3.3		
Kono *et al.* (1987) Japan 1965–83	Japanese Physicians' Study 5477 men	Oral cavity, nasal cavity, pharynx, larynx ICD-8: 140–150, 161	Cigarettes/day	18			Adjusted for age and alcohol drinking
			1–19		1.2	0.3–4.5	
			≥ 20		3.0	0.9–10.4	

Table 2.1.4.27 (contd)

Reference Country and years of study	Subjects	Cancer site ICD code	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Akiba & Hirayama (1990) Japan 1966–81	Six-prefecture Study 122 261 men and 142 857 women	Oral cavity ICD-7: 140–149	Men				Adjusted for age, prefecture of residence, occupation and observation period
			Current smoker	64	2.5	1.3–5.7	
			Cigarettes/day				
			1–14	25	2.2	1.0–5.2	
			15–24	32	2.7	1.3–6.3	
			25–34	5	4.2	1.3–12.8	
			≥ 35	2	4.0	0.6–16.2	*p* for trend = 0.002
			Women				
			Current smoker	5	1.3	0.5–3.2	
Tomita *et al.* (1991) Japan 1975–85	37 646 men	Lip, oral cavity, pharynx		888	Mortality rate		Annual mortality rates per 10 000 persons Average 6.7 years of follow-up
			Nonsmoker		0.19		
			Former smoker		0.38		
			Cigarettes/day				
			15–24		0.41		
			25–34		1.34		
			≥ 35		0.59		
Kuller *et al.* (1991) USA 1972–82	MRFIT Study 361 662 men	Mouth and larynx ICD-9: 140–149; 161			Mortality rate		Annual mortality rates per 10 000 persons Reference group includes former smokers at first screen. Relative risk adjusted for age, diastolic blood pressure, serum cholesterol level and race (black/non-black)
			Nonsmoker	35	1.5		
			Cigarettes/day				
			1–15	9	3.4		
			16–25	30	7.0		
			26–35	24	9.5		
			36–45	39	17.3		
			≥ 46	16	21.1		
					Relative risk		
			Current smoker		6.6	$p < 0.0001$	
Akiba (1994) Japan 1968–87	Life Span Study 61 505 survivors	Oral cavity, pharynx ICD-9: 140–49		69			[†][Upper limit not obtained]
			Former smoker		0.4	0.1–1.2	
			Current smoker		1.1	0.6–[†]	

Table 2.1.4.27 (contd)

Reference Country and years of study	Subjects	Cancer site ICD code	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Doll *et al.* (1994) UK 1957–91	British Doctors' Study 34 439 men	Upper respiratory sites		98	Mortality rate		Annual mortality rate per 100 000 men
			Nonsmoker		1		
			Former smoker		3		
			Current smoker		24		
			Cigarettes/day				
			1–14		12		
			15–24		18		
			≥ 25		48		p for trend < 0.05
Chyou *et al.* (1995) USA (Hawaii) 1965–68	American Men of Japanese Ancestry Study 7995 men	Upper aero-digestive tract ICD-8: 140–149; 150; 161	Former smoker	21	1.7	0.8–3.5	Adjusted for age and alcohol intake
			Current smoker	59	3.2	1.7–5.9	
			Cigarettes/day				
			1–20	13	2.2	0.99–4.8	
			21–29	31	2.4	1.2–4.7	
			≥ 30	35	3.0	1.5–5.8	p for trend = 0.002
			Duration (years)				
			1–24	18	2.1	0.97–4.3	
			25–34	35	2.7	1.4–5.3	
			≥ 35	25	3.0	1.5–5.9	p for trend = 0.0006
Murata *et al.* (1996) Japan 1984–93	Chiba Center Association Study 17 200 male participants	Oral cavity, pharynx, oesophagus, larynx ICD-9: 140–150; 161	Cigarettes/day				
			1–10		1.3		
			11–20		1.8		
			> 21		3.3	$p < 0.05$	p for trend < 0.05
Yuan *et al.* (1996) China 1986–1993	Shanghai Men's Study 18 244 men	Head and neck ICD-9: 140–149; 161	Ever-smoker	43	5.2	$p < 0.05$	Adjusted for age and alcohol consumption
			Current smoker				
			Cigarettes/day				
			< 20	32	3.8	$p < 0.05$	
			≥ 20	53	6.7	$p < 0.05$	

Table 2.1.4.27 (contd)

Reference Country and years of study	Subjects	Cancer site ICD code	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Engeland *et al.* (1996) Norway 1966–93	Norwegian Cohort Study 26 132 men and women	Upper aero-digestive tract ICD-7: 141; 143–148; 150; 161	Former smoker	15	0.5	0.3–1.1	Analysis for men only because of the small number of cases in women
			Current smoker				
			Cigarettes/day				
			1–4	12	1.2	0.6–2.7	
			5–9	9	1.1	0.5–2.7	
			10–14	16	1.8	0.9–3.8	
			≥ 15	16	5.4	2.5–12.0	
Nordlund *et al.* (1997) Sweden 1964–89	Swedish Census Study 26 000 women	Upper aero-digestive tract ICD-7: 141; 143-148; 150; 161		94			Adjusted for age and place of residence
			Former smoker		0.9	0.2–3.8	
			Current smoker		2.1	1.3–3.6	
			Cigarettes/day				
			1–7		1.6	0.8–3.3	
			8–15		3.2	1.6–6.6	
			≥ 16		1.9	0.5–7.9	
			Age at starting smoking (years)				Further adjusted for amount smoked daily
			> 23		1.0	–	
			20–23		0.4	0.1–2.0	
			< 19		1.0	0.3–2.8	p for trend = 0.777

Table 2.1.4.27 (contd)

Reference Country and years of study	Subjects	Cancer site ICD code	Smoking categories	Number of cases	Relative risk	95% CI	Comments
Kjaerheim *et al.* (1998) Norway 1968–92	10 960 men	Upper aero- digestive tract ICD-7: 141; 143; 144; 145, 147, 148, 150, 161	Never/occasional smoker	5	1.0	 0.6–4.8	Adjusted for age and alcohol consumption
			Former smoker	11	1.7		All categories include smokers of cigarettes or pipes.
			Current smoker (g/day)				
			< 15	34	2.6	1.0–6.8	*p* for trend < 0.002
			≥ 15	15	4.7	1.7–13.2	
			Never/occasional smoker	4	1.0	–	Further adjusted for diet (consumption of oranges and bread)
			Former smoker	11	2.0	0.6–6.4	
			Current smoker (g/day)				
			< 15	30	2.7	1.0–7.7	
			≥ 15	15	4.4	1.4–13.5	*p* for trend = 0.005 Similar results were obtained for cigarettes and pipes analysed separately.
Liaw & Chen (1998) China, Province of Taiwan 1982–94	Taiwanese Study 11 096 men and 3301 women	Lip, oral cavity and pharynx	Current smoker	13 men 0 women	4.2	0.5–32.9	ICD-9 was used, but no codes were reported.
			Cigarettes/day				Adjusted for age and alcohol consumption
			≤ 10		2.3	0.2–25.5	
			11–20		4.7	0.6–38.8	
			> 20		7.5	0.7–86.7	*p* for trend = 0.05
			Duration (years)				
			21–30		6.0	0.6–55.2	
			> 30		4.5	0.5–38.4	*p* for trend = 0.08
			Age at starting smoking (years)				
			≤ 20		5.7	0.7–46.1	
			> 24		4.5	0.5–43.5	*p* for trend = 0.11
			Pack–years				
			≤ 20		1.9	0.2–21.2	
			20–40		3.9	0.4–34.4	
			> 41		11.6	1.2–109.1	*p* for trend = 0.01

CI, confidence interval

Table 2.1.4.28. Case–control studies on tobacco smoking and cancers of the upper aerodigestive tract: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Blot *et al.* (1988) USA 1984–85	Men: 762 cases and 837 controls; women: 352 cases and 431 controls	Population-based study in four regions Incident cases of pathologically confirmed oral and pharyngeal cancer identified through local cancer registries; aged 18–79 years; 75% of all incident cases Controls selected by random-digit dialling (aged 18–64 years) and from Health Care Financing Administration rosters (aged 65–79 years), frequency-matched by age, sex and race
Ferraroni *et al.* (1989) Italy 1983–88	Men: 43 cases and 1334 controls; women: 7 cases and 710 controls	Hospital-based study in four hospitals in Milan Cases confirmed histologically, aged ≤ 75 years Controls with traumatic, non-traumatic orthopaedic and acute surgical conditions and ear, nose, throat, skin and dental disorders included; malignant tumours, digestive tract disorders and coffee-, alcohol- or tobacco-related conditions excluded; median age, 56 years
Merletti *et al.* (1989) Italy 1982–84	Men: 86 cases and 385 controls; women: 36 cases and 221 controls	Population-based study Cases histologically confirmed as squamous invasive carcinoma Controls selected from random samples of files of residents of Turin stratified by sex and age
Talamini *et al.* (1990) Italy 1986–89	Men: 291 cases and 1272 controls; women: 45 cases and 380 controls	Hospital-based study in two areas of northern Italy; study restricted to abstainers from alcohol Cases histologically confirmed as cancer of oral cavity (183) or pharynx (153) Controls: patients from the same hospitals admitted for acute illnesses, without malignant tumours or conditions related to tobacco or alcohol consumption
Barra *et al.* (1991) Italy 1985–90	Men: 236 cases, 577 cancer controls and 1122 non-cancer controls; women: 36 cases, 446 cancer controls and 762 non-cancer controls	Hospital-based study in the Pordenone province Cases histologically confirmed Cancer controls with cancers not related to tobacco or alcohol consumption: colorectal, renal cell, prostate, thyroid, and haematological. Non-cancer controls admitted for acute illnesses, without malignant tumours or conditions related to tobacco or alcohol consumption

Table 2.1.4.28 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
La Vecchia *et al.* (1991) Italy 1987–89	Men: 89 cases and 875 controls; women: 16 cases and 294 controls	Hospital-based study in five hospitals in Milan Incident cases of histologically confirmed oral (35) or oropharyngeal (70) cancer, aged < 75 years Controls admitted for acute, non-neoplastic or digestive diseases unrelated to alcohol or tobacco consumption; aged 21–74 years
De Stefani *et al.* (1992) Uruguay 1988–90	Men: 109 cases and 273 controls	Hospital-based study in a cancer institute Cases of cancer of the mouth and pharynx Controls with diseases unrelated to tobacco or alcohol use, admitted to the same hospital during the same time period
Franceschi *et al.* (1992) Italy 1986–90	Men: 104 cases and 726 controls	Hospital-based study in the Pordenone province and the greater Milan area (Lombardy region) Cases histologically confirmed Non-cancer controls admitted to the same hospitals for acute illnesses unrelated to tobacco or alcohol consumption
Marshall *et al.* (1992) USA 1975–83	Men: 201 cases and 201 controls; women: 89 cases and 89 controls	Population-based study Cases from 20 major hospitals in three New York counties, histologically confirmed (90% squamous-cell carcinoma) Controls selected by sampling dwellings, individually matched on neighbourhood, age and sex
Zheng *et al.* (1992a) China 1988–90	Men: 115 cases and 269 controls; women: 89 cases and 145 controls	Population-based study in the urban Shanghai area, linked to the Shanghai Cancer Registry Controls randomly selected from the Shanghai Resident Registry
Day *et al.* (1993) USA 1984–85	Men: 729 cases and 785 controls; women: 336 cases and 397 controls	Population-based study in four regions Incident cases of histologically confirmed oral and pharyngeal cancer identified through local cancer registries Controls selected by random-digit dialling (aged 18–64 years) and Health Care Administration rosters (aged 65–79 years), frequency-matched by age, sex and race

Table 2.1.4.28 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Kune *et al.* (1993) Germany 1982	Men: 41 cases and 398 controls	Population-based study Incident cases of histologically confirmed squamous-cell oral and pharyngeal cancer at a general hospital in Heidelberg; mean age, 64 years Community controls from Melbourne Colorectal Cancer Study; mean age, 65 years
Mashberg *et al.* (1993) USA 1972–83	Men: 359 cases and 2280 controls	Hospital-based study in a veterans' medical centre in New Jersey Cases histologically confirmed as invasive squamous-cell carcinoma or carcinoma *in situ* Controls without evidence of cancer or dysplasia of the pharynx, larynx, lung or oesophagus
Negri *et al.* (1993) Italy 1984–92	Men: 372 cases and 1575 controls; women: 67 cases and 531 controls	Hospital-based study Cases histologically confirmed Controls: patients admitted to the same network of hospitals for acute, non-neoplastic, non-digestive conditions
Spitz *et al.* (1993) USA 1987–91	Men: 70 cases and 70 controls; women: 38 cases and 38 controls	Population-based study in Texas Cases histologically confirmed as squamous-cell carcinoma Controls selected from blood and platelet donors, matched on age, sex and ethnicity
De Stefani *et al.* (1994) Uruguay 1988–92	Men: 246 cases and 253 controls	Hospital-based study in a cancer institute Incident cases of histologically confirmed squamous-cell carcinoma of the oral cavity and pharynx, aged 40–89 years; participation rate, 100% Controls free of benign oral tumours, non-neoplastic conditions of the mouth and pharynx, digestive diseases, or diseases related to tobacco and alcohol consumption; frequency-matched by age; participation rate, 100%
Kabat *et al.* (1994) USA 1977–90	Men: 1097 cases and 2075 controls; women: 463 cases and 873 controls	Hospital-based study in 28 hospitals in eight cities Cases histologically confirmed Controls: patients with diseases unrelated to tobacco or alcohol consumption, and without history of tobacco-related cancer, matched on age, sex, race, hospital and date of interview

Table 2.1.4.28 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Muscat *et al.* (1996) USA 1981–90	Men: 687 cases and 619 controls; women: 322 cases and 304 controls	Hospital-based study Cases histologically confirmed Controls with conditions unrelated to tobacco use, identified from daily hospital admission logs, matched on sex, age, race and date of admission
Sanderson *et al.* (1997) Netherlands 1980–90	Women: 303 cases	Population-based study Cases of squamous-cell carcinoma of the oral cavity and oropharynx Controls: data from a large national survey on public health conducted by the National Central Bureau of Statistics; matched on sex and age
Lewin *et al.* (1998) Sweden 1988–91	Men: 545 cases and 641 controls	Population-based study in two areas Cases identified at weekly conferences at all ear, nose and throat departments in the study area (90%) and from regional cancer registers (10%); aged 40–79 years; 90% eligible cases Controls selected by random sampling from a population register stratified by region and age; response rate, 85%
Talamini *et al.* (1998) Italy and Switzerland 1992–97	Men: 10 cases and 79 controls; women: 22 cases and 145 controls	Multicentre hospital-based study; analysis restricted to abstainers from alcohol Cases histologically confirmed Controls admitted for acute non-neoplastic conditions unrelated to alcohol consumption or tobacco use
Rao *et al.* (1999) India 1980–84	678 cases and 635 controls (men only)	Hospital-based study in Mumbai Cases of cancer of the oral cavity and pharynx Controls with infectious diseases and benign tumours, free from cancer, admitted during the same period as controls [no matching]
Bosetti *et al.* (2000) Italy and Switzerland 1984–97	Women: 195 cases and 1113 controls	Two multicentre hospital-based studies Cases histologically confirmed Controls admitted for acute non-neoplastic conditions, frequency-matched by age and residence

Table 2.1.4.28 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Dikshit & Kanhere (2000) India 1986–92	Men: 247 cases and 260 controls	Population-based study in Bhopal Cases of oropharyngeal cancer collected by a population-based cancer registry Controls randomly selected from a group of 2500 men surveyed for tobacco habits in the general population, stratified by age
Moreno-Lopez *et al.* (2000) Spain	Men: 63 cases; women: 12 cases; 150 controls	Hospital-based study in three hospitals in the Madrid community Cases histologically confirmed Controls selected from healthy subjects with no history of cancer or oral disease, in health care centres corresponding to the hospitals
Zavras *et al.* (2001) Greece 1995–98	Men: 68 cases and 69 controls; women: 42 cases and 46 controls	Hospital-based study in three university hospitals in Athens Cases histologically confirmed Controls hospitalized for conditions unrelated to cancer, matched on age and sex

Table 2.1.4.29. Case–control studies on tobacco smoking and cancers of the upper aerodigestive tract

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Blot *et al.*	Oral cavity and			Men			Adjusted for age, race, study location,
(1988)	pharynx	659	593	Ever-smoker	1.9	1.3–2.9	alcohol consumption and respondent
USA	ICD-9:	485	239	Current smoker	3.4	2.3–5.1	status
1984–85	141 tongue			Cigarettes/day			
	143 gum	80	173	1–19	1.2	0.7–1.8	
	144 floor of mouth	312	288	20–39	2.1	1.4–3.1	
	145 other	262	130	≥ 40	2.8	2.8–4.4	
	146 oropharynx			Duration (years)			
	148 hypopharynx	45	138	1–19	0.8	0.5–1.3	
	149 other sites	286	281	20–39	1.9	1.2–2.8	
	within lip, oral	313	171	≥ 40	3.6	2.3–5.6	
	cavity and pharynx			Age at starting smoking (years)			
		38	47	≥ 25	1.8	0.9–3.3	
		279	285	17–24	1.8	1.2–2.7	
		325	258	< 17	2.1	1.4–3.2	
				Women			
		298	229	Ever-smoker	3.0	2.0–4.5	
		258	129	Current smoker	4.7	3.0–7.3	
				Cigarettes/day			
		60	104	1–19	1.8	1.1–2.9	
		145	94	20–39	3.6	2.3–5.8	
		93	31	≥ 40	6.2	3.6–11.3	
				Duration (years)			
		15	59	1–19	1.0	0.5–1.9	
		127	105	20–39	2.9	1.8–4.6	
		153	64	≥ 40	5.0	3.0–8.3	
				Age at starting smoking (years)			
		54	54	≥ 25	2.8	1.6–4.8	
		153	116	17–24	3.1	2.0–4.9	
		89	59	< 17	2.9	1.7–4.9	

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Ferraroni *et al.* (1989)	Mouth and pharynx	2	380	Former smoker	0.9		Adjusted for age, sex, education, marital status, social class, coffee and alcohol consumption
Italy				Cigarettes/day			$p < 0.01$ for all current cigarette smokers combined
1983–88		5	267	< 15	3.6		
		25	332	15–24	11.1		
		12	159	≥ 25	11.0		
Merletti *et al.* (1989)	Oral cavity and oropharynx	Men	Men	Tobacco/day (g)			Adjusted for age
Italy	ICD-9:	3	58	1–7	0.9	0.2–3.9	
1982–84	140.3 upper lip	27	91	8–15	4.6	1.8–11.9	
	140.4 lower lip	37	106	16–25	5.2	2.1–13.3	
	141 tongue	14	45	> 25	5.2	1.9–14.6	
	143 gum			Duration (years)			
	144 floor of mouth	4	54	1–20	1.0	0.2–5.1	
	145 other parts of mouth	5	52	21–30	1.7	0.4–6.9	
	146 oropharynx	29	79	31–40	5.0	1.6–16.2	
		26	77	41–50	5.0	1.8–13.8	
		17	38	> 50	7.1	1.9–26.0	
				Age at starting smoking (years)			
		9	42	> 20	3.4	1.1–10.6	
		24	119	18–20	3.1	1.2–8.4	
		27	91	15–17	4.6	1.8–12.2	
		21	48	< 15	7.0	2.6–18.4	

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Merletti *et al.* (1989) (contd)		Women	Women	Tobacco/day (g)			Adjusted for age
		10	32	1–7	5.6	2.0–15.3	
		13	52	≥ 8	5.9	2.3–15.0	
				Duration (years)			
		9	60	1–30	5.5	1.8–16.8	
		8	15	31–40	6.1	2.1–18.1	
		6	9	> 40	5.7	1.9–16.9	
				Age at starting smoking (years)			
		10	31	> 20	4.7	1.8–12.4	
		13	53	≤ 20	6.7	2.4–18.4	
		Men	Men	Tobacco (g/day)			Multivariate logistic regression model; adjusted for age, educational level, area of birth, alcohol consumption and type of alcoholic beverage Trends not seen for women for any variable
				1–7	1.0	–	
				8–15	4.4	1.0–18.3	
				16–25	5.1	1.2–21.0	
				> 25	6.2	1.4–28.3	
				Duration (years)			
				1–20	1.0	–	
				21–30	0.7	0.1–4.4	
				31–40	2.5	0.3–18.4	
				41–50	3.9	0.4–34.6	
				> 50	34.0	2.6–436.4	
				Age at starting smoking (years)			
				< 15	1.0	–	
				15–17	0.6	0.3–1.5	
				18–20	0.4	0.2–0.9	
				> 20	0.4	0.1–1.1	

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Talamini *et al.* (1990) Italy 1986–89	Oral cavity and pharynx (nasopharynx and salivary glands excluded)	3	34	Former smoker	4.1	0.5–93.6	Non-drinkers only; adjusted for age and sex
				Current smoker			
				Cigarettes/day			
		2	12	< 15	3.8	0.2–58.2	
		10	22	≥ 15	12.9	2.3–106.3	*p* for trend < 0.001
Barra *et al.* (1991) Italy 1985–90	Oral cavity and pharynx			Cigarettes/day			Adjusted for age, sex, education, occupation and alcohol consumption
				Cancer controls			
		58	134	≤ 14	5.2	2.9–9.2	
		73	119	15–24	5.8	3.2–10.5	
		49	48	≥ 25	9.6	4.9–18.9	*p* for trend < 0.01
				Non-cancer controls			
		58	254	≤ 14	5.8	3.3–10.1	
		73	268	15–24	6.1	3.5–10.9	
		49	87	≥ 25	12.2	6.4–23.2	*p* for trend < 0.01
				Duration (years)			
				Cancer controls			
		57	237	< 30	2.7	1.5–4.9	
		78	123	30–39	7.0	3.9–12.6	
		107	186	≥ 40	7.4	4.0–13.6	*p* for trend < 0.01
				Non-cancer controls			
		57	537	< 30	2.7	1.5–4.7	
		78	258	30–39	6.9	3.9–12.1	
		107	288	≥ 40	8.8	4.9–15.6	*p* for trend < 0.01

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Barra *et al.* (1991) (contd)				Age at starting smoking (years)			
				Cancer controls			
		26	121	≥ 25	2.8	1.4–5.4	
		122	298	17–24	4.7	2.7–8.1	
		101	155	≤ 16	6.8	3.8–12.2	*p* for trend < 0.01
				Non-cancer controls			
		26	192	≥ 25	3.3	1.7–6.2	
		122	583	17–24	4.9	2.9–8.4	
		101	331	≤ 16	6.6	3.8–11.5	*p* for trend < 0.01
La Vecchia *et al.* (1991) Italy 1987–89	Oral cavity and oropharynx (nasopharynx and salivary glands excluded)	11	244	Former smoker	4.3		Data stratified by sex and decade of age
				Cigarettes/day			
		61	372	≤ 25	11.0		
		23	123	> 25	17.9		
De Stefani *et al.* (1992) Uruguay 1988–90	Mouth and pharynx	87	122	Current smoker	1.0	–	Adjusted for age, county, area of residence, education, income and alcohol consumption; light smokers used as reference group
		19	112	Former smoker	0.3	0.1–0.6	
				Cigarettes/day			
		16	74	1–10	1.0	–	
		41	74	11–20	2.0	0.9–4.4	
		26	34	21–30	3.1	1.3–7.6	
		23	52	≥ 31	1.9	0.8–4.5	
				Duration (years)			
		7	58	1–29	1.0	–	
		20	58	30–39	2.3	0.8–6.4	
		40	47	40–49	4.8	1.7–13.4	
		39	71	≥ 50	4.3	1.5–12.3	

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Franceschi	Mouth	18	260	Former smoker	3.6	1.0–12.6	Adjusted for age, area of residence,
et al. (1992)	ICD-9:	78	306	Current smoker	11.8	3.6–38.4	occupation and alcohol use
Italy	143 gum			Cigarettes/day			
1986–90	144 floor of mouth	18	206	≤ 14	4.5	1.3–15.8	
	145 other parts of	51	229	15–24	11.0	3.3–36.4	
	mouth	26	125	≥ 25	9.6	2.8–33.1	p for trend ≤ 0.01
	149 other parts			Duration (years)			
	within lip, oral	17	229	≤ 29	3.5	1.0–12.3	
	cavity and pharynx	36	157	30–39	11.0	3.2–36.3	
		41	174	≥ 40	14.3	4.1–49.6	p for trend ≤ 0.01
				Age at starting smoking (years)			
		40	280	≥ 20	6.5	2.0–21.8	
		59	282	≤ 19	11.0	3.3–36.4	p for trend ≤ 0.01
Marshall *et al.*	Oral cavity:	290	290	Pack–years			Matched pairs analysis
(1992)	tongue, oropharynx,			1–20	1.3	0.7–2.4	
USA	floor of mouth,			21–30	2.7	1.2–6.0	
1975–83	pharynx,			31–40	2.9	1.5–5.9	
	hypopharynx			41–50	7.0	3.3–15.1	
				51–70	7.7	3.7–15.9	
				≥ 71	5.7	2.7–12.1	p for trend < 0.0001

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Zheng *et al.* (1992a) China 1988–90	Oral cavity and pharynx ICD-9: 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth 146 oropharynx 148 hypopharynx 149 other parts within lip, oral cavity and pharynx	115	269	Pack–years			Analysis for men only
				< 25	0.8	0.4–1.4	
				≥ 25	2.2	1.2–4.1	*p* for trend ≤ 0.05
Day *et al.* (1993) USA 1984–85	Oral cavity and pharynx ICD-9: 141 tongue 143 gum 144 floor of mouth 145 other parts of mouth 146 oropharynx 148 hypopharynx 149 other sites within lip, oral cavity and pharynx	Whites	Whites				Adjusted for age, sex, study location, alcohol consumption and respondent status
		568	256	Current smoker	3.6	2.6–4.8	
				Cigarettes/day			
		90	186	1–19	1.2	0.8–1.7	
		349	308	20–39	2.2	1.6–2.9	
		306	144	≥ 40	2.8	2.0–4.0	
				Duration (years)			
		38	152	1–19	0.6	0.4–1.0	
		313	293	20–39	1.9	1.3–2.5	
		386	191	≥ 40	3.3	2.3–4.6	
				Age at starting smoking (years)			
		71	74	≥ 25	2.2	1.4–3.5	
		356	322	17–24	1.9	1.4–2.6	
		308	241	< 17	2.0	1.4–2.7	

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Day *et al.*		Blacks	Blacks				
(1993) (contd)		147	81	Current smoker	2.3	1.1–4.7	
				Cigarettes/day			
		39	62	1–19	1.2	0.5–2.6	
		93	57	20–39	2.1	1.0–4.4	
		36	14	≥ 40	2.8	1.0–7.7	
				Duration (years)			
		14	28	1–19	0.9	0.3–2.4	
		84	72	20–39	1.6	0.7–3.3	
		66	33	≥ 40	2.9	1.2–7.2	
				Age at starting smoking (years)			
		14	18	≥ 25	1.2	0.4–3.6	
		67	56	17–24	1.7	0.8–3.8	
		84	59	< 17	1.8	0.8–3.9	
Kune *et al.* (1993) Germany 1982	Oral cavity and pharynx			Former smoker	3.9	0.5–34.0	Adjusted for age, alcohol consumption, vitamin C and fibre intake
				Current smoker	13.8	1.1–112.5	

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Mashberg *et al.* (1993) USA 1972–83	Oral cavity and oropharynx	9	309	Minimal smoking	1.0	–	Adjusted for age, race and alcohol drinking; reference groups may have been inappropriate.
		9	307	Former smoker	0.8	0.3–2.2	
				Current smoker			
				Cigarettes/day			
		41	269	6–15	4.0	1.9–8.5	Trends seen and commented upon, but not analysed
		109	538	16–25	4.4	2.2–8.9	
		61	216	26–35	5.6	2.7–11.7	
		94	381	≥ 36	4.0	1.9–8.2	
				Duration (years)			Further adjusted for average cigarette consumption
		23	438	Nonsmoker and 1–15	1.0	–	
		55	440	16–30	0.7	0.3–3.6	
		203	1017	31–45	1.5	0.4–5.3	
		78	385	≥ 46	1.9	0.5–7.1	
				Pack–years			
		25	419	Nonsmoker and 1–5	1.0	–	
		37	395	5–25	3.1	1.3–7.3	
		143	708	25–50	5.5	2.5–12.1	
		78	378	50–75	4.5	2.0–10.2	
		76	380	> 75	4.0	1.8–9.0	
Negri *et al.* (1993) Italy 1984–92	Oral cavity and pharynx ICD-9: 141–149			Moderate/former smoker	3.6		Adjusted for alcohol consumption
				Heavy and/or pipe/cigar smoker	9.4		
Spitz *et al.* (1993) USA 1987–91	Upper aero-digestive tract			Cigarettes/day			Univariate analysis
				1–14	4.2	1.4–12.8	
				15–24	7.9	3.2–19.1	
				≥ 25	11.0	4.4–27.4	*p* for trend < 0.001
				≥ 25	4.8	2.3–10.0	Adjusted for alcohol, mutagen sensitivity and educational level

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
De Stefani *et al.* (1994) Uruguay 1988–92	Oral cavity and pharynx (lip, salivary glands and nasopharynx excluded)			Pack–years			Adjusted for age, area of residence and education
		36	82	1–26	1.5	0.6–3.9	
		62	55	27–45	3.3	1.3–8.3	
		70	44	46–70	4.2	1.6–10.9	
		71	38	≥ 71	4.5	1.7–11.6	
Kabat *et al.* (1994) USA 1977–90	Oral cavity and pharynx: tongue, floor of mouth, gums, gingiva, buccal mucosa, palate, retromolar area, tonsil, other pharynx (nasopharynx excluded)	Men	Men				Adjusted for age, years of schooling, alcohol consumption, race, time period and type of hospital
		246	811	Former smoker	1.1	0.8–1.5	
		676	667	Current smoker	3.3	2.4–4.3	
				Cigarettes/day			
		284	376	1–20	1.0	–	
		128	116	21–30	1.5	1.1–2.1	
		264	175	≥ 31	1.8	1.4–2.4	
				Duration (years)			Also adjusted for amount smoked and smoking status
		97	355	1–20	1.0	–	
		469	776	21–40	1.3	0.96–1.7	
		355	347	≥ 41	1.8	1.3–2.7	
		Women	Women				Adjusted for age, years of schooling, alcohol consumption, race, time period and type of hospital
		79	210	Former smoker	1.4	1.0–2.0	
		271	192	Current smoker	4.3	3.2–5.9	
				Cigarettes/day			
		143	132	1–20	1.0	–	
		54	28	21–30	1.7	0.9–2.9	
		74	32	≥ 31	1.9	1.1–3.2	
				Duration (years)			
		35	108	1–20	1.0	–	Also adjusted for amount smoked and smoking status
		201	216	21–40	1.5	0.9–2.4	
		114	79	≥ 41	1.8	0.97–3.4	

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Muscat *et al.*	Oral cavity and	Men	Men	Cumulative tar (kg)			Adjusted for age, residence, urban/rural
(1996)	pharynx	61	99	< 1.4	1.0	0.6–1.6	status, birthplace, education and total
USA	ICD-9:	99	119	1.4–3.5	0.9	0.6–1.6	alcohol consumption
1981–90	141 tongue	174	122	3.5–6.8	1.6	1.0–2.5	
	143 gum	283	141	> 6.8	2.1	1.4–3.2	*p* for trend < 0.01
	144 floor of mouth			Pack–years			
	145 other parts of	69	131	1–19	0.7	0.5–1.1	
	mouth	142	132	20–39	1.4	0.9–2.1	
	146 oropharynx	186	108	40–59	2.0	1.3–3.1	
	148 hypopharynx	219	110	> 60	2.2	1.4–3.3	*p* for trend < 0.01
	149 other sites	Women	Women	Cumulative tar (kg)			
	within lip, oral	47	55	< 1.4	1.8	1.1–3.0	
	cavity and pharynx	60	34	1.4–3.5	2.8	1.6–4.9	
		85	33	3.5–6.8	3.2	1.9–5.6	
		53	15	> 6.8	4.6	2.5–8.7	*p* for trend < 0.01
				Pack–years			
		49	66	1–19	1.6	1.0–2.6	
		72	37	20–39	3.3	2.0–5.9	
		76	21	40–59	5.5	2.9–10.1	
		48	13	> 60	5.3	2.5–11.3	*p* for trend < 0.01
Sanderson	Oral cavity and			Cigarettes/day			Adjusted for age and alcohol
et al. (1997)	oropharynx	57	350	1–19	1.3	0.9–2.0	
Netherlands		79	241	> 19	2.2	1.5–3.3	
1980–90							

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Lewin *et al.* (1998) Sweden 1988–91	Head and neck	116	234	Former smoker	1.9	1.3–2.8	Adjusted for age, region and alcohol
		501	448	Ever-smoker	4.0	2.8–5.7	
		385	214	Current smoker	6.5	4.4–9.5	
				Tobacco/day (g)			
		202	211	< 15	3.4	2.3–5.1	
		230	189	15–24	4.4	2.9–6.5	
		69	48	≥ 25	4.8	2.9–8.1	
				Duration (years)			
		50	156	< 30	1.2	0.7–1.9	
		168	148	30–44	3.9	2.6–5.9	
		283	144	≥ 45	7.2	4.8–10.8	
				Age at starting smoking (years)			
		33	49	≥ 25	2.6	1.5–4.6	
		101	102	20–24	3.8	2.4–5.9	
		257	220	15–19	4.0	2.7–5.9	
		110	77	< 15	5.0	3.2–7.9	
				Total consumption (kg tobacco)			
		53	145	< 125	1.5	1.0–2.4	
		181	146	126–250	4.3	2.9–6.5	
		267	157	> 250	5.9	4.0–8.8	
Talamini *et al.* (1998) Italy and Switzerland 1992–97	Oral cavity and pharynx; naso-pharynx and salivary gland excluded	7	33	Former smoker	2.2	0.8–6.2	Analysis restricted to abstainers from alcohol
				Current smoker			
				Cigarettes/day			Adjusted for study centre, age, sex and education
		6	44	< 25	1.5	0.5–4.6	
		3	5	≥ 25	7.2	1.1–46.6	*p* for trend = 0.07
Rao *et al.* (1999) India 1980–84	Oropharynx ICD-9: 141.0, 145.3, 146.9	45	98	Cigarette smoker	1.3	0.8–2.2	Adjusted for age and area of residence; in the study area, cigarette smoking was not as common as bidi smoking.

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Bosetti *et al.*	Oral cavity and	19	111	Former smoker	1.6	0.9–2.9	Adjusted for education, body-mass
(2000)	pharynx			Current smoker			index and alcohol consumption
Italy and				Cigarettes/day			
Switzerland		57	139	1–14	3.6	2.3–5.6	
1984–97		47	93	≥ 15	4.6	2.7–7.6	*p* for trend < 0.0001
				Duration (years)			
		29	138	< 28	1.6	1.0–2.7	
		75	88	≥ 28	5.1	3.3–7.7	*p* for trend < 0.0001
Dikshit &	Oropharynx			Cigarettes/day			Adjusted for age and bidi smoking
Kanhere (2000)	ICD-9: 141.0, 141.6,	15		1–10	1.5	0.5–4.4	
India	145.3, 145.4, 146.0–	18		11–20	5.7	2.2–15.0	
1986–92	146.9, 147.0–147.9,	9		> 20	11.4	2.7–48.8	
	148.0–149.0						
Moreno-Lopez	Oral cavity			Cigarettes/day			Adjusted for alcohol consumption and
et al. (2000)	ICD-9:	22	38	1–20	3.1	1.4–6.7	daily tooth brushing
Spain	140 lip	23	13	≥ 20	8.3	3.4–20.4	*p* for trend < 0.05
	141 tongue						
	143 gum						
	144 floor of mouth						
	145 other parts of mouth						
	146 oropharynx						

Table 2.1.4.29 (contd)

Reference Country and years of study	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Zavras *et al.*	Oral cavity	Men	Men				Adjusted for age, hospital and alcohol
(2001)	ICD-9:	8	22	Former smoker	0.4	0.1–1.3	consumption; very few cases in women
Greece	141 tongue	56	46	Current smoker	3.0	1.2–7.9	
1995–98	143 gum			Pack–years			
	144 floor of mouth	10	17	1–25	1.0	0.3–3.0	
	145 other parts of	14	14	> 25-50	1.4	0.5–4.3	
	mouth	32	15	> 50	2.8	1.0–8.0	*p* for trend = 0.03
	148 hypopharynx	Women	Women				
	149 other parts	8	3	Former smoker	6.2	1.2–31.4	
	within lip, oral	5	5	Current smoker	0.7	0.1–3.7	
	cavity and pharynx			Pack–years			
		7	5	1–25	1.9	0.5–7.8	
		5	2	26–50	4.1	0.6–26.9	
		1	1	> 50	0.9	0.0–24.6	*p* for trend = 0.30
				Men and women combined			Also adjusted for sex
		16	25	Former smoker	0.9	0.4–2.1	*p* for trend = 0.01
		61	51	Current smoker	3.0	1.4–6.6	
				Pack–years			
		17	22	1–25	1.3	0.6–3.0	
		19	16	26–50	1.7	0.7–4.3	
		33	16	> 50	3.3	1.3–8.5	

CI, confidence interval

Table 2.1.4.30. Case–control studies on tobacco smoking and cancers of the upper aerodigestive tract cancer: smoking cessation

Reference (country and years of study)	Cancer subsite ICD code	No. of cases	No. of controls	Years since quitting	Relative risk	95% CI	Comments
Blot *et al.*	Oral cavity and	Men	Men				Adjusted for age, race, study location, alcohol
(1988)	pharynx	485	239	Current smoker	3.4	2.3–5.1	consumption and respondent status
USA	ICD-9:	64	98	1–9	1.1	0.7–1.9	
1984–85	141 tongue	56	114	10–19	1.1	0.7–1.9	
	143 gum	43	141	≥ 20	0.7	0.4–1.2	
	144 floor of mouth	Women	Women				
	145 other	258	129	Current smoker	4.7	3.0–7.3	
	146 oropharynx	24	39	1–9	1.8	0.9–3.6	
	148 hypopharynx	10	35	10–19	0.8	0.4–1.9	
	149 other sites within lip, oral cavity and pharynx	4	26	≥ 20	0.4	0.1–1.4	
Merletti *et al.*	Oral cavity and	Men	Men				Adjusted for age
(1989)	oropharynx	68	195	0–1	5.4	2.3–16.8	
Italy	ICD-9:	11	42	2–5	4.4	1.6–12.4	
1982–84	140.3 upper lip	2	63	> 5	0.4	0.1–2.7	
	140.4 lower lip	5	85	Nonsmoker	1.0	–	
	141 tongue	Women	Women				Adjusted for age
	143 gum	18	68	0–1	7.4	3.0–18.3	
	144 floor of mouth	5	16	> 1	3.7	1.3–10.8	
	145 other parts of	13	137	Nonsmoker	1.0	–	
	mouth	Men	Men	0–1	1.0	–	Multivariate logistic regression model
	146 oropharynx			2–5	0.7	0.3–1.8	adjusted for age, educational level, area of
				> 5	0.3	0.1–1.8	birth, alcohol consumption and type of
		Women	Women	0–1	1.0	–	alcoholic beverage
				> 1	1.5	0.3–8.9	

Table 2.1.4.30 (contd)

Reference (country and years of study)	Cancer subsite ICD code	No. of cases	No. of controls	Years since quitting	Relative risk	95% CI	Comments
Barra *et al.*	Oral cavity and			Cancer controls			Adjusted for age, sex, education, occupation
(1991)	pharynx	43	120	< 10	3.9	2.0–7.8	and alcohol consumption
Italy		22	151	≥ 10	1.4	0.6–3.1	*p* for trend < 0.01 with both groups of
1985–90		21	445	Nonsmoker	1.0	–	controls
				Non-cancer controls			
		43	239	< 10	3.9	2.0–7.8	
		22	261	≥ 10	1.6	0.8–3.5	
		21	769	Nonsmoker	1.0	–	
De Stefani	Mouth and pharynx	84	121	Current smoker	1.0	–	Adjusted for age, county, residence,
et al. (1992)		10	25	1–4	0.6	0.2–1.4	education, income and alcohol consumption
Uruguay		7	11	5–9	1.1	0.4–3.3	
1988–90		5	77	≥ 10	0.1	0.0–0.3	
Franceschi	Mouth	78	306	Current smoker	11.8	3.6–38.4	Adjusted for age, area of residence,
et al. (1992)	ICD-9:	13	122	< 10	3.8	1.0–14.4	occupation and alcohol use
Italy	143 gum	3	138	≥ 10	0.7	0.1–3.9	*p* for trend ≤ 0.01
1986–90	144 floor of mouth						
	145 other parts of mouth						
	149 other parts within lip, oral cavity and pharynx						

Table 2.1.4.30 (contd)

Reference (country and years of study)	Cancer subsite ICD code	No. of cases	No. of controls	Years since quitting	Relative risk	95% CI	Comments
Day *et al.*	Oral cavity and	Whites	Whites				Adjusted for age, sex, study location, alcohol
(1993)	pharynx	568	256	Current smoker	3.6	2.6–4.8	consumption and respondent status
USA	ICD-9:	70	107	1–9	1.1	0.7–1.6	
1984–85	141 tongue	63	128	10–19	1.1	0.7–1.6	
	143 gum	41	147	≥ 20	0.6	0.3–0.9	
	144 floor of mouth	Blacks	Blacks				
	145 other	147	81	Current smoker	2.3	1.1–4.7	
	146 oropharynx	13	24	1–9	1.1	0.4–3.1	
	148 hypopharynx	1	13	10–19	0.1	0.0–1.3	
	149 other sites within lip, oral cavity and pharynx	3	15	≥ 20	0.3	0.1–1.7	
Mashberg *et al.*	Oral cavity and	9	309	3–10	1.3	0.3–6.5	
(1993) USA	oropharynx	6	147	≥ 11	0.5	0.1–2.6	
1972–83		3	160	Minimal smoking	1.0	–	
Kabat *et al.*	Oral cavity and	Men	Men				Adjusted for age, years of schooling, alcohol
(1994)	pharynx	676	668	Current smoker	1.0	–	consumption, race, time period, type of
USA		113	225	1–9	0.6	0.4–0.8	hospital, and intensity and duration of
1977–90		59	276	10–19	0.3	0.2–0.5	smoking
		70	306	≥ 20	0.5	0.3–0.9	
		Women	Women				
		271	193	Current smoker	1.0	–	
		40	69	1–9	0.5	0.3–0.8	
		24	82	10–19	0.3	0.2–0.5	
		15	59	≥ 20	0.3	0.1–0.8	
Lewin *et al.*	Head and neck	385	214	Current smoker	6.5	4.4–9.5	Adjusted for age, region and alcohol
(1998)		61	75	1–10	3.2	2.0–5.2	
Sweden		32	76	11–20	1.7	1.0–2.9	
1988–90		23	83	≥ 21	0.9	0.5–1.7	

CI, confidence interval

Table 2.1.4.31. Case–control studies on tobacco smoking and cancers of the upper aerodigestive tract: type of tobacco and/or cigarette

Reference (country and years of study)	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Merletti *et al.*	Oral cavity and	Men	Men	Type of tobacco			Adjusted for age
(1989)	oropharynx	13	84	> 66% blond	2.4	0.8–7.2	
Italy	ICD-9:	7	37	Mixed	2.9	0.9–10.1	
1982–84	140.3 upper lip	48	142	> 66% black	4.8	1.9–12.1	
	140.4 lower lip			Use of filter			
	141 tongue	20	97	> 66% with filter	3.2	1.2–9.0	
	143 gum	13	42	Mixed	4.7	1.5–14.9	
	144 floor of mouth	35	124	> 66% without filter	4.2	1.6–11.0	
	145 other parts of	Women	Women	Type of tobacco			
	mouth	12	63	> 66% blond	6.0	2.2–16.1	
	146 oropharynx	4	9	Mixed	4.7	1.3–16.3	
		7	12	> 66% black	6.9	2.5–19.1	
				Use of filter			
		15	69	> 66% with filter	6.3	2.4–16.6	
		3	6	Mixed	5.4	1.3–22.2	
		5	9	> 66% without filter	5.2	1.8–15.1	
		Men	Men	Type of tobacco			Multivariate analysis
				> 66% blond	1.0	–	adjusted for age, education,
				Mixed	0.7	0.2–2.7	area of birth, alcohol
				> 66% black	1.0	0.4–2.6	consumption and type of
				Use of filter			alcoholic beverage
				> 66% with filter	1.0	–	
				Mixed	1.2	0.4–3.5	
				> 66% without filter	1.2	0.5–2.8	

Table 2.1.4.31 (contd)

Reference (country and years of study)	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
De Stefani *et al.* (1992) Uruguay 1988–90	Mouth and pharynx			Type of cigarette			Adjusted for age, county, residence, education, income and alcohol consumption
		16	72	Manufactured	1.0	–	
		90	162	Hand-rolled	2.5	1.2–5.2	
Franceschi *et al.* (1992) Italy 1986–90	Mouth ICD-9: 143 gum 144 floor of mouth 145 other parts of mouth 149 other parts within lip, oral cavity and pharynx			Tar yield			Adjusted for age, area of residence, occupation and alcohol use *p* for trend ≤ 0.01
		53	364	Low tar (< 22 mg)	7.1	2.2–23.3	
		42	185	High tar (≥ 22 mg)	14.4	4.2–49.5	
Mashberg *et al.* (1993) USA 1972–83	Oral cavity and oropharynx			Untipped cigarettes (cigarettes/day)			Adjusted for age, race and alcohol drinking
				6–15	7.8	2.4–19.0	
				16–25	7.7	3.6–16.5	
				26–35	12.3	5.3–28.6	
				≥ 36	7.6	3.5–16.8	
				Filter-tipped cigarettes (cigarettes/day)			
				6–15	1.5	0.5–4.2	
				16–25	3.6	1.6–7.7	
				26–35	1.9	0.7–5.0	
				≥ 36	2.3	1.0–5.2	

Table 2.1.4.31 (contd)

Reference (country and years of study)	Cancer subsite ICD code	No. of cases	No. of controls	Smoking categories	Relative risk	95% CI	Comments
Kabat *et al.* (1994) USA 1977–90	Oral cavity and pharynx	Men	Men				Adjusted for age, years of schooling, alcohol consumption, race, time period and hospital
		221	126	Non-filter only	1.0	–	
		96	105	Filter for 1–9 years	0.5	0.4–0.8	
		280	334	Filter for ≥ 10 years	0.5	0.4–0.7	
		57	80	Filter only	0.6	0.4–0.9	
		Women	Women				
		46	17	Non-filter only	1.0	–	
		38	20	Filter for 1–9 years	0.8	0.3–1.8	
		125	89	Filter for ≥ 10 years	0.5	0.2–1.0	
		57	63	Filter only	0.6	0.3–1.2	

CI, confidence interval

Table 2.1.4.32. Case-series on tobacco smoking and cancers of the upper aerodigestive tract

Reference Country and years of study	Cancer subsites	%	No. of cases	Age	Histological types	Exposures		Comments
al-Idrissi (1990) Saudi Arabia 1982–89	Nasopharynx Tongue Oral cavity Larynx Pharynx Oropharynx	43 17 15 14 6 5	42 men 23 women	Mean age, 48.6 ± 14.9 years	100% squamous- cell carcinoma; all others excluded	 No tobacco habit Tobacco smoking Al-Shamma	% 32.3 41.5 26.2	Cases histologically confirmed Al-Shamma (mixture of tobacco, pepper and oil) is frequently chewed instead of smoking tobacco.

Table 2.1.4.33. Case–control studies on tobacco smoking and second primary tumours in patients with a primary cancer of the upper aerodigestive tract

Reference Country, cohort collection period and follow-up period	Initial population study	Cases (second primary tumours)	Controls (no second primary tumours)	Exposure categories	Relative risk	95% CI	Factors adjusted for; comments
Day *et al.* (1994) USA 1984–85 follow-up until 1989	1090 patients with cancer of the oral cavity or pharynx (ICD-9: 141, 143–146, 148–149); follow-up of at least 6 months	80 meta-chronous cases in the oral cavity, pharynx, larynx, oesophagus and lung (56 men and 24 women)	189 controls (132 men and 57 women) matched by sex and study area	Ever-smoker	3.8	0.6–5.2	Matched analysis; model adjusted for age at index cancer diagnosis and index tumour stage; odds ratios adjusted for age, stage of disease and alcohol intake; adjustment for race, education, marital status, occupation, location or radiation therapy had no effect. †ever-smokers
				Current smoker	4.3	1.6–12	
				Cigarettes/day†			
				0–20	1.0	–	
				20–39	1.8	0.5–6.2	
				≥ 40	3.6	0.9–14.0	
				Duration (years)†			
				0–20	1.0	–	
				20–39	3.2	0.9–12	
				≥ 40	4.7	1.3–17	
Barbone *et al.* (1996) Italy 1984–91 follow-up until 1994	380 patients with incident first cancer of the oral cavity, larynx or pharynx; median follow-up, 40 months	62 multiple second primary tumours, of which 39 were meta-chronous cases in the oral cavity, pharynx, larynx, oesophagus and nasal cavities (34 men and 5 women)	Not available	Never or very light smoker	1.0	–	Hazard ratios adjusted for age, sex, area of residence, occupation, smoking habits, alcohol intake, β-carotene intake, index tumour grade and stage *p* for trend = 0.08
				Light	2.3	0.4–12.2	
				Intermediate	2.7	0.5–13.4	
				Heavy	4.3	0.7–26.9	
Cianfriglia *et al.* (1999) Italy 1989–92 follow-up until 1997	200 patients with first incident cancer of the oral cavity and oro-pharynx (ICD-10: C01–C06; C09) and curative-intended treatment; median follow-up, 3.2 years	28 cases: 24 second, 3 third and 1 fourth primary tumour (22 men and 6 women)	Population covered by southern and central Italian cancer registries	Site of second tumour:	SIR†		†Standardized incidence ratios Heavy smokers accounted for higher incidence rates of second primary tumours, but the results were not adjusted for alcohol consumption. Information on multiple synchronous tumours available
				Oropharynx	250.0	208.7–291.2	
				Oral cavity	137.5	103.7–171.3	
				Lip	22.2	17.7–29.8	
				Larynx	8.0	6.9–9.4	
				Lung	2.5	2.2–2.8	

CI, confidence interval

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2.1.5 *Cancer of the pancreas*

(*a*) *Cohort and case–control studies*

The designs of the case–control and cohort studies are summarized in Table 2.1.5.1 and 2.1, respectively. Additional data have come from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (Stolzenberg-Solomon *et al.*, 2001), which followed a cohort of more than 27 000 male smokers between 1985 and 1997. Pancreatic cancer cases were ascertained from the Finnish Cancer Registry, which hold records of almost 100% of all cases in Finland.

All but two of the published cohort and case–control studies (Murata *et al.*, 1996; Liaw & Chen, 1998) showed an increased risk for pancreatic cancer in ever-smokers (Tables 2.1.5.2 and 2.1.5.3). The conclusion that smoking is a cause of this cancer reached in the *IARC Monograph* on tobacco smoking (IARC, 1986) remains unchanged; smokers have about twice as high a risk for this cancer as never-smokers.

A number of cohort studies have reported associations between smoking and the subsequent development of pancreatic cancer. Pancreatic cancer was ascertained mainly by linkage to population-based cancer registries, death notification systems or pathology laboratories. Some studies only recorded smoking habits at time of enrolment; thus data on prolonged tobacco consumption were not readily available.

Several case–control studies on the relationship between smoking and pancreatic cancer have also been published since 1986. These studies were designed to measure the effect of smoking, alcohol consumption and coffee drinking. Some studies also measured the effect of certain dietary items. Two types of control group were used: hospital-based controls, mainly with conditions not thought to be associated with smoking or tobacco, or neighbourhood-matched controls selected using electoral rolls or random-digit telephone dialling. Verification of pancreatic cancers ranged from 100% (i.e. only those with histological verification were included in a study) to about 30%. However, whether or not subanalyses were carried out on cases diagnosed with histology, this made little difference to the results. Because pancreatic cancer is rapidly fatal, most studies questioned proxies for the case about the smoking characteristics of the patients. Some studies also interviewed proxies of the control patients, but again, restricting the analyses to direct interviews rather than proxy interviews made little difference to the direction of the association.

(*b*) *Factors affecting risk*

(i) *Duration and intensity*

Table 2.1.5.3 shows the results of studies that considered dose–response relationships. Most studies found clear evidence demonstrating that the risk for cancer of the pancreas increases with daily cigarette consumption and the number of years of smoking.

(ii) *Cessation*

Eight studies (Mack *et al*., 1986; Cuzick & Babiker, 1989; Bueno de Mesquita *et al*., 1991; Howe *et al*., 1991; Silverman *et al*., 1994; Ji *et al*., 1995; Muscat *et al*., 1997; Partanen *et al*., 1997) reported on the risk of pancreatic cancer according to the number of years since quitting. Five of these studies found a decreasing monotonic trend in risk associated with the number of years for which the subjects had stopped smoking (Mack *et al*., 1986; Howe *et al*, 1991; Silverman *et al*., 1994; Ji *et al*., 1995; Partanen *et al*., 1997). A further study reported that the excess risk in former smokers disappeared after less than 10 years since quitting, but did not provide quantitative estimates (Fuchs *et al*., 1996) (Table 2.5.1.4).

(iii) *Type of cigarette*

Friedman *et al*. (1998) compared rates of pancreatic cancer development between those who reported smoking mentholated cigarettes and those who smoked non-mentholated cigarettes. The rate ratio was 0.6 for men (95% CI, 0.3–1.4) and 0.8 for women (95% CI, 0.3–1.8); the difference in risk between mentholated and non-mentholated cigarettes was not statistically significant and the confidence intervals were wide, so that no firm conclusion can be made.

Three case–control studies (Table 2.1.5.5; Bueno de Mesquita *et al*., 1991; Ghadirian *et al*., 1991; Howe *et al*., 1991) compared filter-tipped with untipped cigarettes. Ghadirian *et al*. (1991) observed an approximately twofold higher risk for pancreatic cancer in heavy smokers of untipped cigarettes than in smokers of filter-tipped cigarettes. Overall, however, there was no difference in effect.

(*c*) *Population characteristics*

(i) *Sex*

The effect of sex on risk was investigated in two case–control studies (Mack *et al*., 1986; Clavel *et al*., 1989) and four cohort studies (Akiba & Hirayama, 1990; Engeland *et al*., 1996; Fuchs *et al*., 1996; Tulinius *et al*., 1997). Relative risks were similar for men and women and no consistent evidence of an effect of sex on risk was observed.

(ii) *Ethnic group*

The role of ethnic group in the association between tobacco smoking and pancreatic cancer was investigated among African Americans and Caucasians in the USA (Silverman *et al*., 1994). No evidence of heterogeneity by ethnic group was obtained.

(*d*) *Confounding factors*

In addition to age and sex, other potential confounding factors considered in several studies included consumption of alcohol and coffee. The excess risk due to smoking remained after adjustment for some or all of these factors (Hiatt *et al*., 1988; Lyon *et al*., 1992; Zheng *et al*., 1993; Silverman *et al*., 1994; Engeland *et al*., 1996).

Five studies were carried out simultaneously in Utrecht, The Netherlands (Bueno de Mesquita *et al*., 1991), Toronto, Canada (Howe *et al*., 1991), Montreal, Canada (Ghadirian *et al*., 1991), Opole, Poland (Zatonski *et al*., 1993) and Adelaide, Australia (Baghurst *et al*., 1991), as part of the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) programme of the IARC, to elucidate the roles of alcohol and tobacco in the development of pancreatic cancer. These were reviewed by Boyle *et al*. (1996).

Table 2.1.5.1. Case–control studies on tobacco smoking and cancer of the pancreas: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Wynder *et al*. (1973) USA 1950–64	Men: 100 cases and 200 controls; women: 42 cases and 107 controls	Hospital-based study. Cases from nine hospitals. Controls: hospitalized patients without tobacco-related disease, matched for age, sex and ethnicity
MacMahon *et al*. (1981) USA 1974–79	Men: 218 cases and 306 controls; women: 149 cases and 337 controls	Hospital-based study. Cases from 11 hospitals. Controls: hospitalized patients without tobacco or alcohol-related disease
Durbec *et al*. (1983) France 1979–80	Men: 37 cases and 100 controls; women: 32 cases and 99 controls	Cases selected in three hospitals; neighbourhood controls
Whittemore *et al*. (1983) USA 1962–66	Men: 122 cases and 781 controls	Population-based study. Cases from the University of Harvard and University of Pennsylvania. Data obtained by postal survey. Controls: randomly selected classmates
Wynder *et al*. (1983) USA 1981	Men: 153 cases; women: 122 cases; 7994 controls	Hospital-based study. Cases from 15 hospitals. Controls: hospitalized patients without tobacco-related disease
Kinlen & McPherson (1984) UK 1952–54	Men: 109 cases and 218 controls; women: 107 cases and 214 controls	Cases not specified. Controls: patients with cancers unrelated to smoking
Gold *et al.* (1985) USA 1978–80	Men and women: 201 cases, 201 hospital controls and 201 community controls	Hospital-based study in 16 hospitals; 62% cases histologically confirmed. Hospital controls: patients with heart, other circulatory and digestive diseases excluding any type of cancer; matched to cases on age, ethnicity, sex, hospital and date of admission. Community controls: selected by random-digit dialling, matched to cases on age, ethnicity, sex and telephone exchange
Hsieh *et al.* (1986) USA 1981–84	Men and women: 176 cases and 273 controls	Hospital-based study in 11 large hospitals 100% cases histologically confirmed Controls: patients with cancers of the breast, colon, stomach, uterus, benign tumours, hernia, colitis enteritis or other minor conditions

Table 2.1.5.1 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Mack *et al.* (1986) USA 1976–81	Men and women: 490 cases and 490 controls	Population-based study. Histologically confirmed cases identified by cancer registry; neighbourhood controls matched on age, sex, ethnicity and place
Wynder *et al.* (1986) USA 1981–84	Men: 127 cases and 371 controls; women: 111 cases and 325 controls	Hospital-based study in 18 hospitals in six cities. Cases: identified by histology or discharge summary. About three controls/case, matched for sex, age, ethnicity, hospital, year of admission, without tobacco-related disease
La Vecchia *et al.* (1987) Italy 1983–86	Men: 99 cases and 471 controls; women: 51 cases and 134 controls	Hospital-based study. Cases histologically confirmed. Controls admitted to hospitals for traumatic or surgical conditions, orthopaedic disorders, disorders of ear, nose and throat, skin or teeth
Clavel *et al.* (1989) France 1982–85	Men: 98 cases and 161 controls; women: 63 cases and 107 controls	Hospital-based study; 63% of cases histologically confirmed; controls had cancers and benign conditions unrelated to smoking or alcohol; two controls matched to each case by age, sex, hospital and interviewer
Cuzick & Babiker (1989) UK 1983–86	Men: 123 cases and 150 controls; women: 93 casess and 129 controls	Hospital-based study in 3 major city hospitals; 30.1% of cases histologically confirmed. Hospital controls and general practitioner controls had diseases unrelated to smoking
Ferraroni *et al.* (1989) Italy 1983–88	Men: 136 cases and 1334 controls; women: 78 cases and 610 controls	Hospital-based study. All cases histologically confirmed
Falk *et al.* (1990) USA 1979–83	Men and women: 198 cases and 209 controls	Hospital-based study in 29 hospitals; 83% cases histologically confirmed. Hospital controls matched for ethnicity, age, sex and hospital
Baghurst *et al.* (1991) Australia 1984–87	Men and women: 104 cases and 253 controls	Population-based study within the IARC SEARCH[a] programme. Controls obtained from a random sample of the electoral roll. Analysis matched by age and sex
Bueno de Mesquita *et al.* (1991) Netherlands 1984–88	Men and women: 176 cases and 487 controls	Population-based study within the IARC SEARCH[a] programme; 68% of cases histologically confirmed. Controls selected from municipal population registries
Ghadirian *et al.* (1991) Canada 1984–88	Men: 97 cases and 239 controls; women: 82 cases and 116 controls	Population-based study within the IARC SEARCH[a] Programme; 83% of cases histologically confirmed. Controls selected by random-digit dialling and from telephone directories, and matched to cases on age, sex and residence

Table 2.1.5.1 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Howe *et al.* (1991) Canada 1983–86	Men: 141 cases and 270 controls; women: 108 cases and 235 controls	Population-based study within the IARC SEARCH[a] Programme; 69% of cases histologically confirmed. Controls selected randomly from population lists in the same study area
Vioque & Walker (1991) Multinational; early 1960s to beginning of 1980s	Men and women: 108 cases and 374 controls	Hospital-based study. Data collected by the Boston Collaborative Drug Surveillance Programme in six countries: Canada, Israel, New Zealand, Scotland, USA and former West Germany; age- sex- and hospital-matched controls
Lyon *et al.* (1992) USA 1984–87	Men and women: 149 cases and 363 controls	Population-based study. Cases from the Utah Cancer Registry. Controls selected by random-digit dialling
Mizuno *et al.* (1992) Japan 1989–90	Men: 68 cases and 68 controls; women: 56 cases and 56 controls	Hospital-based study in seven hospitals. Cases and hospital controls matched on age, sex and institute. Controls: patients with benign digestive, circulatory and other disorders
Kalapothaki *et al.* (1993) Greece 1991–92	Men: 115 cases, 115 hospital controls and 115 visitor controls; women: 66 cases, 66 hospital controls and 66 visitor controls	Hospital-based study in eight major teaching hospitals. Cases (all histologically confirmed) and controls matched by hospital, gender and age. Controls: patients with fractures, appendicitis, ear, nose and throat conditions, goitre, varicose veins and sciatica
Zatonski *et al.* (1993) Poland 1985–88	Men: 68 cases and 89 controls; women: 42 cases and 106 controls	Population-based study within the IARC SEARCH[a] programme; 43.6% cases histologically confirmed
Silverman *et al.* (1994) USA 1986–89	Men: 244 cases and 1328 controls; women: 235 cases and 774 controls	Population-based study; 85% cases histologically confirmed. Controls aged 30–64 years selected by random-digit dialling, those aged 65–79 years selected by stratified random sampling from the Health Care Financing Administration's rosters. Cases and controls matched by area, age, sex and ethnicity
Gullo *et al.* (1995) Italy 1987–89	Men: 319 cases; women: 251 cases; 570 matched controls	Hospital-based study in 14 university and community hospitals. Cases and controls matched for age, sex, socioeconomic status and area; 70% cases histologically confirmed. Controls: patients with minor trauma or disorders unrelated to alcohol, coffee or tobacco consumption
Ji *et al.* (1995) China 1990–93	Men: 264 cases and 852 controls; women: 187 cases and 701 controls	Population-based study among permanent residents of 10 urban districts; cases identified by the Shanghai Cancer Registry; 37% of cases histologically confirmed. Controls randomly selected from Shanghai residents' registry

Table 2.1.5.1 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Siemiatycki *et al.* (1995) Canada 1979–86	Men: 116 cases, 1705 hospital controls with cancer and 533 population controls	All cases histologically confirmed. Control group had cancer at sites not previously demonstrated as affected by cigarette smoking
Fernandez *et al.* (1996) Italy 1983–92	Men: 229 cases and 1031 controls; women: 133 cases and 377 controls	All cases histologically confirmed. Controls: hospital patients with acute, non-neoplastic, non-digestive, non-smoking- and non-alcohol-related disorders
Lee *et al.* (1996) China, Province of Taiwan 1989–94	Men and women: 282 cases and 282 controls	Hospital-based study; 45.7% of cases histologically confirmed. Controls matched on age and sex had no history of pancreatic cancer.
Nishi *et al.* (1996) Japan 1987–92	Men and women: 141 cases and 282 controls	Population-based study. Controls matched for sex, age and place of residence selected using random-digit dialling
Ohba *et al.* (1996) Japan 1987–92	Men: 85 cases; women: 56 cases; and 282 controls	Cases: data obtained by direct interview; 41.8% of cases histologically confirmed. Controls matched on age, sex and residence randomly selected from telephone directories, data collected from self-administered questionnaires and telephone back-up
Fryzek *et al.* (1997) USA 1994–95	Men and women: 66 cases and 131 controls	Hospital-based study in five large hospitals and two teaching hospitals. Cases diagnosed by cytology. Controls selected by random-digit dialling. Cases and controls matched by age, sex, ethnicity and county of residence
Muscat *et al.* (1997) USA 1985–93	Men: 290 cases and 572 controls; women: 194 cases and 382 controls	Hospital-based study; all cases histologically confirmed. Controls without pancreatic cancer hospitalized for conditions unrelated to tobacco use. Cases and controls matched by hospital, sex, age, ethnicity and year of diagnosis
Partanen *et al.* (1997) Finland 1984–87	Men and women: 662 cases and 1770 controls	Population-based study. Cases from the Finnish Cancer Registry diagnosed 1984–87 and decedent in 1990. Cancer controls include 1014 patients with stomach, 441 with colon and 315 with rectum cancers
Mori *et al.* (1999) India 1994–96	Men and women: 79 cases and 146 controls	Hospital-based study; 100% of cases of histologically confirmed pancreatic ductal adenocarcinoma. Controls selected from healthy hospital visitors, matched to cases on sex and age
Villeneuve *et al.* (2000) Canada 1994–97	Men: 322 cases and 2452 controls; women: 261 cases and 2361 controls	Population-based study in 8 provinces, within the Canadian National Enhanced Cancer Surveillance System (NECSS); all cases histologically confirmed. Strategies for selection of controls varied by province.

[a] SEARCH, Surveillance of Environmental Aspects Related to Cancer in Humans

Table 2.1.5.2. Additional cohort studies on tobacco smoking and cancer of the pancreas

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Hammond & Horn (1958a,b) USA 1952–55	American Cancer Society Study 187 783 men	117 deaths		Regular smoker	1.5	
Hammond (1966) USA 1959–63	Cancer Prevention Study (CPS) I 440 558 men and 562 671 women	274 men, 108 women		Men	Mortality ratio	
				Ever-smoker		
				aged 45–64 years	2.7	
				aged 65–79 years	2.7	
				Women		
				Ever-smoker	1.8	
				Heavy smoker	2.6	
Kahn (1966) USA 1954–62	US Veterans' Study 293 958 men	415 deaths		Former smoker	1.3	
				Occasional smoker	1.1	
				Cigarettes/day		
				1–9	1.4	
				10–20	1.8	
				21–39	2.2	
				≥ 40	2.7	
Lossing *et al.* (1966) Canada 1956–62	Canadian War Veterans Study 78 000 men	28 deaths in cigarette smokers		Cigarettes/day		Number of nonsmoking men not given
				1–9	1.4	
				10–20	2.0	
				≥ 21	2.4	
Weir & Dunn (1970) USA 1954–62	Californian Study 68 153 men	71 deaths		Ever-smoker	2.4	Decreasing relative risk with increasing consumption unexplained
				Cigarettes/day		
				1–10	2.9	
				20	2.5	
				≥ 30	1.4	

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Cederlöf *et al.* (1975) Sweden 1963–72	Swedish Census Study 25 444 men, 26 467 women	46 deaths in men		Former smoker	4.8 ($p < 0.05$)	
				Cigarettes/day		
				1–7	1.6	
				8–15	3.4	
				≥ 16	5.9	
		37 deaths in women		Former smoker	5.5	
				Cigarettes/day		
				1–7	2.4	
				8–15	2.5	
				≥ 16	3.0	
Doll & Peto (1976) UK 1951–71	British Doctors' Study 34 440 men	78 deaths		Tobacco (g)/day	Mortality rate	Annual mortality rate per 100 000 men
				0	14	
				1–14	14	
				15–24	18	
				≥ 25	27	*p* for trend < 0.1
				Former smoker	12	
Doll *et al.* (1980) UK 1951–73	British Doctors' Study 6194 women	14 deaths		Tobacco (g)/day	Mortality rate	Annual mortality rate per 100 000 women
				0	9	
				1–14	4	
				15–24	24	
				≥ 25	16	
				Former smoker	11	
Hirayama (1981) Japan 1965–78	Six-prefecture Study 122 261 men, 142 857 women	251 deaths in men			Mortality rate	Annual mortality rate per 100 000 men
				Never-smoker	13.3	
				Former smoker	15.4	
				Occasional smoker	12.8	
				Cigarettes/day		
				1–9	14.7	
				10–19	19.8	
				≥ 20	20.3	

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Hirayama (1981) (contd)		417 deaths (251 men, 166 women)		 Current smoker	Relative risk 1.6	Relative risk for men and women combined. Effect persisted after adjustment for social class and meat and green/leafy vegetable consumption
Heuch *et al.* (1983) Norway 1967–78	[About 11 000] Norwegian men (some overlap with Norwegian Cohort Study)	22 cases		≥ 10 cigarettes/day	2.0 (p = 0.087)	Analysis confined to histologically confirmed cases
Hiatt *et al.* (1988) USA 1978–85	Kaiser Permanente Medical Care Program Study II 122 894 persons	49 cases	Age, sex, ethnic origin, blood glucose, alcohol, coffee and tea	Former smoker Current smoker < ½ pack/day ½–1 pack/day 1–2 packs/day > 2 packs/day	0.8 (0.4–2.0) 1.8 (0.4–8.1) 1.9 (0.6–6.2) 2.1 (0.6–8.2) 6.6 (1.4–31.8)	Nested case–control study
Mills *et al.* (1988) USA 1976–82	Adventists' Health Study 34 198 persons	40 cases	Age and sex	Former smoker Current smoker	1.5 (0.7–3.4) 5.4 (1.8–16.5)	

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Hirayama (1989) Japan 1965–81	Six-prefecture Study 122 261 men, 142 857 women	679 deaths (399 men, 280 women)		Daily smoker		
				Men	1.6 (1.2–2.0)	
				Women	1.5 (1.0–1.9)	
			Age		Mortality rate	
				1–14 cigarettes/day	24.6	
				15–29 cigarettes/day	26.5	
				30–39 cigarettes/day	28.4	
				40–49 cigarettes/day	30.7	
				≥ 50 cigarettes/day	43.9	*p* for trend = 0.002
Akiba & Hirayama (1990) Japan 1965–81	Six-prefecture Study 122 261 men, 142 857 women	554 deaths (322 men, 232 women)	Age, prefecture of residence, occupation and observation period	Ever-smokers (men)	1.5 (1.1–2.1)	
				1–4 cigarettes/day	1.1 (0.3–2.7)	
				5–14 cigarettes/day	1.5 (1.1–2.1)	
				15–24 cigarettes/day	1.6 (1.2–2.2)	*p* for trend = 0.04
				25–34 cigarettes/day	1.2 (0.6–2.2)	*p* for heterogeneity = 0.07
				≥ 35 cigarettes/day	1.3 (0.4–2.9)	
				Ever-smokers (women)	1.6 (1.1–2.3)	
				1–4 cigarettes/day	0.6 (0.1–1.9)	
				5–14 cigarettes/day	1.9 (1.2–2.8)	*p* for trend = 0.02
				≥ 15 cigarettes/day	1.4 (0.4–3.4)	*p* for heterogeneity = 0.03
Kuller *et al.* (1991) USA 1975–85	MRFIT Study		Age, diastolic blood pressure, serum choles-terol levels and race	Current smoker	2.0 ($p < 0.0001$)	

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Friedman & van den Eeden (1993) USA 1964–88	Kaiser Permanente Medical Care Program Study I 175 000 persons	450 cases, 2687 controls	Ethnicity and age	Former smoker	1.3	Nested case–control study; controls matched for sex, age, examination site, date of check-up
				Current smoker		
				> 20 years	1.6 (1.1–2.2)	
				< 1 pack/day	1.8 ($p < 0.01$)	
				1–2 packs/day	1.6 ($p < 0.01$)	
				> 2 packs/day	3.0 ($p < 0.01$)	
Tverdal *et al.* (1993) Norway 1972–88	Norwegian Screening Study 44 290 men, 24 535 women	57 deaths	Age and area		Mortality rate	Annual mortality rate per 100 000 persons
				Never-smoker	4.4 (127 325 person–years)	
				Former smoker	6.3 (144 776 person–years	
				Current smoker	13.5 (248 159 person–years)	
				1–9 cigarettes/day	5.5 (56 350 person–years)	
				10–19 cigarettes/day	17.2 (135 167 person–years)	
				≥ 20 cigarettes/day	14.9 (56 441 person–years)	
				Relative risk per 10 cigarettes/day	1.5 (0.9–2.3)	
Zheng *et al.* (1993) USA 1966–86	Lutheran Brotherhood Insurance Study 17 633 men 286 731 person–years	57 deaths	Age and alcohol	Former smoker	1.0 (0.4–2.2)	
				Current smoker		
				< 25 cigarettes/day	1.4 (0.6–3.2)	
				≥ 25 cigarettes/day	3.9 (1.5–10.3)	p for trend ≤ 0.01
Doll *et al.* (1994) UK 1951–91	British Doctors' Study 34 439 men	205 deaths			Mortality rate	Annual mortality rate per 100 000 men
				Nonsmoker	16	
				Former cigarette smoker	23	
				Current cigarette smoker	35	p for trend = 0.001
				1–14 cigarettes/day	30	
				15–24 cigarettes/day	29	
				≥ 25 cigarettes/day	49	p for trend = 0.001

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Shibata *et al.* (1994) USA 1981–90	Leisure World Study 13 979 persons 100 921 person–years	65 cases (28 men, 37 women)	Sex and age	Former smoker (quit ≥ 20 years)	1.4 (0.7–2.6)	
				Recent quitter (< 20 years) and current smoker	1.2 (0.7–2.2)	
McLaughlin *et al.* (1995) USA 1954–80	US Veterans' Study 248 046 men 3 252 983 person–years	1264 deaths	Attained age and calendar-year time-period	Former smoker	1.1 (0.9–1.3)	
				Current smoker	1.7 (1.5–1.9)	
				1–9 cigarettes/day	1.4 (1.1–1.8)	
				10–20 cigarettes/day	1.7 (1.4–1.9)	
				31–39 cigarettes/day	1.8 (1.5–2.2)	
				≥ 40 cigarettes/day	1.6 (1.1–2.3)	p for trend < 0.01
Engeland *et al.* (1996) Norway 1966–93	Norwegian Cohort Study 11 857 men and 14 269 women Person–years: about 230 000 men and 310 000 women	224 cases (109 men, 115 women, 55% histo-logically verified)		Men		
				Former smoker	0.9 (0.6–1.5)	
				Current smoker		
				1–4 cigarettes/day	0.9 (0.5–1.8)	
				5–9 cigarettes/day	1.0 (0.5–2.1)	
				10–14 cigarettes/day	1.3 (0.7–2.4)	
				≥ 15 cigarettes/day	1.6 (0.8–3.2)	
				Unknown consumption	7.9 (1.1–58)	
				Women		
				Former smoker	0.6 (0.2–1.5)	
				Current smoker		
				1–4 cigarettes/day	0.9 (0.4–1.8)	
				≥ 5 cigarettes/day	1.8 (1.1–3.0)	

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Fuchs *et al.* (1996) USA 1980–92	Nurses' Health Study (1976–92) and Health Professionals Follow Up Study (1986–94) 49 428 men 2 116 229 person–years	186 cases	Sex, body-mass index, history of diabetes mellitus and age	Men		
				Former smoker	1.3 (0.7–2.3)	
				Current smoker	3.0 (1.6–6.3)	
				1–10 pack–years	0.9 (0.3–2.6)	
				11–25 pack–years	1.3 (0.7–2.7)	
				26–50 pack–years	1.5 (0.7–3.1)	
				> 50 pack–years	2.8 (1.3–5.7)	*p* for trend = 0.004
				Women		
				Former smoker	1.1 (0.7–1.7)	
				Current smoker	2.4 (1.6–3.6)	
				1–10 pack–years	1.1 (0.6–1.9)	
				11–25 pack–years	1.6 (1.0–2.7)	
				26–50 pack–years	2.1 (1.4–3.3)	
				> 50 pack–years	1.3 (0.7–2.7)	*p* for trend = 0.01
				All		
				Former smoker	1.2 (0.8–1.7)	
				Current smoker	2.5 (1.7–3.6)	
				1–10 pack–years	1.0 (0.6–1.6)	
				11–25 pack–years	1.5 (1.0–2.3)	
				26–50 pack–years	1.9 (1.3–2.8)	
				> 50 pack–years	1.8 (1.1–3.0)	*p* for trend = 0.04
				Current consumption		
				Men		
				1–10 pack–years	1.3 (0.3–5.4)	
				11–25 pack–years	2.7 (1.4–5.1)	
				26–50 pack–years	2.8 (1.8–4.4)	
				> 50 pack–years	2.1 (1.2–3.8)	*p* for trend < 0.001

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Fuchs *et al.* (1996) (contd)				Women		
				1–10 pack–years	1.0 (0.6–1.7)	
				11–25 pack–years	1.2 (0.7–2.0)	
				26–50 pack–years	1.2 (0.7–2.1)	
				> 50 pack–years	1.3 (0.6–2.9)	*p* for trend = 0.03
				Past consumption		
				< 15 years		
				1–5 pack–years	0.6 (0.5–6.5)	
				6–15 pack–years	3.9 (0.9–16)	
				16–25 pack–years	4.8 (1.1–22)	
				> 25 pack–years	5.5 (1.1–27)	*p* for trend = 0.01
				≥ 15 years		
				1–5 pack–years	1.6 (0.3–8.1)	
				6–15 pack–years	0.5 (0.1–2.3)	
				16–25 pack–years	0.8 (0.2–3.3)	
				> 25 pack–years	0.5 (0.1–2.2)	*p* for trend = 0.69
Murata *et al.* (1996) Japan 1984–93	Chiba Center Association Study			Cigarettes/day		Small study; small number of cases
		2		1–10	0.3	
		12		11–20	0.7	
		5		≥ 21	0.8	
Yuan *et al.* (1996) China 1986–93	Shanghai Men's Study 18 244 98 267 person– years	21 cases	Age and alcohol consumption	Ever-smoker	1.8	No significant dose– response relationship
				< 20 cigarettes/day	1.5	
				≥ 20 cigarettes/day	2.1	
Harnack *et al.* (1997) USA 1986–94	Iowa Women's Health Study 33 976 women 291 598 person– years	66 cases	Age	Former smoker	1.1 (0.6–2.1)	
				Ever-smoker	2.4 (1.3–4.2)	
				Current smoker		
				< 20 pack–years	1.1 (0.5–2. 5)	
				≥ 20 pack–years	1.9 (1.1–3.3)	*p* for trend = 0.02

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Liaw & Chen (1997) China, Province of Taiwan 1982–94	Taiwanese Study	15 cases		Current smoker	0.3 (0.1–0.9)	Analysis for men only because of small number of deaths in women; small number of cases
Nordlund *et al.* (1997) Sweden 1963–89	Swedish Census Study 26 032 women 600 000 person–years	144 cases	Age and place of residence	Former smoker	2.5 (1.1–5.3)	
				Current smoker	1.8 (1.1–2.9)	
				1–7 cigarettes/day	2.0 (1.2–3.5)	
				8–15 cigarettes/day	1.4 (0.6–3.4)	
				≥ 16 cigarettes/day	1.6 (0.4–6.7)	
			Age, place of residence and amount of tobacco smoked daily	Age at starting smoking (years)		
				20–23	1.1 (0.3–3.2)	
				< 19	0.6 (0.1–2.8)	p for trend = 0.6
Tulinius *et al.* (1997) Iceland 1968–95	Reykjavík Study 11 366 men, 11 580 women	101 cases (65 men, 36 women)	Age	Men		
				Former smoker	2.4 (0.7–7.6)	
				1–14 cigarettes/day	7.2 (2.3–22.3)	
				15–24 cigarettes/day	10.2 (3.4–30.6)	
				≥ 25 cigarettes/day	12.5 (3.7–41.7)	
				Women		
				Former smoker	0.9 (0.3–2.8)	
				1–14 cigarettes/day	1.5 (0.7–3.5)	
				15–24 cigarettes/day	1.7 (0.6–4.4)	
				≥ 25 cigarettes/day	4.5 (1.0–20.1)	

Table 2.1.5.2 (contd)

Reference Country and years of study	Subjects	No. of cases and/or deaths	Covariates adjusted for	Smoking category and/or amount smoked	Relative risk (95% CI)	Comments
Stolzenberg-Solomon *et al.* (2001) Finland 1985–88	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study 27101 men	157 cases	Age (continuous) and intervention (α-tocopheral and β-carotene supplements)	Cigarettes/day		All reference groups comprise light smokers.
				< 14	1.0	
				14–19	1.4 (0.9–2.4)	
				20	1.1 (0.7–1.9)	
				21–25	1.3 (0.8–2.3)	
				> 25	1.8 (1.1–3.0)	*p* for trend = 0.05
				Duration (years)		
				< 30	1.0	
				30–34	1.1 (0.6–2.1)	
				35–39	1.2 (0.7–2.0)	
				40–42	1.5 (0.9–2.5)	
				> 42	1.4 (0.8–2.6)	*p* for trend = 0.22
				Pack–years		
				< 22	1.0	
				22–31	1.2 (0.7–2.0)	
				32–39	1.3 (0.7–2.1)	
				40–49	1.3 (0.7–2.1)	
				> 49	1.7 (1.0–2.7)	*p* for trend = 0.04
				Age at starting smoking (years)		
				< 17	1.0	
				17–18	0.9 (0.6–1.4)	
				19	1.0 (0.5–1.9)	
				20–21	0.9 (0.5–1.4)	
				> 21	1.0 (0.6–1.6)	*p* for trend = 0.85
				Smoke inhalation		
				Never/seldom	1.0	
				Often	0.9 (0.5–1.7)	
				Always	1.3 (0.7–2.2)	*p* for trend = 0.14

CI, confidence interval

Table 2.1.5.3. Case–control studies on tobacco smoking and cancer of the pancreas

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Wynder *et al*.	Men	*Cigarettes/day*		
(1973)		1–10	2.0	
USA		11–20	2.2	$p < 0.25$
1950–64		21–40	3.6	$p < 0.5$
		≥ 41	5.0	Calculated by the Working Group
	Women	1–10	0.7	
		11–20	5.3	
		21–40	1.6	
		≥ 41	0	
MacMahon *et al*.	Men	*Cigarettes/day*		Adjusted for age and sex
(1981)		1–19	1.1	
USA		≥ 20	1.4	
1974–79		Former smoker	1.4	
	Women	1–19	1.5	
		≥ 20	1.6	
		Former smoker	1.3	
Durbec *et al*. (1983) France 1979–80	Men and women		1.3 per 10 g/day current intake	Adjusted for age, sex, neighbourhood and alcohol consumption
Whittemore *et al*.		*Packs/year*		Adjusted for age and years of schooling
(1983)		1–19	1.0	
USA		10–19	2.1	
1962–66		20–29	2.4	
		≥ 30	2.5	Overall $p < 0.05$
Wynder *et al*.	Men	*Cigarettes/day*		Adjusted for age
(1983)		1–10	0.9	
USA		11–20	2.1 ($p < 0.05$)	
1981		21–30	2.3 ($p < 0.05$)	
		> 31	3.0 ($p < 0.05$)	
		Former smoker	1.7 ($p < 0.05$)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Wynder *et al*. (1983) (contd)	Women	*Cigarettes/day*		
		1–10	1.8	
		11–20	1.5	
		21–30	2.0 ($p < 0.05$)	
		Former smoker	1.4	
Kinlen & McPherson (1984) UK 1952–54	Men	*Cigarettes/week*		Adjusted for age and sex
		10–49	1.3 (0.5–3.2)	
		50–149	1.6 (0.8–3.1)	
		≥ 150	1.05 (0.4–3.0)	
		Pipe	1.2 (0.6–2.6)	
	Women	10–49	1.1 (0.4–2.9)	
		50–149	1.6 (0.6–4.1)	
Gold *et al.* (1985) USA 1978–80	Men and women	Ever-smoker	1.4 (0.8–2.3)	Hospital controls
		Smoker > 5 years	1.1 (0.1–1.9)	
		Smoker ≥ 1 pack/day	0.9 (0.6–1.5)	
		Never quitter	1.7 (0.9–3.4) ($p = 0.092$)	
	Men and women	Ever-smoker	1.2 (0.7–2.0)	Community controls
		Smoker > 5 years	1.2 (0.7–2.0)	
		Smoker ≥ 1 pack/day	1.3 (0.8–2.2)	
		Never quitter	2.7 (1.3–5.7) ($p = 0.0064$)	
Hsieh *et al.* (1986) USA 1981–84	Men and women	Former smoker	1.0 (0.6–1.7)	Adjusted for age and sex
		Current smoker <1 pack/day	1.8 (0.8–3.9)	
		Current smoker ≥ 1 pack/day	1.9 (1.1–3.3)	
		χ^2 for trend	5.0 ($p = 0.03$)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Mack *et al.* (1986) USA 1976–81	Men and women	*Pack/day*		
		≤ 1	2.4 (1.7–3.6)	
		> 1	2.1 (1.4–3.2)	
	Men	≤ 1	1.8 (1.3–20.8)	
	Women	≤ 1	2.9 (1.5–5.8)	
Wynder *et al.* (1986) USA 1981–84	Men	Former smoker	1.3 (0.7–2.4)	
		Cigarettes/day		
		1–20	3.5 (1.8–6.5)	
		≥ 21	2.9 (1.5–5.7)	
	Women	Former smoker	1.2 (0.7–2.1)	
		Cigarettes/day		
		1–20	1.5 (0.8–2.7)	
		≥ 21	4.8 (2.4–9.5)	
La Vecchia *et al.* (1987) Italy 1983–86	Men and women	≥ 15 cigarettes/day	1.4 (0.9–2.1)	Adjusted for sex and age
Clavel *et al.* (1989) France 1982–85	Men	Former smoker	1.0 (0.5–2.14)	Adjusted for foreign origin, educational level, coffee and alcohol consumption
		Cigarettes/day		
		1–20	1.7 (0.8–3.7)	
		≥ 21	1.4 (0.6–3.5)	
		Years of cigarette smoking		
		1–29	0.8 (0.4–1.9)	
		30–39	1.0 (0.5–2.3)	
		≥ 40	1.9 (0.8–4.3)	
		Years at first cigarette		
		≤ 17	1.8 (0.7–4.3)	
		18–19	0.9 (0.4–2.2)	
		≥ 20	1.5 (0.7–3.0)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Clavel *et al.* (1989) (contd)	Women	Former smoker	0.8 (0.3–2.5)	
		Cigarettes/day		
		1–20	1.0 (0.3–3.3)	
		≥ 21	2.7 (0.5–14.1)	
		Years of cigarette smoking		
		1–29	1.0 (0.4–2.6)	
		30–39	0.9 (0.2–3.7)	
		≥ 40	1.7 (0.4–6.7)	
		Years at first cigarette		
		≤ 17	3.4 (0.7–15.9)	
		18–19	0.4 (0.0–6.0)	
		≥ 20	0.9 (0.4–2.2)	
Cuzick & Babiker (1989) UK 1983–86	Men	*Cigarettes/day*		Adjusted for age, sex and social class
		< 10	1.3	
		10–20	1.7	
		> 20	4.1 ($p < 0.01$)	
		χ^2 for trend	5.74 ($p < 0.05$)	
	Women	< 10	0.8	
		10–20	1.1	
		> 20	5.5 ($p < 0.1$)	
		χ^2 for trend	1.11 ($p > 0.05$)	
	Men and women	< 10	1.1	
		10–20	1.3	
		> 20	4.4 ($p < 0.01$)	
		χ^2 for trend	5.80 ($p < 0.01$)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Ferraroni *et al.* (1989) Italy 1983–88	Men and women	Former smoker	1.2	Adjusted for age, sex, alcohol, education, marital status, coffee consumption; *p* for trend: 1.25. No difference when adjusted for age and sex only
		Current cigarette smoker		
		Cigarettes/day		
		< 15	0.8	
		15–24	1.2	
		≥ 25	1.4	
Falk *et al.* (1990) USA 1979–1983	Men	*Cigarettes/day*		Adjusted for age, type of respondent, ethnicity, area of residence, income, and pork and fruit intake
		1–19	1.7	
		20–29	2.3 ($p = 0.05$)	
		≥ 30	1.8	
Baghurst *et al.* (1991) Australia 1984–87	Men and women	Former smoker	1.1 (0.6–2.2)	χ^2 for trend with increasing alcohol consumption: 8.26 ($p = 0.004$)
		Current smoker	1.8 (0.9–3.3)	
Bueno de Mesquita *et al.* (1991) The Netherlands 1984–88	Men and women	All smokers		Adjusted for age, sex, response type, energy intake and vegetable consumption
		Cigarettes in lifetime		
		Low ≤ 111 200	1.4 (0.8–2.5)	
		High > 111 200	1.7 (1.0–3.1)	
		χ^2 for trend	3.26	
		Current smoker		
		Low	1.6 (0.7–3.8)	
		High	2.0 (1.0–4.0) ($p < 0.05$)	
		χ^2 for trend	4.02 ($p < 0.05$)	
		Current smoker ≤ 43 years		
		Low	2.1 (0.8–5.5)	
		High	2.3 (0.9–6.1)	
		χ^2 for trend	3.52	
		Current smoker ≥ 44 years		
		Low	0.7 (0.1–6.7)	
		High	1.8 (0.8–4.4)	
		χ^2 for trend	1.69	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Bueno de Mesquita *et al.* (1991) (contd)		Former smoker		
		Cigarettes in lifetime		
		Low ≤ 111 200	1.4 (0.7–2.6)	
		High > 111 200	1.1 (0.4–2.7)	
		χ^2 for trend	0.24	
Ghadirian *et al.* (1991) Canada 1984–88	Men and women	Former smoker		Adjusted for age, sex, schooling and response type
		Cigarettes (lifetime)		
		< 104 025	1.0 (0.3–2.8)	
		104 025–219 000	3.4 (1.2–9.4)	
		219 000–405 150	5.4 (1.8–16.7)	
		> 405 150	4.0 (1.3–12.2)	
		χ^2 for trend	11.70	
		Years of smoking		
		1–20	1.2 (0.4–3.4)	
		21–32	2.9 (1.0–8.1)	
		33–39	3.0 (1.1–8.7)	
		> 39	6.2 (2.0–19.5)	
		χ^2 for trend	11.97	
		Current smoker		
		Cigarettes (lifetime)		
		<146 000	3.6 (1.3–10.0)	
		146 000–301 125	1.9 (0.7–5.4)	
		301 125–459 900	2.4 (0.9–6.2)	
		> 459 900	5.2 (1.7–16.1)	
		χ^2 for trend	8.30	
		Years of smoking		
		1–28	2.1 (0.6–7.2)	
		29–40	2.9 (1.0–8.3)	
		41–48	3.0 (1.1–8.7)	
		> 48	3.2 (1.1–9.2)	
		χ^2 for trend	9.03	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Howe *et al.* (1991) Canada 1983–86	Men	*Packs/year*		Adjusted for calorie and fibre intakes
		0–17.9	0.9 (0.4–1.9)	
		17.9–37.5	1.6 (0.8–3.1)	
		> 37.5	1.6 (0.8–3.2)	
	Women	0–17.9	1.4 (0.7–2.8)	
		17.9–37.5	3.4 (1.5–7.5)	
		> 37.5	4.7 (2.0–11.4)	
	Men and women	Former smoker		
		Packs/year		
		0–17.9	0.7 (0.4–1.3)	
		17.9–37.5	1.6 (0.8–3.2)	
		> 37.5	1.2 (0.6–2.6)	
		Current smoker		
		Packs/year		
		0–17.9	2.1 (1.0–4.5)	
		17.9–37.5	2.9 (1.6–5.4)	
		> 37.5	3.4 (1.9–6.1)	
Vioque & Walker (1991) Multinational; early 1960s to beginning of 1980s	Men and women	Former smoker	0.9 (0.4–1.7)	Adjusted for blood type, age, sex and hospital
		Current smoker	2.3 (0.7–7.3)	
		Packs/day		
		0.5	1.2 (0.5–3.0)	
		1	1.6 (0.8–3.3)	
		≥ 2	1.8 (0.7–4.7)	
Lyon *et al.* (1992) USA 1984–87	Men and women	*Packs/year*		Adjusted for age, coffee consumption and religion
		1–25	1.0 (0.5–2.1)	
		≥ 25	2.7 (1.4–5.2)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Mizuno *et al.* (1992) Japan 1989–90	Men, at onset of study	Ever-smoker	2.4 (1.1–5.3)	Adjusted for age, sex and place of enrolment
		Current smoker	2.8 (1.2–6.4)	
		Cigarettes/day		
		Light smoker (1–12)	6.2 (1.7–22.8)	
		Medium smoker (13–22)	1.8 (0.7–4.9)	
		Heavy smoker (≥ 23)	2.5 (0.8–7.6)	
	Men, 10 years prior study	Former smoker	1.2 (0.4–3.4)	
		Cigarettes/day		
		Light smoker (1–12)	4.5 (1.5–13.2)	
		Medium smoker (13–22)	2.6 (1.0–6.5)	
		Heavy smoker (≥ 23)	2.6 (0.9–7.0)	
Kalapothaki *et al.* (1993) Greece 1991–92	Men and women versus hospital controls	*Cigarettes/day*		Adjusted for age, sex and hospital
		1–10	1.3 (0.5–2.9)	
		11–20	1.5 (0.9–2.7)	
		≥ 21	1.4 (0.8–2.4)	
	Men and women versus visitor controls	1–10	1.0 (0.5–2.3)	
		11–20	1.9 (1.0–3.5)	
		≥ 21	1.8 (0.9–3.6)	
Zatonski *et al.* (1993) Poland 1985–88	Men and women	Ever-smoker	1.5 (0.8–2.8)	Quartiles lifetime cigarette consumption. Adjusted for schooling, age and sex
		Quartile 2	0.8 (0.4–1.8)	
		Quartile 3	2.9 (1.3–6.6)	
		Quartile 4	1.5 (0.7–3.5)	
		χ^2 for trend	3.52 (p = 0.06)	
Silverman *et al.* (1994) USA 1986–89	Men	Years of smoking		Adjusted for age, ethnicity, sex, area, income, alcohol consumption and gallbladder disease
		< 20	1.4 (0.8–2.3)	
		20–39	1.6 (1.1–2.4)	
		≥ 40	1.7 (1.1–2.7)	
		p for trend	0.009	
	Women	< 20	0.7 (0.3–1.3)	
		20–39	2.0 (1.3–3.0)	
		≥ 40	2.8 (1.8–4.3)	
		p for trend	< 0.0001	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Silverman *et al.* (1994) (contd)	Men and women	Ever-smoker	1.7 (1.3–2.2)	
		Former smoker	1.4 (1.1–1.9)	
		Current smoker	2.0 (1.5–2.6)	
		Cigarettes/day		
		< 20	1.3 (0.9–1.7)	
		20–39	2.2 (1.7–3.0)	
		≥ 40	1.8 (1.2–2.8)	
		p for trend	< 0.0001	
		Years of smoking		
		< 20	1.1 (0.7–1.6)	
		20–39	1.8 (1.3–2.4)	
		≥ 40	2.1 (1.6–2.9)	
		p for trend	< 0.0001	
		Packs/year		
		< 20	1.3 (0.9–1.7)	
		20–44	1.9 (1.4–2.6)	
		≥ 45	2.2 (1.6–3.1)	
		p for trend	< 0.0001	
Gullo *et al.* (1995) Italy 1987–89	Men	Former smoker	0.6 (0.4–0.9)	Adjusted for age
		Current cigarette smoker		
		Cigarettes/day		
		≤ 20	0.9 (0.6–1.5)	
		> 20	1.6 (0.9–2.8)	
	Women	Former smoker	1.0 (0.5–1.9)	
		Current cigarette smoker		
		Cigarettes/day		
		≤ 20	2.2 (1.3–3.7)	
		> 20	0.6 (0.1–2.7)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Gullo *et al*. (1995) (contd)	Men and women	Former smoker	0.7 (0.5–1.0)	Adjusted for age and sex
		Current cigarette smoker		
		Cigarettes/day		
		≤ 20	1.3 (1.0–1.9)	
		> 20	1.4 (0.8–2.4)	
Ji *et al*. (1995) China 1990–93	Men	Former smoker	1.2 (0.8–2.0)	Adjusted for income and age (men), income, age, education and green tea drinking (women). Results not affected when analysis restricted to cases with histological confirmation; or whether or not interviews were conducted with next of kin or directly with the subject. Attributable risk: 24.3% (men, 95% CI, 7.1–41.3); 5.9% (women, 95% CI, 1.6–13.4)
		Current smoker	1.6 (1.1–2.2)	
		Cigarettes/day		
		1–9	0.9 (0.5–1.6)	
		10–19	1.3 (0.8–2.0)	
		20–29	1.7 (1.1–2.4)	
		≥ 30	5.0 (2.7–9.3)	
		p for trend	< 0.0001	
		Years of smoking		
		0.5–19	0.8 (0.4–1.5)	
		20–29	1.4 (0.8–2.3)	
		30–39	1.7 (1.0–2.7)	
		≥ 40	2.3 (1.5–3.5)	
		p for trend	< 0.001	
		Packs/year		
		< 15	0.8 (0.5–1.4)	
		15–34	1.5 (1.0–2.2)	
		≥ 35	2.4 (1.6–3.6)	
		p for trend	< 0.0001	
		Age at starting smoking (years)		
		≥ 30	1.5 (1.0–2.3)	
		20–29	1.6 (1.1–2.3)	
		< 20	1.7 (1.0–2.6)	
		p for trend	0.01	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Ji *et al*. (1995) (contd)	Women	Former smoker	1.6 (0.6–4.0)	
		Current smoker	1.4 (0.9–2.4)	
		Cigarettes/day		
		1–9	1.1 (0.5–2.3)	
		10–19	1.3 (0.5–3.2)	
		≥ 20	2.8 (1.1–7.0)	
		p for trend	0.05	
		Years of smoking		
		0.5–19	0.6 (0.2–2.2)	
		20–29	1.4 (0.5–4.0)	
		30–39	1.7 (0.7–4.4)	
		≥ 40	2.0 (0.9–4.4)	
		p for trend	0.06	
		Packs/year		
		< 10	1.0 (0.5–2.0)	
		≥ 10	2.0 (1.0–3.8)	
		p for trend	0.07	
		Age at starting smoking (years)		
		≥ 25	1.2 (0.6–2.1)	
		< 25	2.4 (1.0–5.6)	
		p for trend	0.07	
Siemiatycki *et al.* (1995) Canada 1979–86	Men	Ever-smoker	1.6 (0.9–3.0)	Adjusted for age
		Packs/year		
		≤ 25	1.2 (0.5–2.6)	*p* for trend < 0.05
		25–49	1.7 (0.9–3.5)	
		50–74	1.8 (0.8–3.7)	
		≥ 75	1.9 (0.9–4.1)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Fernandez *et al.* (1996) Italy 1983–92	Men	Former smoker	1.4 (0.9–1.2)	Adjusted for sex, age, area, education and risk factors for pancreatic cancer identified in this population
		Current smoker	1.3 (0.9–1.9)	
	Women	Former smoker	0.9 (0.4–2.0)	
		Current smoker	1.3 (0.8–2.2)	
	Men and women	Former smoker	1.3 (0.9–1.9)	
		Current smoker	1.3 (0.9–1.7)	
Lee *et al.* (1996) China, Province of Taiwan 1989–94	Men and women (all cases)	Ever-smoker	2.3 (1.6–3.3) ($p < 0.01$)	Multivariate model unspecified. Odds ratios for histologically confirmed cases were similar
		Cigarettes/day		
		< 10	2.0 (1.0–4.0)	
		10–20	2.2 (1.4–3.4)	
		> 20	2.7 (1.6–4.7)	
		χ^2 for trend	22.02 ($p < 0.001$)	
		Years of smoking		
		≤ 10	1.4 (0.3–6.8)	
		11–20	1.3 (0.5–3.3)	
		21–30	2.7 (1.1–6.4)	
		> 30	2.5 (1.7–3.7)	
		χ^2 for trend	24.37 ($p < 0.001$)	
		Smoking index (consumption × duration)		
		< 500	1.7 (1.0–3.2)	
		500–999	2.4 (1.5–4.1)	
		≥ 1000	2.6 (1.6–4.4)	
		χ^2 for trend	22.45 ($p < 0.001$)	
Nishi *et al.* (1996) Japan 1987–92	Men and women	Current smoker	1.5 (0.8–3.1)	Among never-drinkers of coffee
			2.0 (0.9–4.2)	Among drinkers of ≥ 3 cups of coffee/day
				Adjusted for age and sex
Ohba *et al.* (1996) Japan 1987–92	Men and women	Former smoker	1.3 (0.7–2.1)	Univariate model. Smoking rates of the study place (Hokkaido) higher than national average
		Current smoker	1.3 (0.8–2.0)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Fryzek *et al.* (1997) USA 1994–95		Former smoker	1.8 (0.9–3.6)	Included cases who quit within 1 year prior to interview
		Ever-smoker	2.0 (1.1–3.8)	
		Current smoker	2.5 (1.1–5.4) ($p < 0.05$)	
		p for trend	0.02	
Muscat *et al.* (1997) USA 1985–93	Men	Former smoker	1.0 (0.7–1.5)	Adjusted for age and education
		Current smoker	1.6 (1.1–2.4)	
		Cigarettes/day		
		1–19	1.5 (0.9–2.4)	
		20–39	1.4 (0.7–2.8)	
		≥ 40	1.8 (0.9–3.6)	
		Years of smoking		
		1–9	0.8 (0.4–1.5)	
		10–19	1.0 (0.6–1.8)	
		20–29	1.3 (0.8–2.0)	
		30–39	1.4 (0.9–2.2)	
		≥ 40	1.3 (0.8–2.1)	
		p for trend	< 0.14	
	Women	Former smoker	1.9 (1.3–2.9)	
		Current smoker	2.3 (1.4–3.5)	
		Cigarettes/day		
		1–19	2.1 (1.3–3.6)	
		20–39	2.3 (0.8–6.3)	
		≥ 40	5.6 (2.0—5.8)	
		Years of smoking		
		1–9	1.3 (0.5–3.6)	
		10–19	1.7 (0.8–3.7)	
		20–29	2.4 (1.3–4.4)	
		30–39	2.2 (1.4–3.7)	
		≥ 40	2.1 (1.3–3.4)	
		p for trend	< 0.01	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Partanen *et al.* (1997) Finland 1984–87	Men and women	Occasional smoker	1.7 (1.0–2.9)	Adjusted for age and sex
		Cigarettes/day		
		1–9	1.6 (1.2–2.2)	
		10–20	1.9 (1.5–2.5)	
		≥ 20	2.3 (1.7–3.2)	
		All smokers (includes smokers of cigarettes, pipes and cigars)	2.0 (1.6–2.4)	
		Age at starting smoking (years)		Adjusted for age and sex
		≤ 14	1.2 (0.8–2.0)	
		15–19	1.03 (1.0–1.7)	
		20–29	1.5 (1.1–1.9)	
		30–39	2.1 (1.2–3.7)	
		≥ 40	2.4 (1.0–5.4)	
		≤ 14	0.6 (0.3–1.1)	Adjusted for age, sex and duration of smoking
		15–19	0.6 (0.4–1.1)	
		20–29	0.8 (0.5–1.3)	
		30–39	1.3 (0.7–2.4)	
		≥ 40	1.6 (0.6–3.8)	
Mori *et al.* (1999) India 1994–96	Men and women	Current smoker	1.0 (0.6–1.6)	
		Cigarettes/day		
		0–9	1.0 (reference)	
		10–19	1.6 (0.6–4.2)	
		≥ 20	5.8 (2.2–15.4)	

Table 2.1.5.3 (contd)

Reference Country and years of study	Subjects	Smoking categories	Odds ratio (95% CI)	Comments
Villeneuve *et al.* (2000) Canada 1994–97	Men	*Duration of smoking (years)*		Adjusted for age, province, number of live births, alcohol, coffee, energy intake and dietary fat
		< 20	0.8 (0.5–1.2)	
		20–39	1.3 (0.9–1.9)	
		≥ 40	1.1 (0.8–1.7)	
		Cigarettes/day		
		1–9	0.8 (0.5–1.4)	
		10–24	1.1 (0.8–1.5)	
		≥ 25	1.2 (0.8–1.8)	
		Packs/year		
		0–14	0.7 (0.5–1.1)	
		15–34	1.2 (0.8–1.7)	
		≥ 35	1.5 (1.0–2.1)	
	Women	*Duration of smoking (years)*		
		< 20	1.1 (0.7–1.7)	
		20–39	1.4 (1.0–2.1)	
		≥ 40	1.8 (1.1–2.8)	
		Cigarettes/day		
		1–9	1.1 (0.7–1.7)	
		10–24	1.5 (1.1–2.1)	
		≥ 25	1.5 (0.9–2.6)	
		Packs/year		
		0–7	0.9 (0.5–1.4)	
		8–22	1.4 (1.0–2.2)	
		≥ 23	1.8 (1.3–2.7)	

CI, confidence interval

Table 2.1.5.4. Case–control studies on tobacco smoking and cancer of the pancreas: smoking cessation

Reference Country and years of study	No. of years since quitting	Odds ratio (relative to never-smokers) (95% CI)		
Mack *et al.* (1986) USA 1976–81	0–4 5–9 ≥ 10 (smoked ≤ 1 pack/day) (smoked > 1 pack/day)	3.3 (1.6–6.9) 2.3 (1.2–4.3) 1.1 (0.7–1.4) 0.9 (0.5–1.7)		
Cuzick & Babiker (1989) UK 1983–86	 < 10 10–20 > 20 χ^2 for trend	*Men* 3.6 ($p < 0.01$) 3.6 ($p < 0.05$) 1.3 8.64 ($p < 0.01$)	*Women* 0.8 1.0 1.1 0.23	*Men and women* 1.7 1.8 1.0 3.14 ($p < 0.1$)
Bueno de Mesquita *et al.* (1991) Netherlands 1984–88	 2–14 ≥ 15	*Low consumption* *(≤ 111 200 cigarettes in lifetime)* 2.0 (0.8–5.0) 1.0 (0.5–2.2)	*High consumption* *(> 111 200 cigarettes in lifetime)* 1.7 (0.6–4.6)	
Howe *et al.* (1991) Canada 1983–86	2–9 10–19 ≥ 20	1.8 1.4 0.7		
Silverman *et al.* (1994) USA 1986–89	1–2 3–5 6–10 11–20 > 20	3.1 (2.0–5.0) 2.0 (1.1–3.5) 1.8 (1.1–2.9) 1.2 (0.8–1.9) 1.3 (0.8–1.9)		
Ji *et al.* (1995) China 1990–93	≤ 1 2–9 ≥ 10 *p* for trend	3.8 (1.4–10.2) 1.6 (0.8–3.0) 0.7 (0.3–1.5) 0.02		
Muscat *et al.* (1997) USA 1985–93	 1–2 3–5 6–10 > 10 *p* for trend	*Men* 1.7 (0.8–3.7) 0.5 (0.2–1.1) 1.2 (0.6–2.3) 1.1 (0.7–1.6) NS	*Women* 10.6 (2.9–39.2) 1.5 (0.6–3.7) 2.1 (0.9–4.5) 1.6 (1.0–2.7) < 0.05	
Partanen *et al.* (1997) Finland 1984–87	*Any tobacco* Early quitters (before 1975) Late quitters (quit 1975–83) Continued smoking	 1.2 (0.9–1.6) 1.8 (1.3–2.6) 2.5 (1.9–3.2)		
	Cigarettes Early quitters (before < 1975) Late quitters (quit 1975–83) Continued smoking	 1.2 (0.9–1.5) 1.8 (1.3–2.5) 2.5 (1.9–3.3)		

Table 2.1.5.5. Case–control studies on tobacco smoking and cancer of the pancreas: type of tobacco and/or cigarettes

Reference Country and years of study	Type of tobacco	Odds ratio (relative to never smokers) (95% CI)				
Bueno de Mesquita *et al*. (1991) Netherlands 1984–88	Filter-tipped cigarettes	1.4 (0.9–2.1)				
	Untipped cigarettes	1.9 (1.2–3.2)				
	Low-tar cigarettes	1.8 (0.7–4.5)				
Ghadirian *et al*. (1991) Canada 1984–88		Quintiles (total cigarettes in lifetime)				
		Q2 (83 850)	Q3 (193 450)	Q4 (319 875)	Q5 (1 814 963)	$\chi2$ for trend
	Filter-tipped cigarettes	0.9	2.5	1.6	2.9 (1.5–5.9)	9.73
	Untipped cigarettes	1.3	1.4	1.4	5.1 (2.0–13.1)	8.88
	Low-tar cigarettes	0.5	2.5	3.0	2.4 (1.1–5.5)	7.07
Howe *et al*. (1991) Canada 1983–86	Packs/year of untipped cigarettes					
	0–17.9	0.9 (0.6–1.4)				
	17.9–37.5	2.1 (1.1–4.2)				
	> 37.5	0.9 (0.4–2.0)				
	Packs/year of filter-tipped cigarettes					
	0–17.9	1.3 (0.8–2.1)				
	17.9–37.5	2.3 (1.4–3.7)				
	> 37.5	2.4 (1.3–4.2)				

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2.1.6 *Cancer of the stomach*

(*a*) *Cohort studies*

A total of 29 prospective cohort studies have examined the association between smoking and stomach cancer. The details of the design of these studies are described in Table 2.1 and Table 2.1.6.1. Summary findings are presented in Table 2.1.6.2.

(i) *Intensity and duration of smoking*

Intensity (cigarettes/day), age at starting smoking and/or duration of smoking were studied in almost all of the cohorts. Sixteen cohort studies reported a statistically significant association between smoking and the risk for stomach cancer, with odds ratios ranging from 1.4 to 2.6 in current smokers (Kahn, 1966; Hirayama, 1982, 1985; Kono *et al*., 1987; Akiba & Hirayama, 1990; McLaughlin *et al*., 1990; Nomura *et al*., 1990a,b; Kneller *et al*., 1991; Kato *et al*., 1992a; Doll *et al*., 1994; McLaughlin *et al*., 1995; Nomura *et al*., 1995; Liaw & Chen, 1998; Gao *et al.*, 1999; You *et al*., 2000; Chao *et al*., 2002). In eight of these studies, significant dose–response relationships were observed between intensity of smoking and the risk for stomach cancer (Kahn, 1966; Hirayama, 1985; Akiba & Hirayama, 1990; McLaughlin *et al*., 1990; Kneller *et al*., 1991; Doll *et al*., 1994; McLaughlin *et al*., 1995; Gao *et al.*, 1999) and in five studies between duration of smoking and risk for stomach cancer (McLaughlin *et al*., 1990; Nomura *et al*., 1995; Liaw & Chen, 1998; You *et al*., 2000; Chao *et al*., 2002). In eight cohort studies, the increase in risk associated with smoking was statistically non-significant (Hammond, 1966; Doll & Peto, 1976; Kato *et al*., 1992b; Tverdal *et al*., 1993; Engeland *et al*., 1996; Yuan *et al*., 1996; Nordlund *et al*., 1997; Mizoue *et al*., 2000). Five studies did not find any association between smoking and stomach cancer (Guo *et al*., 1994; Murata *et al.*, 1996; Chen *et al*., 1997; Tulinius *et al*., 1997; Terry *et al*., 1998).

Many studies that have tested the statistical significance of trend in risk with duration of smoking or number of cigarettes/day have included nonsmokers in the analysis. [The Working Group noted that the preferred approach is to limit testing for trend to exposed persons across gradients of exposure.]

(ii) *Smoking cessation*

Relative risks in former smokers have been examined in 16 studies and two studies have assessed the effect of number of years since quitting (Guo *et al*., 1994; Chao *et al*., 2002). The risk in former smokers ranged from 1.2 to 2.6 in men and women combined, from 0.9 to 2.2 in men and from 0.2 to 1.4 in women. Increasing number of years since cessation and younger age at cessation were associated with a significant trend in decreasing risk (Chao *et al*., 2002).

(iii) *Effect of sex*

Data for men and women were combined in five studies, seven studies presented data separated by sex, 16 studies presented results for men only and one study for women only.

Generally, the numbers of incident cases and of deaths from stomach cancer in women were small. The risks for stomach cancer associated with smoking were assessed separately for women in only seven cohort studies and, of these, only three reported significant increases in risk (Akiba & Hirayama, 1990; Gao *et al*., 1999; Chao *et al*., 2002). In three studies, increases in risk were statistically non-significant (Hirayama, 1982; Kato *et al*., 1992a; Nordlund *et al*., 1997) and, in one study, smoking was not associated with risk for stomach cancer (Engeland *et al*., 1996).

(iv) *Bias and misclassification*

Several limitations of cohort studies should be considered. First, some studies reported a low response rate in the initial survey and a high proportion of individuals who were lost to follow-up, leading to selection bias. Second, most cohorts were followed passively and the information on smoking habits was based only on the initial survey, although many cohort members could have subsequently changed their smoking habits. Therefore, misclassification of former smokers as current smokers is possible. Thus, the risk for stomach cancer is most probably underestimated in most, if not all, cohort studies. The results of cohort studies could also be confounded by the effects of alcohol consumption. Only seven studies adjusted relative risks for alcohol consumption (Kono *et al*., 1987; Kato *et al*., 1992a; Nomura *et al*., 1995; Chen *et al*., 1997; Liaw & Chen, 1998; Mizoue *et al*., 2000; You *et al*., 2000). In most of these studies, the risk for stomach cancer in smokers was significantly different from unity.

(*b*) *Case–control studies*

Forty-five case–control studies detailed in Tables 2.1.6.3 and 2.1.6.4 have reported results regarding the influence of smoking on the risk for stomach cancer. Some very weak, early studies, although reported in Tables 2.1.6.3 and 2.1.6.4 for completeness, will not be considered further here (Wynder *et al*., 1963; Staszewski, 1969; Ames & Gamble, 1983). Twenty-three studies were hospital-based, one was a retrospective mortality study and 18 studies were population-based. In most studies, odds ratios were adjusted for variables such as sex, age, residence, socioeconomic status, income, diet and consumption of fresh fruits and vegetables. Odds ratios were adjusted for alcohol consumption in 18 studies (Hoey *et al*., 1981; Correa *et al*., 1985; Hu *et al*., 1988; You *et al*., 1988; Ferraroni *et al*., 1989; De Stefani *et al*., 1990; Lee *et al*., 1990; Jedrychowski *et al*., 1993; Kabat *et al*., 1993; Siemiatycki *et al*., 1995; Ji *et al*., 1996; Zhang *et al*., 1996; Gammon *et al*., 1997; De Stefani *et al*., 1998; Inoue *et al*., 1999; Ye *et al*., 1999; Lagergren *et al*., 2000; Zaridze *et al*., 2000).

(i) *Intensity and duration*

Thirty-one case–control studies (Haenszel *et al*., 1972; Hoey *et al*., 1981; Correa *et al*., 1985; Risch *et al*., 1985; Hu *et al*., 1988; You *et al*., 1988; De Stefani *et al*., 1990; Kato *et al*., 1990; Lee *et al*., 1990; Wu-Williams *et al*., 1990; Dockerty *et al*., 1991; Saha, 1991; Yu & Hsieh, 1991; Kabat *et al*., 1993; Hansson *et al*., 1994; Inoue *et al*., 1994;

Siemiatycki *et al.*, 1995; Yu *et al.*, 1995; Gajalakashmi & Shanta, 1996; Ji *et al.*, 1996; Zhang *et al.*, 1996; Gammon *et al.*, 1997; De Stefani *et al.*, 1998; Liu *et al.*, 1998; Chow *et al.*, 1999; Inoue *et al.*, 1999; Ye *et al.*, 1999; Lagergren *et al.*, 2000; Mathew *et al.*, 2000; Zaridze *et al.*, 2000; Wu *et al.*, 2001) reported a statistically significant association between smoking and the risk for stomach cancer. Most studies published after 1990 examined the effect of intensity and duration of smoking on the risk for stomach cancer. In most of them, there was a statistically significant dose–response trend between the number of cigarettes smoked daily, duration of smoking and/or age at start and the risk for stomach cancer (Hu *et al.*, 1988; You *et al.*, 1988; De Stefani *et al.*, 1990; Kato *et al.*, 1990; Lee *et al.*, 1990; Wu-Williams *et al.*, 1990; Yu & Hsieh, 1991; Kabat *et al.*, 1993; Hansson *et al.*, 1994; Gajalakashmi & Shanta, 1996; Ji *et al.*, 1996; Zhang *et al.*, 1996; Gammon *et al.*, 1997; De Stefani *et al.*, 1998; Ye *et al.*, 1999; Lagergren *et al.*, 2000; Mathew *et al.*, 2000; Zaridze *et al.*, 2000; Wu *et al.*, 2001). In nine studies, no association was found between smoking and the risk for stomach cancer (Jedrychowski *et al.*, 1986; Buiatti *et al.*, 1989; Ferraroni *et al.*, 1989; Boeing *et al.*, 1991; Buiatti *et al.*, 1991; Agudo *et al.*, 1992; Palli *et al.*, 1992; Jedrychowski *et al.*, 1993; Gao *et al.*, 1999).

(ii) *Smoking cessation*

Twenty-five studies examined relative risks in former smokers and several also examined the effect of cessation of smoking (De Stefani *et al.*, 1990; Kabat *et al.*, 1993; Hansson *et al.*, 1994; Inoue *et al.*, 1994; Ji *et al.*, 1996; Gammon *et al.*, 1997; De Stefani *et al.*, 1998; Chow *et al.*, 1999; Ye *et al.*, 1999; Lagergren *et al.*, 2000; Wu *et al.*, 2001). Quitting smoking was found to decrease the risk for cancer. A significant negative trend for increasing number of years since cessation was reported in six studies (De Stefani *et al.*, 1990; Hansson *et al.*, 1994; Inoue *et al.*, 1994; Gammon *et al.*, 1997; De Stefani *et al.*, 1998; Lagergren *et al*,. 2000), whereas two studies found no effect (Kabat *et al.*, 1993; Ji *et al.*, 1996). However, in examining temporal trends in risk with time since cessation, some studies did not exclude persons who had quit recently, among whom increased risk may reflect cessation due to smoking-attributable disease.

(iii) Subsites of stomach cancer

Several case–control studies presented studies by subsites (De Stefani *et al.*, 1990; Wu-Williams *et al.*, 1990; Saha, 1991; Palli *et al.*, 1992; Kabat *et al.*, 1993; Inoue *et al.*, 1994; Zhang *et al.*, 1996; Gammon *et al.*, 1997; De Stefani *et al.*, 1998; Ye *et al.*, 1999; Zardize *et al.*, 2000; Wu *et al.*, 2001). In all the studies that distinguished between cancer of the gastric cardia and distal stomach, an effect of smoking was seen on the risk for cancers at both sites. Dose–response relationships were observed between number of cigarettes smoked per day, duration of smoking and time since quitting for cancers of both sites. The significant association between smoking and cancer risk persisted when relative risks were examined separately for intestinal and diffuse histological types (Kato *et al.*, 1990; Ye *et al.*, 1999).

(iv) *Effect of sex*

Most studies included both men and women; seven studies reported results for men only and only eight reported results for men and women separately (Haenszel *et al*., 1972; Kato *et al*., 1990; Kabat *et al*., 1993; Inoue *et al*., 1994; Ji *et al*., 1996; Liu *et al*., 1998; Chow *et al*., 1999; Inoue *et al*., 1999). The number of cases of stomach cancer in women was generally small and the increase in risk estimates was generally lower than that for men and was not statistically significant (Kato *et al*., 1990; Inoue *et al*., 1994; Ji *et al*., 1996; Liu *et al*., 1998). However, in the studies in which a sufficient number of cases of stomach cancer in women were included, the relative risks were significant and comparable with those in men (Kabat *et al*., 1993; Chow *et al*., 1999; Inoue *et al*., 1999).

(v) *Effect of ethnicity*

The only study that investigated ethnicity reported a significantly higher risk for African Americans than for Caucasians (Correa *et al*., 1985).

(vi) *Type of tobacco and type of cigarette*

The effects of black and blond tobacco were distinguished only by De Stefani *et al*. (1990, 1998). Five studies evaluated the effect of filter tips (De Stefani *et al*., 1990; Jedrychowski *et al*., 1993; Gammon *et al*., 1997; De Stefani *et al*., 1998; Chow *et al*., 1999) and one study looked at the effect of swallowing tobacco smoke (Saha, 1991). The risk associated with smoking black tobacco was higher than that for smoking blond tobacco (De Stefani *et al*., 1990, 1998). There was no clear difference in risk between smokers of filter-tipped or untipped cigarettes or whether or not smoke is swallowed.

(vii) *Bias and misclassification*

The relative risk for stomach cancer associated with smoking is most probably underestimated, particularly in hospital-based case–control studies, because of a substantial proportion of controls with smoking-related diseases. Of special concern are the studies in which prevalence of smoking was higher in controls than in cases and in which controls with smoking-associated diseases were included (Haenszel *et al*., 1976; Correa *et al*., 1985; Jedrychowski *et al*., 1986; Lee *et al*., 1990; Boeing *et al*., 1991; Agudo *et al*., 1992; Zaridze *et al*., 2000) or in which the diagnoses of hospital controls were not reported (Haenszel *et al*., 1972).

(*c*) Helicobacter pylori *infection*

A positive association between smoking and the risk for stomach cancer could be confounded by the effect of *Helicobacter pylori* infection status. A large body of evidence supports a causative role for *H. pylori* in stomach cancer. In 1994, IARC recognized *H. pylori* as a class 1 human carcinogen (IARC, 1994).

None of the available cohort studies have assessed *H. pylori* infection status. Two case–control studies investigated the interaction between *H. pylori* seropositivity and smoking in relation to the risk for stomach cancer (Zaridze *et al*., 2000; Siman *et al*., 2001). The relative risk for stomach cancer was higher in *H. pylori*-infected men (Zaridze *et al*., 2000). These results suggest that smoking may potentiate the carcinogenic effect of *H. pylori*.

Several studies have shown that *H. pylori* infection status is not associated with smoking habit. Limburg *et al*. (2001) examined the association between seropositivity for *H. pylori* and different risk factors. The proportion of seropositive individuals was similar in nonsmokers (58%) and in smokers (61%). Moreover, the prevalence of CagA-seropositive individuals was higher in nonsmokers (32%) than in smokers (24%). Another study in China looked at the association between the prevalence of *H. pylori* infection and smoking, alcohol consumption and diet. The prevalence of *H. pylori* positivity was lower among ever-smokers than never-smokers, with an odds ratio for ever-smokers of 0.9 (95% CI, 0.7–1.0). In the highest category of smokers, who had a lifetime exposure of more than 14 235 packs, the odds ratio was 0.8 (95% CI, 0.6–1.1) (Brown *et al*., 2002).

Similar evidence has been obtained in Europe. The prevalence of seropositive subjects is similar among never- (50.9%), former (48.7%) and current smokers (45.1%). In fact, the percentage of *H. pylori* seropositivity is somewhat lower among current smokers than among never-smokers (crude odds ratio, 0.8; 95% CI, 0.7–0.9) (EUROGAST Study Group, 1993). In only one study conducted in northern England was smoking more than 35 cigarettes/day found to be associated with higher risk for *H. pylori* positivity (Moayyedi *et al*., 2002). However, it should be noted that the proportion of subjects infected was identical in all categories of low smoking intensity. Overall, there is no association between *H. pylori* infection status and smoking. Therefore, *H. pylori* is of little or no relevance with regard to potential confounding of the association between smoking and stomach cancer.

(*d*) *Precursor lesions*

According to one widely accepted model of gastric carcinogenesis, development of stomach cancer is preceded by several precursor stages, including chronic atrophic gastritis, intestinal metaplasia and dysplasia. An increase in the relative risk for developing these lesions has been shown to be associated with smoking, with a significant positive trend associated with intensity and duration of smoking. The magnitude of the association was stronger for dysplasia than for metaplasia (Kneller *et al*., 1991). You *et al*. (2000) found an increased risk for the progression of precursor lesions to dysplasia and cancer for subjects who had smoked for more than 25 years and a significant trend with increasing duration of smoking.

Overall, the results from both cohort and case–control studies are consistent with a causal role of tobacco smoking in the development of stomach cancer.

Table 2.1.6.1. Additional cohort studies on tobacco smoking and stomach cancer: main characteristics of study design

Reference Country and years of follow-up	Cohort sample	Cases/deaths identification	Comments
Kato *et al.* (1992a) Japan 1985–91	9753 male (≥ 40 years) and female (≥ 30 years) inhabitants of a mountainous area of Aichi prefecture	Death certificates	Questionnaires linked to data from another questionnaire survey conducted in 1983–84 that included information on smoking habits
Kato *et al.* (1992b) Japan 1985–89	5395 patients receiving gastroscopic examination at Aichi Centre Hospital	Linkage with gastro-endoscopic records at Aichi Cancer Centre Hospital, Aichi Cancer Registry and death certificates	Diagnoses at baseline included: atrophic gastritis (mild, moderate/severe), 'extension on the greater curvature', 'extension on the lesser curvature', gastric ulcer and gastric polyp (none with normal gastric mucosa)
You *et al.* (2000) China 1989–94	3433 subjects participating in a gastric cancer-screening study, residents in 14 villages randomly selected within Linqu County, aged 35–64 years	Cases identified by pathological examination of biopsies and endoscopic examination	Diagnosis of cohort members divided into superficial gastritis or chronic atrophic gastritis, intestinal metaplasia and dysplasia (none with normal gastric mucosa)

Table 2.1.6.2. Cohort studies on tobacco smoking and stomach cancer

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)	Comments
Hammond (1966) USA 1959–62	Cancer Prevention Study I 440 558 men, 562 671 women 1 639 211 person–years	562 deaths (343 men, 219 women); 283 deaths in men aged ≥ 45 years		Mortality ratio	Data presented for men only
			Aged 45–64 (n = 131)	1.4	
			Aged 65–79 (n = 79)	1.3	
Kahn (1966) USA 1954–62	US Veterans' Study 293 658 men 2 265 674 person–years	420 deaths		Mortality ratio	Crude mortality ratio
			Non- or occasional smoker	1.0	†Current and former 'cigarette smoker' refer to combined use of cigarettes and other forms of tobacco
			Current cigarette smoker†		
			Total	1.5 ($p < 0.01$)	
			Occasional	0.7	
			Cigarettes/day		
			1–9	1.7	
			10–20	1.4 ($p < 0.01$)	
			21–39	1.6 ($p < 0.01$)	
			≥ 40	1.8 ($p < 0.01$)	p for trend < 0.01
			Current cigarette-only smoker		
			Total	1.6	
			Occasional	0.6	
			Cigarettes/day		
			1–9	2.2	
			10–20	1.6	
			21–39	1.4	
			≥ 40	1.9	
			Former cigarette smoker†		
			Total	1.03	
			Cigarettes/day		
			1–9	0.98	
			10–20	0.8	
			21–39	1.1	
			≥ 40	2.0	

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)		Comments
Kahn (1966) (contd)			*Former cigarette only-smoker*	0.9		
			Cigarettes/day			
			1–9	0.96		
			10–20	0.7		
			21–39	0.8		
			≥ 40	2.1		
Doll & Peto (1976) United Kingdom 1951–71	British Doctors' Study 34 439 men	163 deaths		Mortality rate		Annual mortality rate/100 000 men standardized for age
			Nonsmoker	23		
			Former smoker	21		
			Current smoker	32		
			Cigarettes/day			
			1–14	28		
			15–24	38		
			≥ 25	32		*p* for trend > 0.1
Hirayama (1982) Japan 1965–78	Six-prefecture Study 122 261 men, 142 857 women 3 060 499 person–years	Not given		SMR		Inconsistency between table and text for values in women
			Men	1.5 ($p < 0.001$)		
			Women	1.3 ($p < 0.01$)		
			Age at starting smoking (years)	**Men**	**Women**	
			≥ 20	1.4	1.2	
			< 19	1.7	1.6	
Hirayama (1985) Japan 1965–81	Six-prefecture Study 122 261 men, 142 847 women 3 659 588 person–years	Not given	Current smoker	1.5 ($p < 0.001$)		
			Cigarettes/day			
			1–24	1.48		*p* for trend = 4×10^{-8}
			≥ 25	1.5		
Kono *et al.* (1987) Japan 1965–83	Japanese Physicians' Study 5130 men	116 deaths	*Cigarettes/day*			Never- and former smokers combined used as referents. Low response rate. Relative risks adjusted for age and alcohol drinking
			1–19	1.7 (1.1–2.6)		
			≥ 20	1.8 (1.1–3.0)		

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)	Comments
Akiba & Hirayama (1990) Japan 1965–81	Six-prefecture Study 122 261 men, 142 857 women	4426 deaths (2839 men, 1587 women)	**Men**		Relative risks stratified by prefecture of residence, occupation, attained age and observation period.
			Cigarettes/day		
			1–4	1.4 (1.0–1.8)	
			5–14	1.4 (1.3–1.6)	
			15–24	1.5 (1.4–1.7)	
			25–34	1.4 (1.1–1.7)	
			≥ 35	1.7 (1.3–2.2)	*p* for trend < 0.001
			Total	1.5 (1.3–1.6)	*p* for heterogeneity < 0.001
			Women		
			Cigarettes/day		
			1–4	1.2 (0.8–1.7)	
			5–14	1.3 (1.1–1.5)	
			≥ 15	0.8 (0.5–1.3)	*p* for trend > 0.1
			Total	1.2 (1.0–1.4)	*p* for heterogeneity = 0.04
McLaughlin *et al.* (1990) USA 1954–80	US Veterans' Study 293 916 men 4 531 000 person–years	1520 deaths	Former smoker	1.0 (0.9–1.2)	Relative risks for age at start and duration adjusted for number of cigarettes smoked.
			Current smoker	1.4 (1.2–1.6)	
			Cigarettes/day		
			1–9	1.3 (1.1–1.7)	
			10–19	1.4 (1.2–1.6)	
			20–39	1.5 (1.2–1.8)	
			≥ 40	1.8 (1.3–2.6)	
				p for trend < 0.001	
			Age at starting smoking (years)		
			≥ 20	1.3 (1.0–1.6)	
			15–19	1.5 (1.1–1.9)	
			< 15	1.9 (1.4–2.7)	
				p for trend < 0.01	

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)	Comments
McLaughlin			*Duration (years)*		
et al. (1990)			< 25	1.1 (0.7–1.6)	
(contd)			≥ 25	1.4 (1.1–1.8)	
				p for trend < 0.01	
Nomura *et al.*	American Men of	150 cases	Former smoker	1.0 (0.6–1.7)	Relative risks adjusted for age.
(1990a,b)	Japanese Ancestry Study		Former smoker†	0.9 (0.4–2.0)	†Subjects who had quit ≤ 5
USA	7990 men		Current smoker	2.7 (1.8–4.1)	years before interview
1965–84	140 190 person–years		*Cigarettes/day*		
			1–10	2.7 (1.5–5.1)	
			11–20	2.9 (1.9–4.6)	
			> 20	2.4 (1.4–4.1)	
			Duration (years)		
			≤ 25	3.5 (1.9–6.6)	
			26–35	1.5 (0.9–2.7)	
			> 35	3.5 (2.2–5.6)	
Kneller *et al.*	Lutheran Brotherhood	75 deaths	Ever-smoker	2.1 (0.98–4.4)	Response rate, 68%; 23% of
(1991)	Insurance Study		Occasional smoker	0.7 (0.2–2.8)	cohort lost to follow-up.
USA	17 633 men		Former smoker	2.2 (0.99–4.9)	Diagnosis not confirmed
1966–86	287 000 person–years		*Cigarettes/day*		histologically. Data stratified
			Total	2.6 (1.1–5.8)	by year of birth (5-year
			1–19	2.2 (0.8–6.0)	intervals). Stratification by
			20–29	2.0 (0.7–5.6)	education, immigrant status,
			≥ 30	5.8 (2.1–16.2)	occupation or residential
				p for trend < 0.01	region did not alter results.

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)		Comments
Kneller *et al.* (1991) (contd)			*Pack–years*			
			< 0.01	1.0		
			0.01–17.99	1.3 (0.6–2.7)		
			18.00–32.99	1.4 (0.7–3.1)		
			≥ 33	2.3 (1.2–4.3)		
				p for trend < 0.01		
			Current smoker	≤ 67 years	> 67 years	
			All	4.8 (1.1–21.4)	1.6 (0.5–4.6)	
			≥ 30 cigarettes/day	9.4 (1.8–48.7)	3.8 (0.8–18.9)	
Kato *et al.* (1992a) Japan 1985–91	9753 men and women 55 284 person–years	57 deaths (35 men, 22 women)	Former smoker	2.6 (0.97–7.0)		Information on smoking habits taken from another survey unrelated to study. Small number of observations. Relative risks adjusted for age and sex. Multivariate analysis adjusted for alcohol intake, diet, cooking methods and family history of stomach cancer
			Current smoker	2.3 (1.2–4.6)		
			Cigarettes/day			
			1–19	2.6		
			≥ 20	1.9		
				Men	**Women**	
			Former smoker	2.6 (0.8–8.1)	4.9 (0.6–36.8)	
			Current smoker	2.6 (1.1–6.1)	1.7 (0.4–7.3)	
				Multivariate analysis		
			Current smoker	2.2 (1.1–4.4)		
			Former smoker	2.6 (0.97–7.1)		
Kato *et al.* (1992b) Japan 1985–89	3194 patients (1851 men, 2063 women) 17 289 person–years	45 cases (35 men, 10 women)	Former smoker	1.2 (0.5–2.9)		Relative risk adjusted for age, sex and residence
			≤ 19 cigarettes/day	1.1 (0.4–3.3)		
			≥ 20 cigarettes/day	2.2 (0.9–5.4)		

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)		Comments
Tverdal *et al.* (1993) Norway 1972–88	Norwegian Screening Study 44 290 men, 24 535 women	98 deaths (78 men, 20 women)		Mortality rate		Mortality rate/100 000 person–years adjusted for age and area. No statistical analysis performed. Relative risks per 10 cigarettes/day adjusted for age, cholesterol, systolic blood pressure, physical activity during leisure, body-mass index, height and number of cigarettes smoked
				Men	**Women**	
			Never-smoker	6.9	7.3	
			Former smoker	7.5	10.5	
			Current smoker	18.8	4.1	
			Pipe and cigarettes	22.9		
			Cigarettes/day			
			1–9	20.7		
			10–19	17.2		
			≥ 20	21.3		
			RR per 10 cig./day	1.2 (0.7–1.8)		
Doll *et al.* (1994) UK 1951–91	British Doctors' study 34 439 men	277 deaths		Mortality rate		Annual mortality rate/100 000 men standardized for age and calendar period
			Never-smoker	26		
			Former smoker	25		
			Current smoker	43		
				p for trend ≤ 0.01		
			Cigarettes/day			
			1–14	40		
			15–24	46		
			≥ 25	44		
				p for trend < 0.05		

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)	Comments
Guo *et al.* (1994) China 1985–91	Linxian Intervention Trial Study 29 584 men and women	539 cases in men	Ever-smoker	1.1 (0.8–1.4)	Nested case–control study. Analysis for men only. Odds ratios adjusted for participation in intervention group and cancer history in first-degree relatives
			Cigarettes only	1.0 (0.7–1.3)	
			Cigarettes and pipe	1.3 (1.0–1.8)	
			Cigarettes/day		
			< 10	1.2 (0.9–1.6)	
			10–19	1.0 (0.8–1.4)	
			≥ 20	1.1 (0.8–1.5)	
			Duration (years)		
			< 20	0.9 (0.5–1.4)	
			20–39	1.0 (0.8–1.4)	
			≥ 40	1.3 (0.9–1.9)	
				p for trend = 0.19	
			Pack–years		
			< 10	1.0 (0.7–1.5)	
			1–19	1.0 (0.7–1.4)	
			20–29	1.1 (0.8–1.7)	
			≥ 30	1.2 (0.9–1.8)	
			Years since quitting		
			≥ 3	0.8 (0.4–1.7)	
			< 3	1.0 (0.4–2.3)	
McLaughlin *et al.* (1995) USA 1954–80	US Veterans' Study 177 903 men 3 252 983 person–years	1058 deaths	Ever-smoker	1.3 (1.1–1.4)	Relative risks adjusted for attained age and calendar-year time-period.
			Former smoker	1.0 (0.9–1.2)	
			Current smoker	1.4 (1.2–1.6)	
			Cigarettes/day		
			1–9	1.3 (1.0–1.7)	
			10–20	1.4 (1.2–1.6)	
			21–39	1.4 (1.2–1.8)	
			≥ 40	1.9 (1.3–2.7)	
				p for trend < 0.01	

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)		Comments
Nomura *et al.* (1995) USA 1965–94	American Men of Japanese Ancestry Study 7972 men 177 080 person–years	250 cases	Former smoker Current smoker *Age at starting smoking (years)* ≥ 21 18–20 ≤ 17	1.1 (0.7–1.6) 2.3 (1.7–3.2) 1.9 (1.3–2.9) 2.5 (1.7–3.7) 2.6 (1.7–3.9) *p* for trend < 0.0001		Adjusted for age and alcohol intake. No trend observed for pack–years [data not shown]
Engeland *et al.* (1996) Norway 1966–93	Norwegian Cohort Study 11 863 men, 14 269 women About 540 000 person–years	417 cases (258 men, 159 women)	 Former smoker Current smoker	**Men** 1.3 (0.9–2.0) 1.3 (0.9–1.9)	**Women** 0.8 (0.4–1.6) 1.0 (0.6–1.4)	Response rate, 76%. Relative risks adjusted for age.
Murata *et al.* (1996) Japan 1984–93	Chiba Center Association Study	 23 65 32	Cigarettes/day 1–10 11–20 ≥ 21	 1.0 1.1 1.1		
Yuan *et al.* (1996) China 1986–93	Shanghai Men's Study 18 244 men 98 267 person–years	113 cases	Ever-smoker < 20 cigarettes/day ≥ 20 cigarettes/day	1.4 (0.9–2.1) 1.4 1.3		Relative risks adjusted for age.
Nordlund *et al.* (1997) Sweden 1963–89	Swedish Census Study 26 032 women Almost 600 000 person–years	226 cases	Former smoker Current smoker *Cigarettes/day* 1–7 8–15 ≥ 16	0.2 (0.0–1.3) 1.3 (0.8–1.9) 1.2 (0.7–2.0) 1.2 (0.6–2.3) 1.9 (0.8–4.7)		Relative risks adjusted for age and place of residence.

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)	Comments
Nordlund *et al.* (1997) (contd)			*Age at starting smoking (years)* 20–23 < 19	 0.5 (0.1–1.5) 0.9 (0.4–2.3) *p* for trend = 0.559	Relative risks for age at starting smoking adjusted for amount of tobacco smoked daily
Chen *et al.* (1997) China 1972–93	Shanghai Factory Study 6494 men, 2857 women 101 949 person–years	86 deaths in men	Ever-smoker *Cigarettes/day* 1–19 ≥ 20	1.0 1.1 0.9 *p* for trend = 0.81	Analysis for men only because of few of the women smoked. Relative risks adjusted for factories, age, systolic blood pressure, serum cholesterol and regular alcohol drinking
Tulinius *et al.* (1997) Iceland 1968–95	Reykjavík Study 11 366 men, 11 580 women	246 cases (171 men, 75 women)	Former smoker *Cigarettes/day* 1–14 15–24 ≥ 25	1.2 (0.8–1.8) 1.5 (0.8–2.5) 1.9 (1.1–3.1) 1.0 (0.4–2.4)	Analysis for men only because of small no. of deaths in women. Relative risks adjusted for age
Liaw & Chen (1998) China, Province of Taiwan 1982–94	Taiwanese Study 11 096 men, 3301 women 140 493 person–years	69 deaths (57 men, 12 women)	Ever-smoker *Cigarettes/day* ≤ 10 11–20 > 20 *Duration (years)* ≤ 20 21–30 > 30	1.9 (1.0–3.5) 1.7 (0.9–3.4) 1.6 (0.8–3.1) 3.0 (1.1–8.3) *p* for trend = 0.06 1.7 (0.7–4.4) 0.7 (0.2–2.4) 2.0 (1.1–3.7) *p* for trend = 0.04	Analysis for men only because of small no. of deaths in women. Relative risks adjusted for age and alcohol drinking.

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)	Comments
Liaw & Chen (1998) (contd)			*Age at starting smoking (years)*		
			> 24	1.5 (0.7–3.3)	
			21–24	0.6 (0.2–2.2)	
			≤ 20	2.2 (1.2–4.2)	
				p for trend = 0.02	
			Pack–years		
			< 20	1.3 (0.6–2.8)	
			20–40	1.5 (0.7–3.1)	
			≥ 41	2.8 (1.4–5.8)	
				p for trend < 0.01	
Terry *et al.* (1998) Sweden 1967–92	Swedish Twin Registry Study 11 546 individuals	116 cases	Current smoker	0.8 (0.4–2.3)	
Gao *et al.* (1999) China 1983–94	Shanghai Residential Study		Men		*p* for trend < 0.05 for intensity of smoking and age at starting smoking for men
			urban	1.9[†]	[†]CI does not include 1.0
			suburban	1.3	
			rural	1.3	
			Women (urban)	1.2	
Mizoue *et al.* (2000) Japan 1986–96	Fukuoka Study 4050 men 35 785 person–years	53 cases		**SMR**	Standardized mortality ratio (SMR) adjusted for study area, age and alcohol consumption.
			Former smoker	2.2 (0.8–6.0)	
			Current smoker	2.2 (0.8–5.7)	
			Cigarettes/day		
			1–24	2.2 (0.8–6.0)	
			≥ 25	1.9 (0.6–6.4)	

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)		Comments
You *et al.* (2000) China 1989–94	2628 participants with:	34 cases	*Cigarettes/day*			Information about smoking habit available for only 2436 subjects. Relative risks for progression to dysplasia or stomach cancer, adjusted for sex, age, alcohol consumption and baseline histopathology.
	1240 superficial or chronic atrophic gastritis	1	1–19	1.2 (0.7–1.9)		
			≥ 20	1.4 (0.9–2.3)		
	842 intestinal metaplasia	18		*p* for trend = 0.12		
	546 gastric displasia	15	*Duration (years)*			
	805 normal	0	1–24	1.1 (0.7–1.7)		
			≥ 25	1.6 (1.0–2.7)		
				p for trend = 0.04		
Chao *et al.* (2002) USA 1982–96	Cancer Prevention Study II 467 788 men, 588 053 women	1505 deaths (996 men, 509 women)		**Men**	**Women**	Multivariate models include age, race, education, family history of stomach cancer, consumption of high-fibre cereal products, vegetables, citrus fruits and juices, and use of vitamin C, multivitamins and aspirin. Estimates of *p* for trend excluded non-users of tobacco.
			Current smoker	2.2 (1.8–2.7)	1.5 (1.2–1.9)	
			Cigarettes/day			
			< 20	1.7 (1.2–2.3)	1.3 (0.9–1.8)	
			20	2.5 (1.9–3.3)	1.3 (0.8–1.9)	
			21–39	2.7 (2.0–3.8)	2.2 (1.3–3.5)	
			≥ 40	1.8 (1.3–2.7)	2.2 (1.2–3.9)	
			p for trend	0.539	0.038	
			Duration (years)			
			< 20	1.2 (0.4–3.4)	1.4 (0.7–3.0)	
			20–29	1.0 (0.5–2.0)	1.2 (0.7–2.2)	
			30–39	2.1 (1.5–2.9)	1.8 (1.3–2.6)	
			≥ 40	2.4 (1.8–3.0)	1.5 (1.02–2.1)	
			p for trend	0.059	0.074	
			Age at starting smoking (years)			
			≥ 20	1.9 (1.4–2.5)	1.5 (1.1–2.0)	
			16–19	2.4 (1.9–3.1)	1.6 (1.2–2.3)	
			≤ 15	2.2 (1.6–3.0)	1.6 (0.8–3.0)	
			p for trend	0.075	0.672	

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)		Comments
Chao *et al.* (2002) (contd)			*Pack–years*			
			≤ 19	1.4 (0.9–2.3)	1.6 (1.0–2.4)	
			20–39	2.0 (1.4–2.7)	1.3 (0.8–1.9)	
			40–59	2.7 (2.0–3.6)	1.2 (0.7–2.0)	
			≥ 60	2.1 (1.5–2.8)	2.8 (1.8–4.5)	
			p for trend	0.401	0.053	
			Former smoker	1.6 (1.3–1.9)	1.4 (1.1–1.7)	
			Cigarettes/day			†Two highest categories (21–39 and ≥ 40 cigarettes/ day) grouped together because of small numbers
			< 20	1.3 (0.96–1.7)	1.2 (0.9–1.6)	
			20	1.6 (1.2–2.1)	1.5 (1.02–2.3)	
			21–39	1.6 (1.1–2.3)	1.6 (0.95–2.6)†	
			≥ 40	1.8 (1.4–2.4)		
			p for trend	0.064	0.165	
			Duration (years)			
			< 20	1.1 (0.8–1.5)	1.4 (0.96–2.0)	
			20–29	1.5 (1.2–2.0)	1.7 (1.2–2.6)	
			30–39	1.7 (1.3–2.3)	1.2 (0.8–1.8)†	
			≥ 40	2.0 (1.5–2.7)		
			p for trend	0.0017	0.3208	
			Age at starting smoking (years)			
			≥ 20	1.7 (1.3–2.2)	1.5 (1.1–2.0)	
			16–19	1.6 (1.2–2.0)	1.3 (0.9–1.8)	
			≤ 15	1.3 (0.9–1.8)	0.9 (0.4–2.1)	
			p for trend	0.608	0.605	

Table 2.1.6.2 (contd)

Reference Country and years of study	No. of subjects	No. of cases	Exposure estimates	Relative risk (95% CI)		Comments
Chao *et al*. (2002) (contd)			*Pack–years*			
			≤ 19	1.1 (0.9–1.5)	1.4 (1.0–1.9)	
			20–39	1.6 (1.3–2.1)	1.4 (0.9–2.2)	
			40–59	1.9 (1.4–2.6)	1.2 (0.7–2.2)[†]	
			≥ 60	1.9 (1.4–2.6)		
			p for trend	0.0037	0.828	
			Age at quitting smoking (years)			
			≤ 30	1.2 (0.8–1.7)	1.1 (0.7–1.9)	
			31–40	1.3 (0.9–1.7)	1.8 (1.2–2.7)	
			41–50	1.6 (1.2–2.1)	1.3 (0.8–2.0)	
			≥ 51	1.9 (1.5–2.4)	1.3 (0.9–1.8)	
			p for trend	0.0015	0.683	
			Years since cessation			
			≥ 20	1.2 (0.95–1.6)	1.3 (0.95–1.9)	
			11–19	1.6 (1.3–2.1)	1.5 (1.00–2.1)	
			≤ 10	1.9 (1.5–2.5)	1.3 (0.9–1.9)	
			p for trend	0.0015	0.683	

CI, confidence interval

Table 2.1.6.3. Case–control studies on tobacco smoking and stomach cancer: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Wynder *et al.* (1963) Slovenia, Iceland, Japan and USA Years of study not specified	Men: 367 cases and 401 controls; women: 154 cases and 252 controls	Hospital-based study Cases from Japan (51%), New York (30%), Slovenia (10%) and Iceland (9%) Controls with malignant and non-malignant diseases, individually matched by age and hospital; cancers of the respiratory and upper alimentary tract excluded
Staszewski (1969) Poland 1957–68	Men: 450 cases and 771 controls; women: 178 cases and 383 controls	Hospital-based study Cases confirmed by histopathology (72%) or surgery and/or radiology (28%) as cancer of the cardia (17%), middle part (27%), pylorus (33%) or all stomach (23%) Controls hospitalized for diseases not connected with smoking; cancers of the colon and rectum excluded
Haenszel *et al.* (1972) USA 1963–69	Men: 135 cases and 270 controls; women: 85 cases and 170 controls	Hospital-based study among Japanese Hawaiian migrants (120) and their offspring (100) Cases: 96% confirmed histologically as cancer of the cardia (6%), fundus (8%), prepylorus (10%), antrum (33%), lesser or greater curvatures (25%) or other/unknown site (18%) Controls individually matched by age, sex, hospital and time of visit; gastric ulcer, other stomach diseases and cancer of digestive system excluded
Haenszel *et al.* (1976) Japan 1962–65	Men: 526 cases and 1052 controls; women: 257 cases and 514 controls	Hospital-based study from eight hospitals in Hiroshima (247) and Miyagi (416) Cases: 98% confirmed microscopically as cancer of the cardia (9%), fundus (4%), antrum (40%), prepylorus (31%), or lesser or greater curvatures (14%); aged ≥ 35 years Controls with neoplasms, gastrointestinal, infectious and circulatory diseases and conditions affecting nervous system and sense organs; individually matched for age, sex, hospital and time of visit; gastric ulcer, other stomach diseases and cancer of digestive system excluded
Hoey *et al.* (1981) France 1978–80	Men: 40 cases and 168 controls	Hospital-based study in endoscopy department among French residents of Lyon Cases confirmed histologically; mean age, 65.4 years; 91% of eligible cases Controls with other gastrointestinal diagnoses (hiatal hernia (29%), colorectal polyps (33%), gallstones (17%) and colorectal cancer (21%)); mean age, 59.9 years

Table 2.1.6.3 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Ames & Gamble (1983) USA Years of study not specified	Men: 46 cases and 92 controls	Prospective mortality study on white coal miners Controls: deaths from other cancers (1:1) and from non-cancer/non-accidents (1:1), individually matched by age at death and year of birth (± 3 years)
Correa *et al.* (1985) USA 1979–83	Men: 264 cases and 264 controls; women: 127 cases and 127 controls	Hospital-based study in 26 counties of South Louisiana Cases: 98% confirmed histologically as cancer of the antrum/corpus (87%), cardia (6.5%) or other/unknown site (6.5%) Controls mainly with cardiovascular (20%), gastrointestinal (12%), infectious (11%) or respiratory (10%) diseases; individually matched on age (± 5 years), sex, race and hospital
Risch *et al.* (1985) Canada 1979–82	Men: 163 cases and 163 controls; women: 83 cases and 83 controls	Population-based study Cases confirmed histologically; aged 35–79 years Controls randomly selected from electoral lists, individually matched by age (± 4 years), sex, province of residence and neighbourhood; participation rate, 58%
Jedrychowski *et al.* (1986) Poland 1980–81	Men: 70 cases and 140 controls; women: 40 cases and 80 controls	Hospital- and population-based study using interviews Cases confirmed histologically Controls individually matched by age (± 5 years) and sex: hospital-based (1:1), with orthopaedic problems, heart or endocrinological disorders; obvious gastrointestinal diseases and recent dietary abnormality excluded; population-based (1:1), randomly selected from healthy participants of a medical survey on chronic chest diseases
You *et al.* (1988) China 1984–86	Men: 443 cases and 888 controls; women: 121 cases and 243 controls	Population-based study among residents of Linqu for ≥ 10 years Cases confirmed by histology (50%), endoscopy or surgery (32%) or radiological and clinical examination (17%); aged 35–64 years; 82% of eligible cases Controls randomly selected using rosters, frequency-matched by age and sex; participation rate, 100%

Table 2.1.6.3 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Hu *et al.* (1988) China 1985–86	Men: 170 cases and 170 controls; women: 71 cases and 71 controls	Hospital-based study from two hospitals in Harbin and Heilongjiang province using interviews Cases confirmed histologically; aged 25–80 years Controls with non-neoplastic diseases (chest diseases, general surgery, urological and orthopaedic diseases, trauma); individually matched by sex, age and area of residence
Buiatti *et al.* (1989, 1991) Italy 1985–87	1989 study: men: 640 cases; women: 376 cases; 1991 study: men: 597 cases; women: 326; 1159 controls (705 men and 454 women)	Population-based study among residents of four areas with varying incidence of stomach cancer using interviews Cases confirmed histologically as intestinal (55%), diffuse (23%) or mixed/unclassified (22%); mean age, 65 years; 83% of eligible cases Controls randomly selected from general population, frequency-matched on 5-year age-groups and sex; participation rate, 81%
Ferraroni *et al.* (1989) Italy 1983–88	Men: 243 cases and 1334 controls; women: 154 cases and 610 controls	Hospital-based study from four major hospitals in Milan Cases confirmed histologically; aged ≤ 75 years Controls with traumatic (38%), non-traumatic orthopaedic (15%) and acute surgical conditions (34%) and ear, nose, throat, skin and dental disorders (13%); malignant tumours, digestive tract disorders or any coffee-, alcohol- or tobacco-related conditions excluded; median age, 56 years
De Stefani *et al.* (1990) Uruguay 1985–88	Men: 138 cases and 414 controls; women: 72 cases and 216 controls	Hospital-based study from the University Hospital in Montevideo using interviews Cases confirmed histologically as cancer of the cardia (13%), corpus (9%), antrum (15%) and unclassified (63%); aged 30–89 years; 100% of eligible cases participated. Controls individually matched (1:3) by age (± 5 years) and sex; tobacco- or alcohol-related diseases or gastric conditions excluded
Kato *et al.* (1990) Japan 1985–89	Men: 289 cases and 2013 controls; women: 138 cases and 2415 controls	Hospital-based study at gastroscopy department in Aichi prefecture; self-administered questionnaire Cases confirmed histologically, mainly of diffuse (48%) or intestinal (50%) type Controls with normal gastric mucosa (3014) or atrophic gastritis (1414); other cancers, resected stomach and gastroduodenal diseases excluded 89% participation rate for cases and controls
Lee *et al.* (1990) China, Province of Taiwan 1954–88	Men: 123 cases and 478 controls; women: 87 cases and 332 controls	Hospital-based study in four major hospitals in Taipei using interviews Cases confirmed histologically; 90% of eligible cases participated. Controls from ophthalmic service, group matched by sex and age; participation rate, 96%

Table 2.1.6.3 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Wu-Williams *et al.* (1990) USA 1975–82	Men: 137 cases and 137 controls	Population-based study among white men from Los Angeles County using interviews Cases confirmed histologically as cancer of the cardia (58), fundus/body (10), antrum/pylorus (22) or other site (47); aged < 55 years; 52 % of eligible cases participated. Controls individually matched by age (± 5 years), sex and race (Hispanic white and other white)
Boeing *et al.* (1991) Germany 1985–87	Men and women: 143 cases (almost equal number of men and women) and 579 controls (slightly more women)	Hospital-based study from five hospitals in Bavaria and Hesse using interviews Cases confirmed histologically as cancer of the cardia (17%), corpus (32%), antrum/pylorus (40%) or multiple sites (11%); aged 32–80 years; 85% of eligible cases Controls: 251 visitors and 328 patients with other cancers (12%), metabolic (13%), cardiovascular (30%) and respiratory (5%) diseases, and diseases of digestive organs other than stomach (23%); matched by sex and age (± 3 years); patients with history of atrophic gastritis or intestinal metaplasia excluded; participation rate, 90%
Dockerty *et al.* (1991) New Zealand 1980–84	Men: 797 cases and 8398 controls	Cases and controls from New Zealand Cancer Registry Cases aged ≥ 20 years; 78% of all cases registered at the Registry. Controls with other types of cancer; smoking-related cancers excluded
Saha (1991) UK 8 years	Men: 81 cases and 162 controls; women: 36 cases and 72 controls	Hospital-based study at four hospitals using interviews Cases confirmed histologically as cancer of the cardia (46), body (24) or antrum (47); aged 35–89 years Controls with benign surgical conditions, individually matched by age (± 5 years), sex and social class; respiratory, upper gastrointestinal and vascular diseases excluded
Yu & Hsieh (1991) China 1976–80	Men: 52 cases and 2676 controls; women: 32 cases and 1843 controls	Population-based study among primary and middle-school staff in Shanghai using interviews for cases and self-administered questionnaire for controls Cases confirmed histologically as cancer of the lesser curvature (73%), pylorus (17%), antrum (6%) or other site (4%); 89% of eligible cases participated. Controls from 55 randomly selected schools stratified by districts; participation rate, 91%

Table 2.1.6.3 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Agudo *et al.* (1992) Spain 1987–89	Men: 235 cases and 235 controls; women: 119 cases and 119 controls	Hospital-based study in 4 regions with varying incidences of stomach cancer using a questionnaire Cases confirmed histologically mainly as intestinal (56%) or diffuse (26%) type; mean age, 65.2 years Controls with a wide variety of diagnoses; individually matched by hospital, sex, age (± 3 years) and area of residence; cancers of digestive and respiratory tracts, and chronic respiratory illnesses excluded; aged 31–88 years (mean, 65.5 years)
Hoshiyama & Sasaba (1992a,b) Japan 1984–90	Men: 251 cases and 483 controls	Population-based study among people living in Saitama Prefecture for ≥ 10 years using interviews Cases confirmed histologically as single (216) or multiple (35) cancer; 73% of eligible cases participated. Controls randomly selected from electoral roll with stratification by sex and age; participation rate, 28%
Palli *et al.* (1992) Italy 1985–87	Men: 597 cases and 705 controls; women: 326 cases and 454 controls	Population-based study using interviews Cases from study by Buiatti *et al.* (1991); histologically confirmed as cancer of the cardia (68) or other site (819); cancer of the stump (36) excluded from the analysis Controls randomly selected from 5-year age and sex strata; history of gastric surgery excluded
Jedrychowski *et al.* (1993) Poland 1986–90	Men: 520 cases and 520 controls	Hospital-based study from nine university hospitals in Poland using interviews Cases confirmed histologically as cancer of the cardia (137, of which 58% of intestinal and 20% of diffuse type) or of non-cardia (383, of which 51% of intestinal and 36% of diffuse type); aged < 75 years; 100% of eligible cases participated. Controls admitted mostly for accidents, orthopaedic problems or general surgery; individually matched by age (± 5 years); diseases of the gastrointestinal tract and other cancers excluded; participation rate, 100%
Kabat *et al.* (1993) USA 1981–90	Men: 295 cases and 4544 controls; women: 52 cases and 2228 controls	Hospital-based study in 28 hospitals of seven states using interviews Cases confirmed histologically as cancer of distal oesophagus/gastric cardia (194) or of distal stomach (153) Controls with non-tobacco-related cancers (43%) and non-cancer diagnoses (57%), including fractures, disc problems, eye problems, acute infections and trauma; matched by age (± 5 years), sex, race and hospital; cancers and other diseases of the gastrointestinal tract excluded

Table 2.1.6.3 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Hansson *et al.* (1994) Sweden 1989–92	Men: 218 cases; women: 120 cases; and 679 controls [no information on sex distribution]	Population-based study among residents of five counties in central and northern Sweden using interviews Cases confirmed histologically; aged 40–70 years (mean, 67.7 years); 74% of eligible cases Controls randomly selected from population registers, frequency-matched by sex and age strata; mean age, 67.0 years; participation rate, 77%
Inoue *et al.* (1994) Japan 1988–91	Men: 420 cases and 420 controls; women: 248 cases and 248 controls	Hospital-based study at Aichi Cancer Centre Hospital using self-administered questionnaire Cases identified through Cancer Registry database; confirmed histologically as cancer of the cardia, middle part or antrum; aged ≥ 18 years (mean, 58.0 years) Controls randomly selected from first-visit outpatients, individually matched by sex, age (± 2 years) and date of first visit (± 2 months); history of cancer or any other specific disease excluded; mean age, 57.8 years; participation rate, 98%
Siemiatycki *et al.* (1995) Canada 1979–85	Men: 251 cases and 2238 controls	Hospital- and population-based study among residents of Montreal area using interviews Cases confirmed histologically; aged 35–70 years Controls: 533 population-based, selected from electoral lists stratified by age; participation rate, 72%; 1705 hospital-based; cancers of the lung, bladder, oesophagus, pancreas, liver and kidney excluded
Yu *et al.* (1995) China 1991–93	Men: 453 cases and 453 controls; women: 258 cases and 258 controls	Population-based study among residents of Hongkou district and Nanhui county (Shanghai) using interviews Cases confirmed; aged < 80 years; 91% of eligible cases participated. Controls individually matched for age (± 3 years), sex and residence (street); participation rate, 99%
Gajalakshmi & Shanta (1996) India 1998–90	Men: 287 cases and 287 controls; women: 101 cases and 101 controls	Hospital-based study from Cancer Institute in Chennai (Madras) using interviews Cases confirmed histologically (75%) or by barium meal evidence, exploratory surgery or endoscopy (25%) Controls with cancer mainly of the penis, bone and connective tissue, skin and cervix; individually matched for age (± 5 years), sex, religion and mother tongue; cancers of the gastrointestinal tract, bladder and pancreas and smoking-related cancers excluded

Table 2.1.6.3 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Ji *et al.* (1996) China 1988–89	Men: 770 cases and 819 controls; women: 354 cases and 632 controls	Population-based study among permanent residents in Shanghai using interviews Cases identified through Shanghai cancer registry; confirmed histologically (52%) or by surgery, endoscopy, X-rays or ultrasound (48%) as cancer of the cardia (16%), distal stomach (70%) or unspecified site (14%); aged 20–69 years; 66% of eligible cases participated. Controls randomly selected, frequency-matched for age (5-year categories) and sex; participation rate, 86%
Zhang *et al.* (1996) USA 1992–94	Men: 122 cases and 62 controls; women: 40 cases and 70 controls	Hospital-based study at endoscopy department in New York using self-administered questionnaire Cases confirmed histologically as cancer of oesophagus/cardia (95) or distal stomach (67) Controls were cancer-free, with atrophic/chronic or other types of gastritis (71%) or disease-free (29%)
Gammon *et al.* (1997) USA 1993–95	Men: 477 cases and 555 controls; women: 152 cases and 140 controls	Population-based study using interviews Cases confirmed histologically as cancer of the cardia (261) or other sites (368); aged 30–79 years; 81% of eligible cases participated. Controls aged 30–65 years identified by random-digit dialling and those aged 65–79 years by random sampling of rosters; frequency-matched by age (5-year group) and sex; participation rate, 70%
De Stefani *et al.* (1998) Uruguay 1992–96	Men: 311 cases and 622 controls	Hospital-based study from four major hospitals in Montevideo using interviews Cases confirmed microscopically as cancer of the cardia (24), antrum (240), fundus (25) or of diffuse type (22); aged 25–84 years Controls mainly with eye disorders (33%), hernia (17%), osteoarticular diseases (11%) and skin (9%) and ear (7%) disorders; frequency-matched for age (10-year group), hospital, time of visit and residence; tobacco- and alcohol-related diseases and digestive tract conditions excluded; aged 25–84 years; participation rate for cases and controls, 93%
Liu *et al.* (1998) China 1986–88	Men: 20 195 cases and 52 775 controls; women: 9009 cases and 34 560 controls	Retrospective mortality study Cases aged 35–69 years Controls: death from neoplastic, respiratory and cardiovascular diseases excluded

Table 2.1.6.3 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Chow *et al.* (1999) Poland 1994–97	Men: 302 cases and 314 controls; women: 162 cases and 166 controls	Population-based study among Warsaw residents using interviews Cases from 22 hospitals in Warsaw, confirmed histologically mainly as intestinal (67%) or diffuse (14%); aged 21–79 years; 90% of eligible cases participated. Controls randomly selected from registry, frequency-matched by age (5-year categories) and sex; participation rate, 82%
Gao *et al.* (1999) China 1995	Men: 110 cases and 154 controls; women: 43 cases and 80 controls	Population-based study among Yangzhong residents using interviews Cases from Regional Cancer Registry, confirmed histologically; aged 30–79 years Controls from household registration office, individually matched for sex, age (± 2 years) and town or area of residence; participation rate for cases and controls, 100%
Inoue *et al.* (1999) Japan 1988–95	Men: 651 cases and 12 041 controls; women: 344 cases and 31 805 controls	Hospital-based study at Aichi Cancer Centre Hospital Cases from cancer registry and surgical records, confirmed histologically mainly as differentiated (46%) or non-differentiated (53%) Controls with benign tumours or non-neoplastic polyps (13%), benign and non-specific diseases (43%), or no abnormal findings (44%); cancers or past history of cancer excluded; aged ≥ 18 years
Ye *et al.* (1999) Sweden 1989–95	Men: 348 cases and 779 controls; women: 166 cases and 385 controls	Population-based study using interviews Cases confirmed histologically as cancer of the cardia (90), and distal cancer of intestinal (260) or diffuse (164) type; aged 40–79 years; 62% of eligible cases participated. Controls randomly selected from registers, frequency-matched by age and sex; participation rate, 76%
Lagergren *et al.* (2000) Sweden 1995–97	Men: 223 cases and 681 controls; women: 39 cases and 139 controls	Population-based study among people born in Sweden using interviews Cases of cardia; aged ≤ 80 years, mean 66 years; 83% of eligible cases participated. Controls randomly selected from whole population of Sweden, frequency-matched for age and sex; mean age, 68 years; participation rate, 73%
Mathew *et al.* (2000) India 1988–91	Men: 151 cases and 228 controls; women: 43 cases and 77 controls	Hospital-based study at the Regional Cancer Centre in Trivandrum using interviews Cases confirmed by histology and/or endoscopy or barium meal evidence, aged ≥ 20 years Controls selected from visitors, individually matched for age (± 5 years), sex, religion and residential area; controls with gastric complaints excluded

Table 2.1.6.3 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Zaridze *et al.* (2000) Russia 1996–97	Men: 248 cases and 292 controls; women: 200 cases and 318 controls	Hospital-based study in two cancer hospitals (cases) and two general hospitals (controls) among Moscow residents using self-administered questionnaire Cases confirmed histologically as cancer of the cardia (92) or non-cardia (356); aged < 75 years; 98% of eligible cases participated. Controls with a variety of conditions including respiratory (10%) and heart (10%) diseases, diseases of the nervous system (10%) and hypertension and stroke (9%); cancer and/or gastrointestinal diseases excluded; participation rate, 97%
Wu *et al.* (2001) USA 1992–97	Men: 492 cases and 999 controls; women: 228 cases and 357 controls	Population-based study among whites, Latino-, African and Asian Americans from Los Angeles county using interviews Cases confirmed histologically as cancer of the cardia (277) or distal stomach (443); aged 30–74 years; 56% of eligible cases participated. Controls individually matched by neighbourhood, sex, age (± 5 years) and ethnicity; diagnosis of stomach or oesophageal cancer excluded

Table 2.1.6.4. Case–control studies on tobacco smoking and stomach cancer

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)			Comments, variables adjusted for, significance, limitations of the study
Wynder *et al*. (1963) Slovenia, Iceland, Japan, USA	Men and women					No definition of smoking habit. No participation rate for cases or controls. No relative risk calculated. No consistent difference between cases and controls in terms of type or quantity of tobacco smoked
Staszewski (1969) Poland 1957–68	Men and women	Ever-smoker	1.6			No definition of smoking habit. No participation rate for cases or controls. The majority of cases among men were cancer of the cardia and pylorus, and among women cancer of the cardia. †Index of smoking ≥ 300 ‡Index of smoking = daily amount of tobacco × years of smoking
			Cases	Controls		
		% of smokers	90.0	84.8	$p \le 0.01$	
		% of heavy smokers†	71.9	63.0	$p \le 0.01$	
		Index of smoking‡	472	428	$p < 0.05$	
Haenszel *et al.* (1972) USA, Hawaii 1963–69	Men and women	Any tobacco use	Men and women	Men	Women	* $p < 0.05$ No definition of tobacco use. No response rate for cases or controls. Odds ratios adjusted for sex and age, and for birthplace for Hawaiian Japanese
		Hawaiian Japanese	1.5*	1.4	1.7	
		Migrant	1.9*	1.9*	1.7	
		Offspring	1.1	0.9	1.8	
		≥ 20 vs < 20 cigarettes/day		0.9		
Haenszel *et al.* (1976) Japan 1962–65	Men and women	Any tobacco use				Odds ratio reported for men only, probably because of low prevalence of smoking among women in Japanese populations. Same questionnaire used as in previous study. No response rate for cases or controls. Odds ratios adjusted for prefecture, occupation (farm, non-farm), age and sex. Relative risks probably underestimated because of high proportion of controls with smoking-related diseases. †Data from previous study
		Hiroshima	1.1			
		Miyagi	1.3			
		Hawaii†	1.4			
			All $p > 0.05$			

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Hoey *et al.* (1981) France 1978–80	Men	≥ 7 cigarettes/week	4.8 (1.6–14.8)		Very small study. No participation rate for controls. Significant difference between cases and controls in mean age and weekly alcohol consumption. Little information about potential confounding. Relative risk reduced to 3.8 after adjustment for wine intake, but still statistically significant [95% CI not given].
Ames & Gamble (1983) USA	Men	Current smoker	0.7 (0.2–2.0)		Very small study. Deaths from other cancers used as controls, leading to underestimation of risk
Correa *et al.* (1985) USA 1979–83	Men and women	*Cigarette smoker*	**Whites**	**Blacks**	No response rate for cases or controls. No definition of smoking habit. High proportion of interviews with proxies. Odds ratios adjusted for age, sex, current alcohol consumption, respondent type, education and income. About 30% of controls had cardiac or respiratory diseases. No significant linear trend for no. of cigarettes/day, pack–years or age at starting smoking. Increasing risk with increasing duration of smoking for blacks only ($p < 0.05$). Relative risk for deep inhalers of 1.8 compared with nonsmokers and non-inhalers. Adjustment for vitamin C intake had no effect on relative risk [data not shown].
		Ever-smoker	1.3 (0.8–2.2)	2.6 (1.4–5.0)	
		Former smoker	1.0 (0.5–2.0)	1.9 (0.8–4.2)	
		Current smoker	1.4 (0.8–2.4)	2.7 (1.3–5.3)	
Risch *et al.* (1985) Canada 1979–82	Men and women	20 pack–years	1.3 (1.01–1.6)		No definition of smoking habit or smoking history. Low response rate for controls. Odds ratios adjusted for ethnicity, various foods and type of water supply.
Jedrychowski *et al.* (1986) Poland 1980–81	Men and women	Former smoker	0.8 (0.3–2.1)		No definition of smoking habit. No response rate for cases or controls. Analysis performed with hospital controls only. Odds ratio adjusted for residence only. Relative risk could be underestimated because hospital controls included patients with smoking-related diseases
		Current smoker	0.7 (0.4–1.2)		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
You *et al.* (1988) China 1984–86	Men and women	*Cigarettes /day*			Analysis for men only because there were few women who smoked. Odds ratios adjusted for age, family income and alcohol drinking. Association stronger when analysis restricted to histologically confirmed cases [data not shown].
		< 20	1.3 (0.9–1.9)		
		≥ 20	1.5 (1.0–2.1)		
		p for trend	0.01		
Hu *et al.* (1988) China 1985–86	Men and women	*Cigarettes/day*	**Univariate**	**Multivariate**	No definition of smoking status. No participation rate for cases or controls. Multivariate analysis adjusted for Chinese cabbage and alcohol consumption. Inconsistency between table and text in direction of trend for age at starting analysis, and limit of category surprisingly low.
		< 6	1.0		
		≥ 6	1.8 (1.2–2.6)		
		Duration (years)			
		< 14	1.0		
		14–25	1.6 (0.7–3.6)		
		> 25	2.3 (1.6–3.5)		
			p for trend < 0.001		
		Age at starting smoking (years)			
		> 21	2.2 (1.1–4.4)		
		6–21	1.6 (0.8–3.2)		
		< 6	1.0		
		p for trend	< 0.001		
		Index of smoking[a]			
		< 7	1.0	1.0	
		≥ 7	2.0 (1.4–2.9)	2.0 (1.4–2.7)	
Buiatti *et al.* (1989, 1991) Italy 1985–87	Men and women	Former smoker	0.9 (0.7–1.1)		No definition of smoking history or smoking habit. Odds ratios adjusted for age, sex, study area and place of residence, migration from the south, socioeconomic status, family history of stomach cancer and Quetelet index. Results not presented in tables. No association found for specific histological types separately.
		Current smoker			
		Low	1.0 (0.8–1.4)		
		High	1.2 (0.9–1.7)		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Ferraroni *et al.* (1989) Italy 1983–88	Men and women		**Univariate**	**Multivariate**	No participation rate for cases or controls. Univariate analysis adjusted for age and sex. Multivariate analysis adjusted for age, sex, social class, education, marital status, alcohol and coffee consumption.
		Former smoker	0.9	0.9	
		Cigarettes/day			
		<15	0.9	1.0	
		15–20	1.0	1.0	
		> 25	1.1	1.1	
		χ^2 for trend	0.18	1.19	
De Stefani *et al.* (1990) Uruguay 1985–88	Men and women		**All subsites**	**Cardia and corpus** (*n* = 46)	Analysis for men only because there were few women who smoked. No participation rate for controls. Odds ratios adjusted for age, area of residence, wine intake and vegetable consumption.
		Former smoker	1.9 (0.9–3.8)	1.8 (0.4–8.8)	
		Current smoker	2.7 (1.3–5.5)	5.3 (1.2–24.1)	
		p for trend	0.004	0.002	
		Age at starting smoking (years)			
		≥ 20	0.7 (0.4–1.3)		
		15–19	0.8 (0.5–1.3)		
		≤ 14	1.0		
		p for trend	0.01		
		Cigarettes/day			
		1–9	1.3 (0.5–3.4)	2.9 (0.6–14.8)	
		10–19	1.7 (0.7–4.3)	3.0 (0.6–15.0)	
		≥ 20	1.6 (0.6–3.8)	3.8 (0.8–17.1)	
		p for trend	0.92		
		Duration (years)			
		1–29	1.7 (0.7–4.2)	2.0 (0.3–12.0)	
		30–39	2.3 (0.9–5.4)	2.3 (0.4–12.6)	
		40–49	2.3 (1.0–5.2)	4.1 (0.9–19.4)	
		≥ 50	3.4 (1.5–7.5)	4.0 (0.8–19.4)	
		p for trend	0.002		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
De Stefani *et al.* (1990)		*Years since quitting*			
		≥ 10	0.6 (0.3–1.0)		
		5–9	0.5 (0.2–1.1)		
		1–4	1.2 (0.6–2.3)		
		p for trend	0.028		
		Filter-tipped			
		Non-user	1.0		
		User	1.2 (0.7–2.1)		
		Type of tobacco			
		Blond	1.0		
		Black	1.4 (0.9–2.3)		
Kato *et al.* (1990) Japan 1985–89	Men and women	**All types**	Men	Women	Many more cases than controls were aged ≥ 55 years. Odds ratios adjusted for age and residence. †Group 1, healthy controls; group 2, patients with atrophic gastritis. In a multivariate analysis, odds ratios additionally adjusted for type of breakfast, consumption of salted fish gut and cod roe and past history of gastric ulcer were significantly different from unity for all categories of smokers [data not shown].
		Compared with group 1†			
		Former smoker	1.8 (1.2–2.8)	1.3 (0.5–3.1)	
		Cigarettes/day			
		1–19	1.9 (1.1–3.3)	0.6 (0.2–1.8)	
		≥ 20	2.8 (1.8–4.3)	1.5 (0.6–3.7)	
		Compared with group 2			
		Former smoker	2.1 (1.4–3.3)	1.1 (0.4–2.9)	
		Cigarettes/day			
		1–19	2.5 (1.5–4.4)	0.6 (0.2–1.8)	
		≥ 20	3.5 (2.3–5.5)	2.5 (0.9–6.9)	
		Diffuse type	(*n* = 117)	(*n* = 86)	
		Compared with group 1			
		Former smoker	2.7 (1.4–5.5)	1.0 (0.3–3.4)	
		Cigarettes/day			
		1–19	1.8 (0.7–4.2)	0.5 (0.1–2.1)	
		≥ 20	3.3 (1.7–6.4)	1.1 (0.3–3.6)	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Kato *et al.* (1990) (contd)		**Intestinal type**	(*n* = 166)	(*n* = 49)	
		Compared with group 1			
		Former smoker	1.6 (0.9–2.8)	1.2 (0.3–5.3)	
		Cigarettes/day			
		1–19	2.3 (1.2–4.3)	0.8 (0.2–3.6)	
		≥ 20	3.0 (1.7–5.1)	2.7 (0.8–9.9)	
		Compared with group 2			
		Former smoker	2.0 (1.2–3.4)	0.9 (0.2–4.3)	
		Cigarettes/day			
		1–19	3.1 (1.6–6.0)	0.7 (0.2–3.2)	
		≥ 20	3.8 (2.2–6.6)	6.4 (1.5–27.4)	
Lee *et al.* (1990) China, Province of Taiwan 1954–88	Men and women	Current smoker	1.6 ($p < 0.05$)		No definition of smoking habit. Multivariate analysis adjusted for alcohol drinking, green tea habit and salted meat, fried food, fermented beans and milk, as well as other variables not listed. Relative risks probably underestimated by use of controls with eye diseases possibly causally associated with smoking
		Duration (years)			
		1–30	1.4		
		31–40	1.4		
		≥ 41	1.9 ($p < 0.05$)		
		Cigarettes/day			
		1–10	1.4		
		11–20	1.5		
		≥ 21	1.8 ($p < 0.05$)		
Wu–Williams *et al.* (1990) USA 1975–82	Men		**All pairs**	**Excl. proxies**	Very small study. Very low response rate for cases; no participation rate for controls. High proportion of interviews with proxies (42% of cases, 12% of controls). Numbers in analyses by subsites too small for meaningful conclusion. Matched analysis made without adjustment. [†]Values for which the 95% CI does not include 1.0
		Former smoker	1.3 (0.6–2.5)	1.8	
		Current smoker (packs/day)			
		1	2.2 (1.1–4.7)	5.4[†]	
		2	2.1 (1.0–4.5)	4.0[†]	
		≥ 3	5.2 (1.4–8.6)	17.7[†]	
		Any tobacco			
		Former smoker	1.1 (0.5–2.2)	1.9	
		Current smoker (g/day)			
		1–20	2.3 (1.1–4.8)	6.2[†]	
		> 20–40	2.0 (1.0–4.3)	3.3[†]	
		> 40	5.0 (1.4–17.5)	17.1[†]	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Wu-Williams			**Cardia**	**Fundus/body**	
et al. (1990)		Former smoker	1.0	3.4	
(contd)		Current smoker (packs/day)			
		1	2.3	2.0	
		2	2.2	4.4	
		≥ 3	7.0[†]	9.3	
		Any tobacco			
		Former smoker	0.9	3.5	
		Current smoker (g/day)			
		1–20	2.3	2.1	
		> 20–40	2.6	4.2	
		> 40	7.0[†]	9.3	
			Antrum/pylorus	**All others**	
		Former smoker	0.8	1.4	
		Current smoker (packs/day)			
		1	4.0	1.7	
		2	4.1	1.8	
		≥ 3	7.2	1.8	
		Any tobacco			
		Former smoker	0.4	1.2	
		Current smoker (g/day)			
		1–20	4.8	1.8	
		> 20–40	2.9	1.8	
		> 40	12.1[†]	1.9	
Boeing *et al.* (1991) Germany 1985–87	Men and women	Former smoker Current smoker	0.6 (0.3–1.2) 0.5 (0.3–0.9)		Higher proportion of nonsmokers in cases from two study centres; higher proportion of smokers in hospital controls than in visitor controls; 47% of hospital controls had tobacco-related diseases. Odds ratios adjusted for age, sex and hospital. Significant positive trend observed for pack–years [data not shown]

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Dockerty *et al.* (1991) New Zealand 1980–84	Men	Ever-smoker	1.4 (1.2–1.6)[b] 1.4 (1.2–1.7)[c]		Information on smoking habit abstracted from Cancer Registry records. No definition of smoking habit. No information on histological confirmation of diagnoses
Saha (1991) UK 8 years	Men and women	Former smoker	1.4 (1.7–3.6)		Small no. of cases for the period of study. No participation rate for cases or controls. Statistical analysis limited. Odds ratios not adjusted. Small study
		Current smoker	2.6 (1.2–5.5)		
		Non–swallower	1.3 (1.5–2.4)		
		Swallower	6.4 (3.3–12.5)		
		Cigarettes/day	**Body**[†]	**Antrum**[†]	[†]Cancer of cardia used as reference (odds ratio, 1.0)
		10–19	0.6 (0.9–3.9)	2.1 (0.6–7.5)	
		20–30	1.9 (0.5–7.5)	2.9 (0.9–9.3)	
		Age at starting smoking (years)			
		16–20	0.5 (0.1–3.3)	1.3 (0.3–4.7)	
		21–30	2.0 (0.6–6.9)	1.2 (0.4–3.9)	
		10–15	1.3 (0.3–5.2)	2.5 (0.3–7.8)	
		Swallowers			
		Compared with non-swallower	7.2 (1.3–41.0)		
		Compared with nonsmoker	2.4 (0.6–9.0)		
Yu & Hsieh (1991) China 1976–80	Men and women	*Cigarettes/day*	**Crude**	**Adjusted**	57% of interviews for cases with proxies. Odds ratios adjusted for age, sex, family income, family history of cancer or tuberculosis, blood type and consumption of alcohol, strong tea, fruit and milk
		1–20	3.7	2.1 (0.9–4.6)	
		> 20	20.7	6.2 (2.2–17.0)	
				p for trend = 0.003	
Agudo *et al.* (1992) Spain 1987–89	Men and women	Former smoker	0.9 (0.5–1.7)		Analysis for men only because few women smoked. No participation rate for cases or controls. Odds ratios adjusted for total caloric intake (including alcohol) and consumption of fruit, vegetables, cold cuts and preserved fish.
		Current smoker	0.9 (0.6–1.5)		
		Ever-smoker	0.9 (0.6–1.7)		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Hoshiyama & Sasaba (1992a,b) Japan 1984–90	Men		**Single**	**Multiple**	No definition of smoking status. Very low response rate for controls. No comparison of demographic variables such as education or socioeconomic status between cases and controls. Odds ratios adjusted for sex, age and administrative division.
		Former smoker	1.1 (0.6–1.8)	0.9 (0.3–3.0)	
		Current smoker	1.5 (0.9–2.6)	1.4 (0.5–4.3)	
		Pack–years			
		≤ 40	1.4 (0.8–2.3)	1.1 (0.3–3.3)	
		> 40	1.3 (0.8–2.4)	1.3 (0.4–4.2)	
Palli *et al.* (1992) Italy 1985–87	Men and women		**Gastric cardia**	**Other subsites**	Study population from Buatti *et al.* (1989, 1991). Odds ratios adjusted for age, sex, area and place of residence, migration from the south, socioeconomic status, family history of stomach cancer and Quetelet index. Similar results with pack–years variable [data not shown]
		Current smoker	1.1 (0.6–2.3)	0.9 (0.7–1.1)	
		Former smoker	1.1 (0.5–2.2)	1.1 (0.8–1.4)	
Jedrychowski *et al.* (1993) Poland 1986–90	Men	*Filter status*			Current and former smokers combined because of insufficient distinction in questionnaire. Odds ratios adjusted for hospital, age, sex, occupation, education, sausage consumption, fruit and vegetable consumption and vodka drinking. No relative risks for ever-smokers. No increased relative risk for cigarettes/day, age at starting smoking or smoking before breakfast [data not shown]. Odds ratios seem overadjusted
		With filter/unknown	1.0 (0.7–1.5)		
		With and without filter	1.1 (0.8–1.6)		
		Without filter	1.4 (0.9–2.1)		
		p for trend	0.14		
		Pack–years			
		< 20	1.2 (0.8–1.7)		
		≥ 20	1.1 (0.8–1.6)		
		p for trend	0.58		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)	Comments, variables adjusted for, significance, limitations of the study
Kabat *et al.* (1993) USA 1981–90	Men and women	**Men**	**Distal stomach**	Analysis limited to Caucasians. No participation rate for controls. Odds ratios adjusted for age, education, alcohol consumption, hospital and time of interview.
		Current smoker	1.7 (1.0–3.0)	
		Former smoker	1.4 (0.9–2.4)	
		Cigarettes/day		
		1–20	1.7 (1.0–2.8)	
		21–30	0.8 (0.3–1.8)	
		≥ 31	1.6 (0.9–2.9)	
		Years since quitting†		†Relative to current smokers
		≥ 21	0.6 (0.3–1.2)	
		11–20	1.1 (0.6–1.9)	
		6–10	1.1 (0.6–2.4)	
		1–5	1.0 (0.5–2.0)	
		Women		
		Current smoker	3.2 (1.3–7.7)	
		Former smoker	2.0 (0.8–4.9)	
		Cigarettes/day		
		1–20	1.6 (0.6–3.8)	
		≥ 21	4.8 (1.9–11.9)	
		Years since quitting†		†Relative to current smokers
		1–10	0.7 (0.2–2.2)	
		≥ 11	0.7 (0.2–2.1)	
Hansson *et al.* (1994) Sweden 1989–92	Men and women	Former smoker	1.1 (0.8–1.6)	Odds ratios adjusted for age, sex, socioeconomic status and use of other tobacco
		Current smoker	1.7 (1.2–2.5)	
		Age at starting smoking (years)		
		≥ 21	1.2 (0.7–1.9)	
		16–20	1.4 (0.9–2.0)	
		≤ 15	1.5 (0.9–2.5)	
		p for trend	0.38	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Hansson *et al.* (1994) (contd)		*Duration (years)*			
		1–10	1.1 (0.6–2.1)		
		11–20	1.1 (0.6–2.0)		
		21–30	0.8 (0.5–1.4)		
		31–40	1.8 (1.2–3.0)		
		≥ 41	1.6 (1.1–2.5)		
		p for trend	0.01		
		Cigarettes/day			
		1–5	1.1 (0.7–1.7)		
		6–10	1.4 (0.9–2.1)		
		11–15	2.1 (1.2–3.5)		
		≥ 16	1.2 (0.8–1.8)		
		p for trend	0.10		
		Years since quitting			
		> 31	0.9 (0.5–1.7)		
		21–31	0.9 (0.5–1.7)		
		11–20	1.2 (0.7–2.1)		
		≤ 10	1.3 (0.7–2.2)		
		Current smoker	1.7 (1.2–2.5)		
		p for trend	0.02		
Inoue *et al.* (1994) Japan 1988–91	Men and women	**Men**	**All**	**Cardia** (*n* = 79)	No definition of smoking habit. Odds ratios adjusted for age (continuous) and intake of fresh vegetables. According to the authors, prevalence of smoking in general population in Japan is slightly higher than in hospital controls used (81.6% vs 77% in men), possibly leading to a slight overestimation of risks
		Ever-smoker	2.6 (1.7–3.8)	4.4 (1.8–11.3)	
		Current smoker	2.7 (1.8–4.1)	4.7 (1.8–12.3)	
		Former smoker	2.4 (1.6–3.6)	4.1 (1.6–11.0)	
		Cigarettes/day			
		< 20	2.7 (1.6–4.5)	5.9 (2.0–17.3)	
		≥ 20	2.7 (1.8–4.1)	4.3 (1.6–11.5)	
		Years since quitting			
		≥ 10	2.3 (1.4–3.7)	2.8 (0.9–8.6)	
		1–9	2.5 (1.5–4.1)	4.7 (1.6–13.7)	
		< 1	2.6 (1.2–5.2)	6.9 (1.9–25.0)	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Inoue *et al.* (1994) (contd)			**Middle** (*n* = 133)	**Antrum** (*n* = 170)	
		Ever-smoker	1.8 (1.0–3.1)	2.9 (1.7–5.1)	
		Current smoker	1.9 (1.1–3.4)	3.0 (1.7–5.4)	
		Former smoker	1.6 (0.9–2.9)	2.7 (1.5–5.0)	
		Cigarettes/day			
		< 20	1.4 (0.6–3.0)	3.0 (1.5–6.1)	
		≥ 20	2.2 (1.2–3.9)	3.0 (1.6–5.5)	
		Years since quitting			
		≥ 10	1.7 (0.9–3.4)	2.7 (1.4–5.4)	
		1–9	1.4 (0.7–3.0)	3.0 (1.5–6.1)	
		< 1	3.6 (0.8–5.8)	2.1 (0.7–6.1)	
		Women	**All**	**Cardia** (*n* = 44)	Because of the small number of women who smoked, no detailed analyses were performed
		Ever-smoker	1.2 (0.7–2.0)	1.3 (0.5–3.1)	
			Middle (*n* = 85)	**Antrum** (*n* = 86)	
		Ever-smoker	1.0 (0.5–2.1)	1.3 (0.7–2.6)	
Siemiatycki *et al.* (1995) Canada 1979–85	Men	Ever-smoker	1.7 (1.1–2.6)		Odds ratios adjusted for age, ethnic group, socioeconomic status, consumption of β-carotene, coffee and alcohol. Odds ratios shown are with population controls only. Difference in odds ratios between population and hospital controls was negligible.
		Pack–years			
		≤ 25	1.6 (0.9–2.8)		
		26–49	1.6 (1.0–2.7)		
		50–74	1.7 (1.0–2.9)		
		≥ 75	1.9 (1.0–3.3)		
Yu *et al.* (1995) China 1991–93	Men and women	*Cigarettes/day*			No definition of smoking habit. Odds ratios adjusted for age and sex
		1–9	1.2 (0.8–1.9)		
		10–19	1.1 (0.8–1.5)		
		≥ 20	1.9 (1.4–2.5)		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Gajalakshmi & Shanta (1996) India 1988–90	Men and women	*Any tobacco*	**Model 1**	**Model 2**	Any tobacco included bidi, cigarette and/or chutta. Conditional logistic regression models: Model 1, adjusted for income, education and area of residence; Model 2, additionally adjusted for betel-quid chewing habit and significant dietary factors. Absence of trend with age at starting smoking probably caused by reference age of 20 years or less being too high
		Former smoker	1.8 (1.1–3.1)	1.5 (0.7–3.5)	
		Current smoker	2.7 (1.8–4.1)	2.5 (1.4–4.4)	
		Ever-smoker	2.5 (1.7–3.6)	2.2 (1.3–3.8)	
		Current cigarette smoker	2.0 (1.1–3.6)		
		Age at starting smoking (years)			
		> 30	1.5 (0.4–5.6)		
		21–30	2.1 (0.9–5.1)		
		≤ 20	2.4 (0.9–5.9)		
		p for trend	< 0.1		
		Lifetime exposure (no. of cigarettes)			
		< 50 000 (mild)	1.6 (0.7–3.6)		
		50 000–100 000 (moderate)	2.0 (0.7–5.4)		
		> 100 000 (heavy)	3.1 (0.9–10.5)		
		p for trend	< 0.01		
Ji *et al.* (1996) China 1988–89	Men and women		**Men**	**Women**	Odds ratios adjusted for age, education and income (and alcohol drinking for men only) [†]≥ 20 cigarettes/day
		Former smoker	1.3 (0.9–1.8)	2.0 (0.7–5.6)	
		Current smoker	1.4 (1.1–1.7)	0.9 (0.5–1.4)	
		Cigarettes/day			
		1–9	1.0 (0.7–1.4)	1.1 (0.6–2.0)	
		10–19	1.1 (0.8–1.4)	0.5 (0.2–1.2)	
		20–29	1.8 (1.4–2.3)	2.1 (0.7–6.3)[†]	
		≥ 30	1.4 (0.9–2.1)		
		p for trend	0.0002	0.80	
		Duration (years)			
		0.5–19	1.0 (0.7–1.5)	1.0 (0.4–2.6)	
		20–29	1.4 (1.02–2.0)	1.0 (0.4–2.1)	
		30–39	1.3 (0.9–1.7)	1.1 (0.5–2.4)	
		≥ 40	1.6 (1.2–2.2)	0.9 (0.4–2.2)	
		p for trend	0.002	0.91	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)			Comments, variables adjusted for, significance, limitations of the study
Ji *et al.* (1996) (contd)		*Pack–years*				
		< 10	1.0 (0.7–1.4)	< 10	0.9 (0.4–1.6)	
		10–19	1.1 (0.8–1.5)	10–19	1.0 (0.5–2.1)	
		20–39	1.5 (1.2–2.1)	≥ 20	1.3 (0.5–3.1)	
		≥ 40	1.7 (1.2–2.3)			
		p for trend	0.0002	0.62		
		Age at starting smoking (years)				
		≥ 30	1.0 (0.7–1.4)	≥ 25	0.7 (0.4–1.3)	
		25–29	1.4 (0.9–1.9)	< 25	1.8 (0.9–3.6)	
		20–24	1.6 (1.2–2.2)			
		< 20	1.3 (0.95–1.7)			
		p for trend	0.005	0.37		
		Years since quitting				
		≥ 20	0.7 (0.3–1.6)	≥ 10	3.7 (0.9–14.7)	
		10–19	1.5 (0.8–2.7)	< 10	0.7 (0.1–4.1)	
		5–9	0.9 (0.5–1.9)			
		< 5	2.7 (1.4–5.4)			
		p for trend	0.10	0.48		
		Men	**Cardia** (*n* = 145)	**Distal** (*n* = 530)		
		Former smoker	1.8 (0.97–3.4)	1.1 (0.7–1.7)		
		Current smoker	1.2 (0.8–1.9)	1.4 (1.1–1.9)		
		Cigarettes/day				
		1–9	1.0 (0.5–2.1)	1.0 (0.7–1.6)		
		10–19	1.1 (0.7–1.9)	1.0 (0.8–1.5)		
		20–29	1.4 (0.9–2.3)	1.9 (1.4–2.6)		
		≥ 30	1.9 (0.96–3.7)	1.3 (0.8–2.1)		
		p for trend	0.06	0.0004		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
		Duration (years)			
		0.5–19	1.4 (0.7–2.7)	1.0 (0.6–1.4)	
		20–29	1.2 (0.6–2.3)	1.5 (1.02–2.2)	
		30–39	1.1 (0.6–1.9)	1.4 (1.2–2.5)	
		≥ 40	1.4 (0.9–2.4)	1.8 (1.2–2.5)	
		p for trend	0.28	0.001	
		Pack–years			
		< 10	1.4 (0.8–2.6)	1.0 (0.7–1.5)	
		10–19	0.8 (0.4–1.6)	1.1 (0.7–1.6)	
		20–24	1.3 (0.8–2.2)	1.7 (1.2–2.3)	
		≥ 25	1.6 (0.9–2.7)	1.7 (1.2–2.4)	
		p for trend	0.14	0.0002	
		Age at starting smoking (years)			
		≥ 30	1.0 (0.5–1.8)	1.0 (0.7–1.5)	
		25–29	2.0 (1.1–3.6)	1.2 (0.8–1.9)	
		20–24	1.5 (0.9–2.5)	1.8 (1.3–2.4)	
		< 20	1.0 (0.5–1.7)	1.4 (0.99–1.9)	
		p for trend	0.52	0.002	
		Years since quitting			
		≥ 20	1.5 (0.5–5.2)	0.5 (0.2–1.5)	
		10–19	1.3 (0.5–4.0)	1.4 (0.7–2.8)	
		5–9	1.3 (0.4–4.3)	0.7 (0.3–1.8)	
		< 5	5.5 (1.9–15.9)	2.5 (1.1–5.4)	
		p for trend	0.01	0.10	
Zhang *et al.* (1996) USA 1992–94	Men and women		**Distal stomach**		Odds ratios adjusted for age, sex, race, education, alcohol intake, body-mass index and total calorie intake
		Ever-smoker	1.8 (0.9–3.8)		
		Cigarettes/day			
		1–20	1.6 (0.7–3.5)		
		21–40	3.3 (1.2–9.2)		
		> 40	4.0 (0.6–25.2)		
		p for trend	0.0220		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Zhang *et al.* (1996) (contd)		Continuous variable cigarettes/day			
		Years of smoking			
		1–20	1.2 (0.5–3.2)		
		21–40	1.7 (0.7–4.0)		
		> 40	2.6 (0.9–7.8)		
		p for trend	0.0485		
		Pack–years			
		1–29	1.1 (0.5–2.5)		
		30–59	2.7 (1.1–6.9)		
		> 60	4.6 (1.3–16.6)		
		p for trend	0.0074		
		Continuous variable; pack–years			
		Age at starting smoking (years)			
		> 20	1.4 (0.5–3.9)		
		17–20	2.6 (1.03–6.7)		
		≤ 16	1.8 (0.7–4.5)		
		p for trend	0.1332		
Gammon *et al.* (1997) USA 1993–95	Men and women		**Cardia**	**Other**	Odds ratios adjusted for age, sex, geographical area, race, body-mass index, income and alcohol intake
		Current smoker	2.6 (1.7–4.0)	1.8 (1.2–2.7)	
		Former smoker	1.9 (1.3–2.9)	1.5 (1.1–2.1)	
		Years since quitting			
		> 30	1.1 (0.6–2.0)	1.0 (0.6–1.8)	
		21–30	2.2 (1.3–3.7)	1.5 (0.9–2.4)	
		11–20	1.6 (0.9–2.8)	1.7 (1.0–2.7)	
		< 10	2.9 (1.8–4.8)	1.8 (1.2–2.9)	
		p for trend	< 0.05	< 0.05	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Gammon *et al.* (1997) (contd)		*Cigarettes/day*			
		< 16	1.4 (0.9–2.2)	1.5 (1.0–2.2)	
		16–20	2.2 (1.4–3.4)	1.7 (1.2–2.6)	
		21–30	3.1 (1.9–5.2)	1.4 (0.9–2.5)	
		> 30	2.0 (1.2–3.3)	1.5 (1.0–2.4)	
		p for trend	< 0.05		
		Duration (years)			
		< 20	1.6 (1.0–2.6)	1.0 (0.7–1.6)	
		20–31	1.8 (1.1–2.9)	1.6 (1.0–2.4)	
		32–42	2.7 (1.7–4.2)	1.8 (1.2–2.7)	
		> 42	2.9 (1.8–4.7)	2.1 (1.4–3.1)	
		p for trend	< 0.05	< 0.05	
		Pack–years			
		< 14	0.9 (0.5–1.6)	1.2 (0.8–1.8)	
		14–31	2.3 (1.4–3.6)	1.5 (1.0–2.4)	
		32–54	2.8 (1.8–4.4)	1.7 (1.2–2.6)	
		> 54	2.5 (1.5–4.1)	2.1 (1.3–3.2)	
		p for trend	< 0.05	< 0.05	
		Filter status			
		With filter	2.1 (1.4–3.1)	1.6 (1.1–2.2)	
		With and without filter	1.5 (0.8–2.7)	1.1 (0.6–1.9)	
		Without filter	2.1 (1.3–3.2)	1.5 (1.0–2.3)	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)	Comments, variables adjusted for, significance, limitations of the study
De Stefani *et al.* (1998) Uruguay 1992–96	Men	Former smoker	1.3 (0.8–2.2)	Odds ratios adjusted for age, residence, urban/rural status, total alcohol consumption and vegetable intake
		Current smoker	2.6 (1.6–3.1)	
		Ever-smoker	1.8 (1.2–2.8)	
		Cigarettes/day		
		1–10	1.6 (0.9–2.8)	
		11–20	1.8 (1.2–3.1)	
		21–30	2.5 (1.5–4.5)	
		≥ 31	1.2 (0.7–2.2)	
		p for trend	0.23	
		Duration (years)		
		1–29	1.2 (0.7–2.2)	
		30–39	1.7 (0.9–3.0)	
		40–49	1.9 (1.1–3.0)	
		≥ 50	2.2 (1.3–3.6)	
		p for trend	< 0.001	
		Pack–years		
		1–13	1.6 (0.9–2.6)	
		14–25	1.7 (1.0–2.8)	
		26–50	2.1 (1.3–3.6)	
		≥ 51	2.3 (1.4–3.8)	
		p for trend	< 0.001	
		Years since quitting		
		≥ 15	1.1 (0.7–1.9)	
		10–14	1.0 (0.5–2.1)	
		5–9	1.5 (0.8–2.9)	
		1–4	2.4 (1.3–4.3)	
		Current smoker	2.6 (1.6–4.1)	
		p for trend	< 0.001	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
De Stefani *et al.* (1998) (contd)		*Age at starting smoking (years)*			
		≥ 20	1.8 (1.1–3.0)		
		15–19	1.9 (1.2–3.1)		
		10–14	1.9 (1.2–3.1)		
		< 10	2.3 (1.2–4.3)		
		p for trend	0.01		
		Type of cigarette			
		Blond	1.6 (1.0–2.6)		
		Black	2.0 (1.3–3.3)		
		Manufactured	1.2 (0.6–2.1)		
		Hand–rolled	1.9 (1.2–3.1)		
		Filter-tipped	1.4 (0.9–2.5)		
		Untipped	1.9 (1.3–3.1)		
		Duration (years)	**Cardia**	**Antrum/pylorus**	
		0–31	1.0	1.0	
		32–47	2.9 (0.8–11.6)	1.6 (1.1–2.4)	
		≥ 48	5.3 (1.4–20.2)	2.1 (1.4–3.2)	
		p for trend	0.006	< 0.001	
			Fundus	**Diffuse**	
		0–31	1.0	1.0	
		32–47	0.4 (0.1–1.3)	2.6 (0.9–7.7)	
		≥ 48	1.4 (0.5–3.7)	1.4 (0.4–5.5)	
		p for trend	0.64	0.50	
Liu *et al.* (1998) China 1986–88	Men and women		**Men**†	**Women**†	†Values in parentheses represent standard errors. Odds ratios stratified by 5-year age groups of age at death and study area (county or city district)
		Current Smoker	1.4 (0.03)	1.2 (0.06)	
		Urban	1.4 (0.03)	1.3 (0.05)	
		Rural	1.4 (0.04)	1.1 (0.07)	
		Cigarettes/day	**Urban**	**Rural**	
		1–19	1.3 (0.04)	1.3 (0.05)	
		20	1.4 (0.04)	1.6 (0.06)	
		> 20	1.5 (0.08)	1.7 (0.13)	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Liu *et al.* (1998) (contd)		*Duration (years)*			
		< 20	1.5 (0.05)	1.4 (0.06)	
		20–24	1.3 (0.04)	1.4 (0.04)	
		≥ 25	1.3 (0.04)	1.3 (0.05)	
Chow *et al.* (1999) Poland 1994–97	Men and women		**Men**	**Women**	Odds ratios adjusted for age, education, years lived on a farm, family history of cancer; *p* values for trend not calculated
		Ever-smoker	1.2 (0.8–1.8)	1.8 (1.1–3.0)	
		Former smoker	0.9 (0.6–1.4)	1.8 (0.9–3.7)	
		Current smoker	1.7 (1.1–2.7)	1.8 (1.0–3.3)	
		Cigarettes/day			
		≤ 10	0.7 (0.4–1.2)	1.3 (0.7–2.5)	
		11–20	1.5 (1.0–2.3)	2.5 (0.9–3.7)	
		≥ 21	1.5 (0.9–2.6)	1.8 (1.0–3.3)	
		Duration (years)			
		< 20	0.6 (0.3–1.1)	2.3 (1.0–5.4)	
		20–29	1.0 (0.6–1.8)	1.8 (0.8–3.8)	
		30–39	1.1 (0.7–1.9)	1.6 (0.7–3.7)	
		40–49	2.0 (1.2–3.4)	1.8 (0.7–4.4)[†]	[†]≥ 40 years
		≥ 50	2.0 (1.0–3.9)		
		Age at starting smoking (years)			
		≥ 25	0.6 (0.3–1.3)	1.7 (0.8–3.4)	
		20–24	1.1 (0.7–1.9)	1.1 (0.5–2.4)	
		18–19	1.7 (1.0–2.8)	3.5 (1.5–8.0)	
		< 18	1.3 (0.8–2.1)	2.1 (0.7–6.3)	
		Years since quitting			
		≥ 30	0.7 (0.4–1.5)		
		20–29	0.8 (0.4–1.6)	3.0 (1.0–9.2)[‡]	[‡]≥ 20 years
		10–19	0.9 (0.5–1.7)	1.5 (0.5–4.3)	
		< 10	1.0 (0.5–1.8)	1.3 (0.4–4.0)	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Chow *et al.* (1999) (contd)		*Pack–years*			
		< 10	0.8 (0.4–1.5)	1.8 (0.8–4.2)	
		10–< 20	0.9 (0.5–1.9)	1.8 (0.8–3.8)	
		20–< 30	1.0 (0.6–1.8)	1.4 (0.6–3.3)	
		30–< 40	1.0 (0.6–1.8)	2.3 (1.0–5.2)[§]	[§]≥ 30 pack–years
		40–< 50	2.1 (1.2–3.8)		
		≥ 50	1.9 (1.1–3.3)		
		Filter status			
		With filter	1.2 (0.8–1.9)	1.7 (1.0–3.0)	
		Without filter	0.8 (0.5–1.3)	1.9 (0.5–6.6)	
		With and without filter	1.9 (1.1–3.2)	12.2 (1.4–107.2)	
Gao *et al.* (1999) China 1995	Men and women	Ever-smoker	0.9 (0.5–1.7)		Odds ratios adjusted for age and sex
Inoue *et al.* (1999) Japan 1988–95	Men and women		**Men**	**Women**	Odds ratios adjusted for age, year and season at first hospital visit, family history of gastric cancer, alcohol drinking, preference for salty food and fruit intake
		Former smoker	1.7 (1.3–2.3)	1.4 (0.8–2.3)	
		Current smoker	2.5 (1.9–3.3)	1.7 (1.3–2.4)	
		< 60 years old	(*n* = 314)	(*n* = 182)	
		Former smoker	2.2 (1.4–3.4)	2.1 (1.1–4.1)	
		Current smoker	3.3 (2.2–4.9)	1.7 (1.1–2.5)	
		≥ 60 years old	(*n* = 337)	(*n* = 162)	
		Former smoker	1.4 (0.9–2.0)	0.8 (0.3–2.0)	
		Current smoker	1.9 (1.3–2.7)	2.0 (1.2–3.2)	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)			Comments, variables adjusted for, significance, limitations of the study
Ye *et al.* (1999) Sweden 1989–95	Men and women		**Cardia**	**Distal (intestinal)**	**Distal (diffuse)**	Odds ratios adjusted for age, sex, residence area, body-mass index 20 years before interview, socioeconomic status, use of smokeless tobacco and use of beer, wine and spirits. About 30% of eligible cases died or became too ill to be interviewed; if smoking affects the prognosis of stomach cancer, relative risks could be underestimated
		Former smoker	0.8 (0.4–1.5)	1.4 (0.9–2.0)	1.2 (0.8–2.0)	
		Cigarettes/day				
		1–10	1.7 (0.7–3.8)	1.6 (0.9–2.8)	1.9 (1.0–3.4)	
		11–15	1.2 (0.4–3.8)	1.8 (0.9–3.7)	2.5 (1.2–5.5)	
		≥ 16	2.2 (1.0–4.8)	2.0 (1.1–3.9)	2.7 (1.4–5.1)	
		p for trend	0.04	0.005	0.0004	
		Duration (years)				
		1–30	1.3 (0.5–3.6)	1.2 (0.5–2.9)	1.9 (0.9–3.8)	
		≥ 31	2.2 (1.1–4.3)	2.1 (1.3–3.4)	2.6 (1.5–4.5)	
		p for trend	0.03	0.002	0.0003	
Lagergren *et al.* (2000) Sweden 1995–97	Men and women		**Univariate**	**Multivariate**		Smokers include cigarette, cigar and pipe smokers. Univariate analysis adjusted for age and sex; multivariate analysis further adjusted for alcohol use, educational level, body-mass index, reflux symptoms, intake of fruit and vegetables, energy intake and physical activity. Multivariate analysis for no. of cigarettes/day included adjustments for cigarette smoking, pipe smoking, and snuff use. *p* values for trend not always shown. Odds ratios in multivariate analysis not significantly different from univariate analysis [data not shown]
		Former smoker	3.1 (2.1–4.5)	3.4 (2.2–5.2)		
		Current smoker	3.9 (2.6–5.8)	4.5 (2.9–7.1)		
		Duration (years)				
		1–20	1.8 (1.1–2.9)	2.1 (1.2–3.4)		
		21–35	3.6 (2.3–5.5)	3.9 (2.4–6.2)		
		> 35	4.6 (3.0–6.9)	5.7 (3.6–9.1)		
		Cigarettes/day				
		1–9	2.2 (1.4–3.4)	2.3 (1.4–3.7)		
		10–19	3.0 (2.0–4.5)	3.1 (2.0–4.9)		
		> 19	3.5 (2.3–5.2)	3.6 (2.3–5.7)		
		Years since quitting				
		> 25	1.9 (1.1–3.1)	2.1 (1.2–3.6)		
		11–25	3.7 (2.3–5.8)	4.2 (2.6–7.0)		
		3–10	4.1 (2.4–7.0)	4.9 (2.8–8.7)		
		0–2	4.2 (2.8–6.4)	5.0 (3.2–8.0)		
		p for trend		< 0.0001		

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Mathew *et al.* (2000) India 1988–91	Men and women	*Smoking index*[†]			No response rate for cases or controls. No definition of smoking status. Odds ratios adjusted for age, sex, religion, education and income [†]No. of cigarettes and bidis/week × years of smoking
		1–199	0.8 (0.4–1.8)		
		200–399	2.3 (1.2–4.6)		
		400–599	1.8 (0.9–3.7)		
		≥ 600	2.6 (1.4–4.7)		
		p for trend	0.0008		
Zaridze *et al.* (2000) Russia 1996–97	Men and women		**All types**	**Cardia**	Controls significantly younger and better educated than cases ($p < 0.01$). Odds ratios adjusted for age, education and vodka consumption. Relative risk may be underestimated because of substantial proportion of controls had smoking-associated diseases (> 20%). Relative risks for sites other than cardia show similar trend but no statistically significant increases [data not shown]. Relative risk for women around 1.0
		Former smoker	1.1 (0.6–1.9)	1.2 (0.5–3.1)	
		Current smoker	1.4 (0.9–2.2)	2.0 (0.9–4.5)	
		Cigarettes/day			
		1–11	1.0 (0.6–1.7)	1.2 (0.5–3.0)	
		12–19	1.6 (0.9–2.8)	1.5 (0.6–4.0)	
		≥ 20	1.2 (0.8–2.0)	2.4 (1.0–5.3)	
		p for trend	0.24	0.03	
		Pack–years			
		1–18	0.9 (0.5–1.5)	1.1 (0.4–2.8)	
		19–32	1.5 (0.9–2.5)	1.2 (0.4–3.1)	
		≥ 33	1.5 (0.9–2.5)	3.1 (1.3–7.2)	
		p for trend	0.06	0.01	
		Duration (years)			
		1–26	1.0 (0.6–1.8)	1.0 (0.4–2.7)	
		27–39	1.7 (1.0–2.8)	2.6 (1.1–6.1)	
		≥ 40	1.1 (0.7–1.9)	1.7 (0.7–4.1)	
		p for trend	0.30	0.08	
		Age at starting smoking (years)			
		≥ 20	1.2 (0.7–2.1)	2.1 (0.9–5.0)	
		16–19	1.1 (0.7–1.9)	1.2 (0.5–3.2)	
		< 16	1.4 (0.8–2.3)	1.9 (0.8–4.4)	
		p for trend	0.57	0.21	

Table 2.1.6.4 (contd)

Reference Country and years of study	Subjects	Exposure estimates	Relative risk (95% CI)		Comments, variables adjusted for, significance, limitations of the study
Wu *et al.* (2001) USA 1992–97	Men and women		**Cardia**	**Distal stomach**	Very low participation rate for cases; no response rate for controls. Odds ratios adjusted for age, sex, race, birthplace and education
		Former smoker	1.2 (0.9–1.6)	1.1 (0.8–1.5)	
		Cigarettes/day			
		1–19	1.1 (0.7–1.6)	1.1 (0.8–1.6)	
		≥ 20	1.3 (0.9–1.8)	1.0 (0.7–1.5)	
		Current smoker	2.1 (1.5–3.1)	1.5 (1.1–2.1)	
		Cigarettes/day			
		1–19	2.2 (1.3–3.8)	1.3 (0.8–2.1)	
		20–39	1.6 (1.0–2.6)	1.4 (0.9–2.3)	
		≥ 40	3.8 (2.1–7.0)	2.4 (1.1–4.9)	
		p for trend	< 0.0001	< 0.02	
		Duration (years)			
		≤ 20	1.1 (0.8–1.6)	0.8 (0.6–1.2)	
		21–40	1.4 (1.0–1.9)	1.5 (1.1–2.1)	
		≥ 41	2.3 (1.5–3.4)	1.6 (1.1–2.4)	
		p for trend	< 0.0002	0.002	
		Age at starting smoking (years)			
		≥ 21	1.4 (0.9–2.1)	1.1 (0.8–1.6)	
		17–20	1.2 (0.9–1.8)	1.3 (0.9–1.7)	
		≤ 16	1.7 (1.2–2.4)	1.3 (0.9–1.8)	
		p for trend	0.008	0.09	
		Years since quitting			
		≥ 20	1.1 (0.7–1.7)	1.1 (0.8–1.6)	
		11–19	1.2 (0.8–1.9)	0.9 (0.6–1.4)	
		6–10	1.6 (0.9–2.7)	1.4 (0.9–2.2)	
		1–5	1.4 (0.8–2.4)	1.2 (0.7–2.0)	
		p for trend	0.08	0.31	

CI, confidence interval
[a] Index of smoking = no. of cigarettes × years of smoking/age at starting smoking
[b] Logistic regression adjusted for age, ethnic group and socioeconomic level
[c] Stratified analysis adjusted for age

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2.1.7 *Colorectal cancer*

(*a*) *Overview*

In the last three decades, a total of 60 epidemiological studies have investigated the relationship between tobacco smoke and colorectal cancer, but few were specifically designed to study the effects of tobacco smoking. Although most of the earlier studies did not show any consistent association between tobacco use and risk, several prospective cohort and case–control studies published since the late 1980s have found a significantly increased risk for colorectal cancer among smokers. Also, since the late 1980s, smoking has emerged as a risk factor for colorectal adenomas, a well-established precursor for colorectal cancer. On the basis of these new findings on smoking and colorectal cancer and adenomas, Giovannucci *et al*. (1994a,b) hypothesized that smoking may act as an initiator of colorectal cancer and that an induction period of 35–40 years may be needed to increase incidence. Giovannucci explained that if a long induction is needed for tobacco to play a role in colorectal carcinogenesis, this may explain the lack of association between smoking and colorectal cancer found in earlier cohort studies that had a short follow-up time and in case–control studies that did not obtain complete lifetime smoking histories.

The epidemiological evidence on tobacco smoke and colorectal cancer from prospective cohort and case–control studies is summarized below. Relevant information on each of the cohort studies (source of the cohort, years of follow-up, number of cases) is summarized in Tables 2.1 and 2.1.7.1 and the data obtained are reported in Table 2.1.7.2. Relevant information on case–control study design and results is summarized in Tables 2.1.7.3 and 2.1.7.4, respectively. Site-specific relative risks were presented in the majority of studies. Results for colorectal cancers combined were reported in 12 prospective cohort studies (Hammond, 1966; Garland *et al*., 1985; Wu *et al*., 1987; Giovannucci *et al*., 1994a,b; Chen *et al*., 1997; Kato *et al*., 1997; Liaw & Chen, 1998; Nordlund *et al*., 1997; Tulinius *et al*., 1997; Chao *et al*., 2000; Stürmer *et al*., 2000) and six case–control studies (Dales *et al*., 1979; Olsen & Kronborg, 1993; Boutron *et al*., 1995; Yamada *et al*., 1997; Nusko *et al*., 2000; Lam *et al*., 2001).

(*b*) *Factors affecting risk*

Virtually all the cohort and case–control studies reported risks for colorectal cancer in former and current smokers relative to never-smokers (Tables 2.1.7.2 and 2.1.7.4). Sixteen of the prospective cohort studies were conducted in the USA, 10 in Europe and three in Japan. In most studies, a small elevated risk for colon, rectal or colorectal cancer was found for smokers, but results were statistically significant in only a few studies. In these latter studies, former and/or current smokers experienced a significantly increased risk of 1.2–1.4 for colon cancer (Heineman *et al*., 1994; Chyou *et al*., 1996), rectal cancer (Akiba & Hirayama, 1990; Doll *et al*., 1994; Heineman *et al*., 1994; Chyou *et al*., 1996; Engeland *et al*., 1996) or colorectal cancer (Wu *et al*., 1987; Chao *et al*., 2000; Stürmer *et al*., 2000), relative to never-smokers (Table 2.1.7.4). Of all cohort studies, four showed a lower risk for colorectal cancer among smokers (Hammond & Horn, 1958a,b; Williams *et al*., 1981; Garland *et al*., 1985; Kono *et al*., 1987); the result was statistically significant in one (Williams *et al*., 1981).

A total of 31 case–control studies have examined the association between active smoking and cancer of the colon and rectum (Tables 2.1.7.3 and 2.1.7.4). [The Working Group excluded from their review studies that did not present point risk estimates in association with smoking.]

Nine European case–control studies on tobacco use and colorectal cancer were identified. They were conducted in Yugoslavia (Jarebinski *et al*., 1988; 1989), Denmark (Olsen & Kronborg, 1993), Sweden (Baron *et al*., 1994), France (Tuyns *et al*., 1982; Boutron *et al*., 1995), Italy (Ferraroni *et al*., 1989; D'Avanzo *et al*., 1995; Tavani *et al*., 1998) and Germany (Nusko *et al*., 2000). Ten case–control studies were conducted in Asia, eight in Japan (Tajima & Tominaga, 1985; Kato *et al*., 1990a,b; Hoshiyama *et al*., 1993; Inoue *et al*., 1995; Kotake *et al*., 1995; Murata *et al*., 1996; Yamada *et al*., 1997) and one each in the Republic of Korea (Choi & Kahyo, 1991) and Hong Kong SAR (Lam *et al*., 2001). Eight case–control studies on tobacco use and colorectal cancer have been carried out in the USA; two of these were hospital-based (Williams & Horm, 1977; Dales *et al*., 1979). The population-based studies were conducted among whites in Los Angeles County (Peters *et al*., 1989), Utah (Slattery *et al*., 1990), Wisconsin (Newcomb *et al*., 1995), northern California, Utah and Minnesota (Slattery *et al*., 1997) and Iowa (Chiu *et al*., 2001) and among the multiethnic population in Hawaii (Le Marchand *et al*., 1997).

Of the case–control studies, statistically significant increased risks among former or current smokers or ever-smokers were reported in two studies each on colon cancer (Slattery *et al*., 1990, 1997; Chiu *et al*., 2001), rectal cancer (Inoue *et al*., 1995; Chiu *et al*., 2001) and colorectal cancer (Newcomb *et al*., 1995; Nusko *et al*., 2000). However, one investigator reported a statistically significant reduction in risk for cancer of the colon (Hoshiyama *et al*., 1993) and rectum among smokers (Vobecky *et al*., 1983). Because smokers may stop or reduce smoking because of disease-related symptoms, case–control studies that presented data on smoking status only without data on duration/intensity (i.e. ever-smoked only or former/current smoking only) (Dales *et al*., 1979; Tuyns *et al*., 1983; Vobecky *et al*., 1983; Kato *et al*., 1990a,b; Inoue *et al*., 1995; Ghadirian *et al*., 1998; Nusko *et al*., 2000) are of limited value.

(i) *Intensity of smoking*

The evidence for an association between cigarette smoking and colorectal cancer would be strengthened if dose–response relationships could be demonstrated. In only one cohort study, were parameters including number of cigarettes smoked, pack–years of smoking, duration of smoking and age at which smoking started investigated separately in current and former smokers (Chao *et al*., 2000). In most of the other cohort studies, one or two parameters of intensity of exposure were assessed. Number of cigarettes smoked per day was most frequently assessed (Hammond, 1966; Doll *et al*., 1980; Williams *et al*., 1981; Carstensen *et al*., 1987; Klatsky *et al*., 1988; Akiba & Hirayama, 1990; Doll *et al*., 1994; Heineman *et al*., 1994; Chyou *et al*., 1996; Nyrén *et al*., 1996; Tulinius *et al*., 1997; Knekt *et al*., 1998; Chao *et al*., 2000; Terry *et al*., 2001). Statistically significant dose–response trends with amount smoked daily were reported for colon cancer (Heineman *et al*., 1994; Chyou *et al*., 1996), rectal cancer (Doll *et al*., 1994; Heineman *et al*., 1994; Chyou *et al*., 1996) and colorectal cancer (Chao *et al*., 2000; Stürmer *et al*., 2000).

Number of cigarettes smoked daily was evaluated in over half of the case–control studies (Williams & Horm, 1977; Jarebinski *et al*., 1989; Peters *et al*., 1989; Slattery *et al*., 1990; Choi & Kahyo, 1991; Kune *et al*., 1992; Hoshiyama *et al*., 1993; Baron *et al*., 1994; D'Avanzo *et al*., 1995; Kotake *et al*., 1995; Newcomb *et al*., 1995; Murata *et al*., 1996; Slattery *et al*., 1997; Yamada *et al*., 1997; Tavani *et al*., 1998; Chiu *et al*., 2001; Lam *et al*., 2001). Statistically significant positive trends of increasing risk with increasing number of cigarettes smoked daily were reported for colon cancer (Newcomb *et al*., 1995; Slattery *et al*., 1997), rectal cancer (Newcomb *et al*., 1995) and colorectal cancer (Yamada *et al*., 1997). In two studies, this pattern of increasing risks was apparent only in men (Slattery *et al*., 1990) or older men (aged ≥ 70 years) (Lam *et al*., 2001) but not among women in the same study.

(ii) *Duration of smoking*

Studies on colorectal cancer have been varied in their assessment of duration of smoking. Only a few studies actually evaluated years of smoking whereas others considered age at starting smoking, years since initiation of smoking or pack–years, combining duration and intensity of smoking. Five of the cohort studies have looked at years of smoking (Hsing *et al*., 1998; Chao *et al*., 2000), age at starting smoking (Heineman *et al*., 1994; Chao *et al*., 2000), years since initiation of smoking (Giovannucci *et al*., 1994a,b) and pack–years of smoking (Giovannucci *et al*., 1994a ; Heineman *et al*., 1994; Chao *et al*., 2000; Stürmer *et al*., 2000). Some evidence exists to suggest that risk for colorectal cancer increased with earlier age at initiation (Heineman *et al*., 1994; Chao *et al*., 2000) and with increasing number of years of smoking (Chao *et al*., 2000). In one study, risk increased with years since smoking initiation but this was observed among heavier smokers (i.e. subjects who smoked at least 10 cigarettes per day at starting smoking) only (Giovannucci *et al*., 1994a). Three studies showed a statistically significant trend of increasing risk with increasing pack–years of smoking (Heineman *et al*., 1994; Chao *et al*., 2000; Stürmer *et al*., 2000) but, in a fourth study, this association was limited to those who started smoking before the age of 30 years (Giovannucci *et al*., 1994b).

Some case–control studies have examined risk patterns in relation to years of smoking (Jarebinski *et al*., 1989; Choi & Kahyo, 1991; Olsen & Kronborg, 1993; Baron *et al*., 1994; D'Avanzo *et al*., 1995; Newcomb *et al*., 1995; Slattery *et al*., 1997; Tavani *et al*., 1998; Chiu *et al*., 2001), age at starting smoking (Tajima & Tominaga, 1985; Choi & Kahyo, 1991; D'Avanzo *et al*., 1995; Newcomb *et al*., 1995; Slattery *et al*., 1997; Tavani *et al*., 1998) and pack–years of smoking (Tajima & Tominaga, 1985; Kune *et al*., 1992; Hoshiyama *et al*., 1993; Baron *et al*., 1994; Boutron *et al*., 1995; D'Avanzo *et al*., 1995; Siemiatycki *et al*., 1995; Le Marchand *et al*., 1997; Slattery *et al*., 1997; Yamada *et al*., 1997; Chiu *et al*., 2001). The risk for colon and rectal cancer increased significantly with increasing number of years of smoking in one study; this relationship was observed even after adjustment for other smoking variables including number of cigarettes smoked per day (Newcomb *et al*., 1995). In two studies, risk for colon cancer (Newcomb *et al*., 1995; Slattery *et al*., 1997) and rectal cancer (Newcomb *et al*., 1995) increased significantly with earlier age at initiation. In one study that included both sexes, this association was found in men only (Slattery *et al*., 1997) whereas in the study of women only (Newcomb *et al*., 1995), any effect of age at initiation was eliminated after adjusting for years of smoking for both colon and rectal cancer. In three studies, the risk for colon cancer (Slattery *et al*., 1997) and rectal cancer (Le Marchand *et al*., 1997; Yamada *et al*., 1997) increased significantly with increasing pack–years of smoking.

(iii) *Smoking cessation*

Modest differences in risk exist between former and current smokers (Tables 2.1.7.2 and 2.1.7.4). The benefit of smoking cessation by years since stopping was evaluated in two cohort studies (Wu *et al*., 1987; Chao *et al*., 2000). The risks in both men and women remained substantially elevated (relative risk, 1.6–1.7) even after 20 years of smoking cessation in one study (Wu *et al*., 1987) but the risk was substantially reduced (to near unity) in another (Chao *et al*., 2000).

Results from case–control studies are also somewhat inconsistent. Risk patterns by years of cessation (D'Avanzo *et al*., 1995; Newcomb *et al*., 1995; Slattery *et al*., 1997; Tavani *et al*., 1998) or age at stopping (Choi & Kahyo, 1991) have been investigated. Cessation was not associated with risk in two studies (Choi & Kahyo, 1991; Tavani *et al*., 1998), but was significantly associated with reduced risk in one (D'Avanzo *et al*., 1995). In one study, women who stopped smoking for 20 or more years still showed an elevation in risk of 10–30% compared with never-smokers (Newcomb *et al*., 1995). In another study, relative to never-smokers, former smokers who had stopped smoking within the first 15 years of starting smoking actually showed a higher risk than current smokers (Slattery *et al*., 1997).

(iv) *Length of follow-up*

Giovannuci *et al*. (1994a,b) proposed that smoking may act as an initiator of colorectal cancer and that a long induction period (i.e. 35–40 years) is needed before an effect on risk can be observed. However, the available results are not entirely compatible with their hypothesis. Of the cohort studies in which smoking was a significant risk factor for colon cancer (Heineman *et al*., 1994; Chyou *et al*., 1996), rectal cancer (Doll *et al*., 1994; Heineman *et al*., 1995; Chyou *et al*., 1996) or colorectal cancer (Wu *et al*., 1987 (men only); Giovannuci *et al*., 1994a; Chao *et al*., 2000; Stürmer *et al*., 2000), the length of follow-up was 6 years or less in two studies (Wu *et al*., 1987; Giovannuci *et al*., 1994a), between 13 and 14 years in two studies (Chao *et al*., 2000; Stürmer *et al*., 2000) and greater than 20 years in three studies (Doll *et al*., 1994; Heineman *et al*., 1994; Chyou *et al*., 1996). In the British Doctors' study, an elevated but non-significant risk for rectal cancer in smokers had already been observed after the first 20 years of follow-up ($p = 0.09$). The magnitude of risk for rectal cancer in smokers was essentially the same after 20 years as after 40 years of follow-up (Doll & Peto, 1976; Doll *et al*., 1994) although the result became statistically significant with longer follow-up (Doll *et al*., 1994).

(*c*) *Population characteristics*

(i) *Sex*

There is some suggestion that the association between smoking and colorectal cancer may be stronger in men than in women although the evidence for this is far from consistent. Nine cohort studies showed sex-specific results (Hammond, 1966; Wu *et al*., 1987; Sandler *et al*., 1988; Akiba & Hirayama, 1990, Tverdal *et al*., 1993; Doll *et al*., 1994; Engeland *et al*., 1996; Tulinius *et al*., 1997; Chao *et al*., 2000). In one study, a significantly increased risk associated with smoking was observed only in women and not in men (Tulinius *et al*., 1997). In three other studies, an increased risk was more apparent in men than in women (Wu *et al*., 1987; Akiba & Hirayama, 1990; Tverdal *et al*., 1993). In another study, the association between smoking and colorectal cancer was equally strong in both sexes (Chao *et al*., 2000). Ten case–control studies also presented sex-specific results (Williams *et al*., 1977; Slattery *et al*., 1990; Kune *et al*., 1992; Boutron *et al*., 1995; D'Avanzo *et al*., 1995; Inoue *et al*., 1995; Le Marchand *et al*., 1997; Slattery *et al*., 1997; Chiu *et al*., 2001; Lam *et al*., 2001). Of the studies in which smoking was implicated as a risk factor, three showed no clear gender differences (Le Marchand *et al*., 1997; Slattery *et al*., 1997; Chiu *et al*., 2001) but in two studies, smoking was a risk factor only in men (Slattery *et al*., 1990) or older men (Lam *et al*., 2001).

(ii) *Ethnicity*

Almost all the cohort and case–control studies were conducted in Australia, Canada, Europe, the United Kingdom and the USA and included only Caucasian study subjects. One case–control study in the USA was conducted in African Americans (Dales *et al*., 1979) and another included Caucasians and various Asian groups (Le Marchand *et al*., 1997). Approximately one-fourth of the cohort studies (Kono *et al*., 1987; Akiba & Hirayama, 1990; Akiba, 1994) and of the case–control studies (Tajima & Tominaga, 1985; Kato *et al*., 1990a,b; Choi *et al*., 1991; Hoshiyama *et al*., 1993; Inoue *et al*., 1995; Kotake *et al*., 1995; Murata *et al*., 1996; Yamada *et al*., 1997; Lam *et al*., 2001) were conducted in Asia, mostly in native Japanese. There are no apparent differences in the association between smoking and colorectal cancer in members of different racial or ethnic groups.

(*d*) *Subsites of colorectal cancer*

Smoking and risk for cancer of the colon and for rectal cancer were investigated separately in the majority of cohort and case–control studies. Risk patterns are generally consistent between rectal and colon cancer in most of the cohort studies (Hammond & Horn, 1958a,b; Carstersen *et al*., 1987; Tverdal *et al*., 1993; Akiba, 1994; Heineman *et al*., 1994; Chyou *et al*., 1996; Nyren *et al*., 1996; Chao *et al*., 2000; Terry *et al*., 2001) and case–control studies (Tuyns *et al*., 1982; Vobecky *et al*., 1983; Tajima & Tominaga, 1985; Peters *et al*., 1989, Kato *et al*., 1990a; Choi & Kahyo, 1991; Kune *et al*., 1992; Baron *et al*., 1994; D'Avanzo *et al*., 1995; Le Marchand *et al*., 1997; Tavani *et al*., 1998). However, in four cohort studies (Klatsky *et al*., 1988; Akiba & Hirayama, 1990; Doll *et al*., 1994; Engeland *et al*., 1996) and eight case–control studies (Williams *et al*., 1977; Kato *et al*., 1990b; Hoshiyama *et al*., 1993; Inoue *et al*., 1995; Kotake *et al*., 1995; Newcomb *et al*., 1995; Siemiatycki *et al*., 1995; Murata *et al*., 1996), any effect of smoking was more apparent for rectal cancer than for colon cancer. A stronger smoking association for colon cancer was found in two cohort studies (Hsing *et al*., 1998; Knekt *et al*., 1998) but in none of the case–control studies.

In three large population-based case–control studies and one cohort study (Heineman *et al*., 1994) in which smoking was also implicated as a cause of colon cancer, the effect of smoking by colon subsite was investigated. In two studies, there were no clear differences in the effects of smoking by colon subsite (Heineman *et al*., 1994; Slattery *et al*., 1997). In one case–control study, any effect of smoking was limited to the left colon (Newcomb *et al*., 1995). In another case–control study, the effects of smoking varied by colon subsite and were not consistent in men and women (Le Marchand *et al*., 1997).

(*e*) *Confounding*

It is of note that even among the 'positive' cohort and case–control studies, the magnitude of risk between the highest and lowest exposure (i.e. in people who have never used tobacco) was modest (20–60% increase in risk). The treatment of potential confounders is particularly important when evaluating the overall evidence on the association of smoking with colorectal cancer. Inadequate adjustment for various potential confounders (e.g. alcohol, physical activity, body size, dietary factors) or unidentified confounders could account for the small increase in risk found with smoking in some studies. For example, smokers are more likely than nonsmokers to be physically inactive (IARC, 2002), to use alcohol, to have poorer dietary habits (e.g. low consumption of fruits and vegetables and high consumption of fat and meat) and they are less likely to be screened for colorectal cancer (Margetts & Jackson, 1993). Each of these factors, in turn, is positively associated with colorectal cancer risk (Potter *et al*., 1993). Thus, smoking may appear to increase the risk for colorectal cancer even if it has no direct effect on risk, if these potential confounders are inadequately controlled for or not controlled for in the analysis.

Few potential confounders were adjusted in most of the cohort studies. In some one-third of the published studies, only age or other relevant demographic factors were considered (Hammond & Horn, 1958a,b; Hammond, 1966; Doll *et al*., 1980; Williams *et al*., 1981; Garland *et al*., 1985; Carstensen *et al*., 1987; Sandler *et al*., 1988; Akiba & Hirayama, 1990; Tverdal *et al*., 1993; Akiba, 1994; Doll *et al*., 1994; Engeland *et al*., 1996). Some studies adjusted only for demographic factors and alcohol use (Kono *et al*., 1987; Chyou *et al*., 1996; Hsing *et al*., 1998). Less than half of the studies considered two or more of the potential confounders mentioned above (Wu *et al*., 1987; Klatsky *et al*., 1988; Bostick *et al*., 1994; Giovannucci *et al*., 1994a,b; Heineman *et al*., 1994; Nyrén *et al.*, 1996; Knekt *et al.*, 1998; Singh & Fraser, 1998; van Wayenburg *et al.*, 2000; Chao *et al.*, 2000; Stürmer *et al.*, 2000; Terry *et al.*, 2001). The extent to which residual effects of potential confounders can explain the small increase in risk associated with smoking cannot be determined for certain. In some studies, adjustment for alcohol (Hirayama, 1989) and other risk factors (Giovannucci *et al.*, 1994a) substantially reduced the magnitude and the significance of the effect of smoking. In other studies, the risk estimate associated with smoking was reduced by up to 10% although the association remained statistically significant (Chao *et al.*, 2000; Stürmer *et al.*, 2000). None of the prospective studies has evaluated whether the association between smoking and colorectal cancer was modified by other characteristics such as alcohol intake, body size, and others.

In about half of the case–control studies, demographic factors and at least two of the potential confounders discussed above were adjusted for the analyses (Slattery *et al.*, 1990; Choi & Kahyo, 1991; Kune *et al.*, 1992; Olsen & Kronborg, 1993; Baron *et al.*, 1994; D'Advanzo *et al.*, 1995; Newcomb *et al.*, 1995; Siemiatycki *et al.*, 1995; Le Marchand *et al.*, 1997; Slattery *et al.*, 1997; Yamada *et al.*, 1997; Ghadirian *et al.*, 1998; Tavani *et al.*, 1998; Chiu *et al.*, 2001). In addition, two studies investigated whether the association between smoking and colorectal cancer was modified by other characteristics (Newcomb *et al.*, 1995; Slattery *et al.*, 1997). Newcomb and coworkers reported a significant interaction between body-mass index and risk for rectal cancer (but not colon cancer) such that the risk for cancer at this site was significantly greater among heavier women. In the study of colon cancer by Slattery *et al* (1997), smokers with a high body-mass index displayed higher risk than those with a low body-mass index. However, the influence of β-carotene and other antioxidants on risk appeared to vary by smoking levels, but the nature of the effect differed according to whether the sources of antioxidants were dietary or from supplements. Although no systematic confounding factor has been identified, limited results (Newcomb *et al.*, 1995; Slattery *et al.*, 1997) show that body size, dietary factors and other potential confounders need to be adequately controlled for in the analysis before any association between smoking and colorectal cancer can be accepted.

(*f*) *Colorectal polyps*

Twenty-seven informative studies have investigated the association between tobacco smoking and risk of colorectal polyps, mostly of the adenomatous type, a well-established precursor for colorectal cancer. These studies are presented in Table 2.1.7.5. Prevalent cases were investigated in most of the studies, although the risk of reccurrence was the end-point in two studies (Jacobson *et al.*, 1994; Baron *et al.*, 1998). In contrast to the weak and inconsistent findings on tobacco use and risk of colon and rectal cancer, the epidemiological evidence on the relationship between smoking and colorectal polyps is generally consistent and more compelling. A significant positive association between smoking and risk of polyps has been found in all but five studies (Kato *et al.*, 1990b; Kono *et al.*, 1990; Sandler *et al.*, 1993; Baron *et al.*, 1998; Breuer-Katschinski *et al.*, 2000). In five studies that presented results separately for men and women (Lee *et al.*, 1993; Jacobson *et al.*, 1994; Boutron *et al.*, 1995; Kahn *et al.*, 1998; Nagata *et al.*, 1999), the association appeared equally strong in men and women. Significant positive dose–response trends with number of cigarettes smoked daily (Kikendall *et al.*, 1989; Monnet *et al.*, 1991; Zahm *et al.*, 1991; Kearney *et al.*, 1995; Kahn *et al.*, 1998), years of smoking (Monnet *et al.*, 1991; Zahm *et al.*, 1991; Olsen & Kronborg, 1993; Nagata *et al.*, 1999) and pack–years of smoking (Kikendall *et al.*, 1989; Monnet *et al.*, 1991; Zahm *et al.*, 1991; Honjo *et al.*, 1992; Lee *et al.*, 1993; Giovannucci *et al.*, 1994a,b; Jacobson *et al.*, 1994; Boutron *et al.*, 1995; Honjo *et al.*, 1995; Martínez *et al.*, 1995; Longnecker *et al.*, 1996; Nagata *et al.*, 1999; Almendingen *et al.*, 2000) have been found.

The benefit of smoking cessation has been evaluated. Point estimates for former smokers were calculated in 14 studies. Some studies found a decrease relative to current smokers to a non-significantly elevated risk (Zahm *et al.*, 1991; Kearney *et al.*, 1995; Longnecker *et al.*, 1996; Martínez *et al.*, 1997; Almendingen *et al.*, 2000), while the risk remained significantly elevated in others (Monnet *et al.*, 1991; Honjo *et al.*, 1992; Olsen & Kronborg, 1993; Martínez *et al.*, 1995; Kahn *et al.*, 1998).

A few studies also investigated trends, and the results are inconclusive. In one study, the risk for colorectal adenomas was higher than for current smokers after 10 years of smoking cessation (Monnet *et al.*, 1991), whereas in another study, the risk was close to unity after only 2 years of smoking cessation (Kikendall *et al.*, 1989).

Studies also varied in the potential confounders that were considered. In about half of the studies, demographic factors and several of the potential confounders discussed for colorectal cancer (physical activity, alcohol consumption, body size, dietary factors and screening history) were controlled for in the analysis (Olsen & Kronborg, 1993; Giovannucci *et al.*, 1994a,b; Jacobson *et al.*, 1994; Honjo *et al.*, 1995; Kearney *et al.*, 1995; Martínez *et al.*, 1995; Nelson *et al.*, 1995; Longnecker *et al.*, 1996; Martínez *et al.*, 1997; Kahn *et al.*, 1998; Almendingen *et al.*, 2000; Breuer-Katschinski *et al.*, 2000). Several studies adjusted for demographic factors and alcohol use only (Kikendall *et al.*, 1989; Kono *et al.*, 1990; Cope *et al.*, 1991; Zahm *et al.*, 1991; Honjo *et al.*, 1992; Sandler *et al.*, 1993; Boutron *et al.*, 1995), whereas only age was adjusted for in other studies (Hoff *et al.*, 1987; Demers *et al.*, 1988; Stemmermann *et al.*, 1988; Kato *et al.*, 1990b; Monnet *et al.*, 1991; Lee *et al.*, 1993; Manus *et al.*, 1997; Nagata *et al.*, 1999). In a study that examined the joint effect of smoking and alcohol, a statistically significant increase in risk was found only among subjects who were both smokers and drinkers (Cope *et al.*, 1991) although a non-significant twofold increase in risk was also found among smokers who were non-drinkers.

Most relative risk estimates for smoking and colorectal polyps range between 2 and 3, whereas the risk estimates for colorectal cancer range between 1.2 and 1.4. The reasons for the apparent paradox have stimulated considerable discussion (Boutron *et al.*, 1995; Terry & Neugut, 1998; Potter, 1998; Boutron-Ruault, 1999; Poole, 1999; Boutron-Ruault & Rabkin, 2000; Stürmer *et al.*, 2000; Terry *et al.*, 2000). The probable high prevalence of adenomas in most unscreened control groups selected for colorectal cancer studies may have diluted the association between colorectal cancer and smoking (Terry & Neugut, 1998). The strength of an association between a risk factor and a causal intermediate (e.g.

colorectal polyp) may be stronger than the association with the end-point of interest (e.g. colorectal cancer) if other pathways to that end-point exist (Poole, 1999; Terry *et al.*, 2000). Finally, because prevalences of colorectal polyps of at least 20% have been estimated for subjects aged 50 years or older in the USA, the rare disease assumption may not apply and the odds ratios reported would be inflated estimates of the relative risk (Terry *et al.*, 2000).

Table 2.1.7.1. Additional cohort studies on tobacco smoking and colorectal cancer: main characteristics of study design

Reference Country and years of study	Name of study (if available)	Cohort sample	Cases/deaths identification	Comments
Garland *et al.* (1985) USA 1957–77	Western Electric Health Study	1954 male employees at the Western Electric Company in Chicago, aged 40–55 years	Death certificates and medical and hospital records	Study primarily investigating dietary vitamin D and calcium intake and risk of colorectal cancer
Sandler *et al.* (1988) USA 1963–75		91 909 residents in Washington County, aged ≥ 25 years	County-wide cancer register or death certificates	
Kato *et al.* (1997) USA 1985–94	New York University Women's Health Study	15 785 women recruited from New York City and Florida, aged 34–65 years	Active follow-up and linkage to state cancer registries and National Death Index	Study mainly investigating diet and colorectal cancer
Stürmer *et al.* (2000) USA 1982–95	Physicians' Health Study	22 071 male physicians, aged 40–84 years	Yearly questionnaires	
Baron *et al.* (1998) USA 4 years		751 participants in a multi-centre clinical trial of β-carotene and vitamins C and E, with at least one recent large bowel adenoma	Cases ascertained by colonoscopy	Randomized intervention trial
Nagata *et al.* (1999) Japan 1992–95		31 552 (14 427 men, 17 125 women) residents of Takayama, aged ≥ 35 years	Cases ascertained by colonoscopy at two major hospitals	
Olsen & Kronborg (1993) Denmark 1986–90		17 284 residents of Funen Island, participating in a randomized control trial for colorectal cancer screening, aged 45–74 years	Cases ascertained by Haemoccult-II test	Nested case–control study; controls matched by age, sex and date of testing

Table 2.1.7.2. Cohort studies on smoking and risk of colorectal cancer

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Hammond & Horn (1958a,b) USA 1952–55	American Cancer Society Study 187 783 men	84 colon, 55 rectal deaths	Ever-smoker	0.8	0.9		Age
Hammond (1966) USA 1959–63	Cancer Prevention Study I 440 558 men, 562 671 women	Colorectal deaths 572 men, 349 women	*Men*				Stratified by age and sex. Baseline group included those who never smoked regularly
			Regular smoker			1.0 (age: 45–64 years)	
			Heavy smoker			1.2 (age: 65–79 years)	
			Women				
			Regular smoker			0.8 (age: 45–64 years)	
			Heavy smoker			0.7 (age: 45–64 years)	
Kahn (1966) USA 1954–62	US Veterans' Study 248 195 men	513 colon, 216 rectal deaths	Former smoker	1.3	1.0		A few cancers of the small intestines were included with colon cancers
			Current smoker	1.2	0.9		
			Cigarettes/day				
			10–20	1.1	0.7		
			21–39	1.3	1.0		
Doll & Peto (1976) UK 1951–71	British Doctors' Study 34 440 men	195 colon, 78 rectal deaths	Former smoker	1.0	1.0		Age, calendar year
			Ever-smoker	1.3	2.3		
			Current, any tobacco smoking	1.3	2.3		
			g tobacco/day				
			1–14	1.3	1.7		
			15–24	1.2	2.3		
			≥ 25	1.2	4.5		
			p for trend	> 0.05	0.09		

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Doll *et al.* (1980) UK 1951–73	British Doctors' Study 6194 women	7 rectal deaths	Current smoker	Not available			Age, calendar year
			Cigarettes/day				
			1–14		0.8		
			15–24		3.0		
			≥ 25		9.6		
			p for trend		> 0.05		
Rogot & Murray (1980) USA 1954–69	US Veterans' Study 248 195 men	1093 colon, 370 rectal deaths in smokers	Former smoker	1.3	1.1		A few cases of cancers of the small intestine were included with colon cancers; no. of deaths in never smokers not given
			Current smoker	1.1	1.1		
Williams *et al.* (1981) USA 1948–82 24 years	Framingham Heart Study 5209 men and women	58 colon (28 men, 30 women)	Packs/day		Not available		Age, not sure about sex. Not all colon (*n* = 88) and none of rectal (*n* = 26) were included in analysis
			<1	0.5			
			1	0.3			
			>1	0.3			
Garland *et al.* (1985) USA 1957–77	Western Electric Company Study 1954 men	49 colorectal deaths	Non-cancer comparison group,			9.5†	†No relative risk calculated Numbers indicate average number of cigarettes smoked per day.
			Colorectal cancer group Cigarettes/day			7.4†	
Carstensen *et al.* (1987) Sweden 1963–79	Swedish Census Study 25 129 men	117 colon, 69 rectal deaths	Former smoker	1.1	1.0		Age, residence Former smokers were excluded in test for trends.
			Current, any tobacco, g/day				
			1–7	1.4	2.0		
			8–15	1.5	1.1		
			≥ 15	1.5	1.3		
			p for trend	0.07	0.65		

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Kono *et al*. (1987) Japan 1965–83	Japanese Physicians' Study 5130 men	39 colorectal deaths	Never/past/occasional			1.0	Age, alcohol use
			Current smoker				
			1–19 cigs/day			0.9 (0.4–1.9)	
			≥ 20 cigs/day			0.9 (0.4–2.2)	
Wu *et al*. (1987) USA 1981–85	Leisure World Study 11 644 men and women	126 colorectal cancers (58 men, 68 women)	*Men*				Age; odds ratio for smoking in men was significant (1.49) after adjustment for sex, alcohol consumption, physical activity and body mass index
			Former >20 years			1.7 (0.8–3.6)	
			Former ≤ 20 years			2.6 (1.3–5.3)	
			Current			1.8 (0.6–5.2)	
			Women				
			Former >20 years			1.6 (0.8–3.0)	
			Former ≤ 20 years			0.7 (0.3–1.5)	
			Current			1.4 (0.7–1.0)	
Klatsky *et al*. (1988) USA 1978–84	Kaiser Permanente Medical Care Program Study 106 203 men and women	203 colon cancers (92 men, 111 women), 66 rectal cancers (33 men, 33 women)	Former smoker	1.0 (0.7–1.4)	1.3 (0.7–2.3)		Age, race, alcohol and coffee intake, body size, education, serum cholesterol; 10% random sample of controls used in analyses
			Current smoker				
			< 1 pack/day	0.8 (0.5–1.3)	1.1 (0.5–2.3)		
			≥ 1 pack/day	1.4 (0.8–2.3)	1.0 (0.4–2.8)		
Sandler *et al*. (1988) USA 1963–75	22 773 men, 25 369 women	Colorectal deaths (194 men, 286 women)	Current smoker				Age Nonsmokers were never smokers who did not live with smokers.
			Men			1.4 (0.9–2.2)	
			Women			0.8 (0.5–1.1)	
Hirayama (1989) Japan 1965–81	Six-prefecture Study 122 261 men, 142 847 women	574 colon deaths (256 men, 318 women) (91 sigmoid cancers)	Daily smoker	Proximal colon, 1.2 (0.9–1.6); Sigmoid colon, 1.4 (0.7–2.8)			Age Smoking was not significant after adjusting for alcohol and dietary factors (1.2; 95% CI, 0.6–2.3).

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Akiba & Hirayama (1990) Japan 1965–81	Six-prefecture Study 122 261 men, 142 847 women	Colon (190 men, 257 women) and rectal (254 men, 211 women) cancer deaths	*Men*				Prefecture of residence, occupation, attained age (5-year interval), observation period (see Hirayama, 1989)
			Any cigarettes	1.1 (0.8–1.5)	1.4 (1.0–1.9)		
			Cigarettes/day				
			1–4	0.9 (0.2–2.6)	1.4 (0.5–3.2)		
			5–14	1.0 (0.7–1.6)	1.3 (0.9–1.9)		
			15–24	1.1 (0.7–1.6)	1.4 (1.0–2.0)		
			25–34	1.2 (0.5–2.4)	1.5 (0.7–2.9)		
			≥ 35	1.8 (0.6–4.2)	1.1 (0.3–2.9)		
			p for trend	> 0.1	0.09		
			Women				
			Any cigarettes	0.9 (0.6–1.3)	0.9 (0.6–1.5)		
			Cigarettes/day				
			1–4	1.1 (0.4–2.4)	0.5 (0.1–1.7)		
			5–14	0.9 (0.5–1.4)	0.9 (0.5–1.5)		
			≥ 15	0.5 (0.1–1.6)	2.1 (0.8–4.3)		
			p for trend	> 0.1	> 0.1		
Chute *et al.* (1991) USA 1976–84	Nurses' Health Study 118 404 women	191 colon, 49 rectal cancers	Former smoker	1.2 (0.9–1.7)	1.9 (1.0–3.6)		Age [†]for ≥ 15 cigarettes/day
			Current smoker	1.0 (0.7–1.4)	1.1 (0.5–1.3)		
			Cigarettes/day				
			1–14	1.0 (0.6–1.7)	1.2 (0.4–3.7)		
			15–24	1.0 (0.0–1.6)	1.1 (0.5–2.5)[†]		
			> 24	1.0 (0.6–1.7)			
			p for trend	0.88	0.65		

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Tverdal *et al*. (1993) Norway 1972–88	Norwegian Screening Study 44 290 men, 24 535 women	Colon (53 men, 30 women), rectal (50 men, 16 women) cancer deaths	*Men*				Age, area
			Former smoker	1.2	1.4		†Among male current smokers of cigarettes only, the relative risk per 10 cigarettes was 1.2 (95% CI, 0.7–2.2) for colon and 0.8 (95% CI, 0.4–1.6) for rectal cancers [assuming this was calculated using 1–9 cigarettes per day as the baseline group]
			Current smoker	1.5	1.8		
			Cigarettes/day				
			1–9	0.7†	1.7†		
			10–19	1.7	1.7		
			≥ 20	1.3	1.7		
			Women				
			Former smoker	0.9	NA		
			Current smoker	1.1	0.6		
Akiba (1994) Japan 1963–87	Life Span Study 61 505 men and women	324 colon (172 men, 152 women), 218 rectal (122 men, 96 women) cancers	Former smoker	0.9 (0.6–1.4)	1.3 (0.8–2.0)		City, sex, population group, atomic bomb exposure, birth year (10-year interval), attained age (5-year interval)
			Current smoker	1.2 (0.9–1.6)	1.0 (0.7–1.4)		
Bostick *et al*. (1994) USA 1986–92	Iowa Women's Health Study 35 215 women	212 colon cancers	Fomer smoker	0.9 (0.6–1.3)			Age, total energy, height, parity, total vitamin E intake; total vitamin E by age interaction term; vitamin A supplement
			Current smoker	1.1 (0.7–1.6)			

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Doll *et al*. (1994) UK 1951–91	British Doctors' Study 34 439 men	437 colon and 168 rectal deaths	Former smoker	1.4	1.5		Age, calendar period
			Current smoker	1.3	2.3		
			p for trend	0.37	0.06		
			Current smoker				
			Cigarettes/day				
			1–14	1.4	1.3		
			15–24	1.1	1.9		
			≥ 25	1.4	4.5		
			p for trend	0.06	0.03		
Giovannucci *et al*. (1994a) USA 1976–90	Nurses' Health Study 118 334 women	586 colorectum deaths	Current smoker			0.9 (0.7–1.2)	
			Years since starting smoking				
			≤ 10 cigarettes/ day				
			1–19 years			0.8 (0.4–1.4)	
			20–29 years			1.0 (0.7–1.4)	
			30–34 years			0.8 (0.5–1.1)	
			35–39 years			0.8 (0.6–1.2)	
			40–44 years			1.0 (0.7–1.5)	
			≥ 45 years			1.1 (0.6–2.0)	
			≥ 10 cigarettes/ day				
			1–19 years			0.4 (0.1–1.3)	
			20–29 years			1.1 (0.7–1.6)	
			30–34 years			0.8 (0.5–1.2)	
			35–39 years			1.5 (1.1–2.0)	
			40–44 years			1.6 (1.1–2.3)	
			≥ 45 years			2.0 (1.1–3.5)	
			Smoking				
			>10 pack–years				
			Before age 30	1.2 (0.9–1.5)	2.1 (1.2–3.4)	1.3 (1.0–1.8)	
			After age 30			1.0 (0.8–1.3)	

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Giovannucci *et al*. (1994b) USA 1986–92	Health Professionals' Follow-up Study 47 935 men	239 colorectum deaths (44 rectal)	Current smoker			1.4 (0.8–2.2)	Age, family history of colorectal cancer, body-mass index, intake of saturated fat, fibre, folate, and alcohol
			Pack–years				
			1–9			1.3 (0.8–2.1)	
			10–19			1.5 (1.0–2.3)	
			20–29			1.7 (1.1–2.5)	
			30–39			1.4 (0.8–2.2)	
			≥ 40			1.5 (1.0–2.1)	
			p for trend			0.12	
			Before age 30				All the risk estimates for pack–years smoked after age 30 years were < 1.0 when also adjusted for smoking before age 30 years.
			1–4			1.6 (1.0–2.6)	
			5–10			1.6 (1.0–2.6)	
			11–15			2.1 (1.2–3.4)	
			≥ 16			2.0 (1.3–3.2)	
			p for trend			0.001	
			After age 30				
			1–4			0.8 (0.5–1.5)	
			5–10			0.9 (0.6–1.5)	
			11–15			0.8 (0.5–1.3)	
			≥ 16			0.7 (0.4–1.1)	
			p for trend			0.18	
			Years since starting smoking				Age, body-mass index, family history of colorectal cancer, intake of saturated fat, folate, dietary fibre and alcohol
			≤ 10 cigarettes/day				
			1–19 years			–	
			20–29 years			1.3 (0.6–2.6)	
			30–34 years			1.3 (0.6–2.7)	
			35–39 years			1.2 (0.7–2.1)	
			40–44 years			1.8 (1.2–2.9)	
			≥ 45			1.6 (1.1–2.0)	

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Giovannucci *et al*. (1994b) (contd)			**≥ 10 cigarettes/day**				
			1–19 years			1.9 (0.6–6.3)	
			20–29 years			0.8 (0.3–2.2)	
			30–34 years			0.8 (0.2–2.6)	
			35–39 years			1.2 (0.6–2.3)	
			40–44 years			1.7 (0.9–3.3)	
			≥ 45 years			2.6 (1.5–4.4)	
Heineman *et al*. (1994) USA 1954–80	US Veterans' Study 248 046 men	3812 colon and 1100 rectal deaths	Current smoker	1.2 (1.1–1.4)	1.4 (1.2–1.7)		Age, social class, physical activity. [Note that 'unknown' cigarette use was also associated with an increased risk.]
			Former smoker	1.3 (1.2–1.5)	1.4 (1.1–1.7)		
			Unknown	1.2 (1.1–1.4)	1.4 (1.1–1.8)		
			Cigarettes/day				
			1–9	1.1 (1.0–1.3)	1.3 (1.0–1.7)		
			10–20	1.2 (1.1–1.4)	1.4 (1.1–1.7)		
			21–39	1.3 (1.1–1.4)	1.6 (1.3–2.1)		
			≥ 40	1.6 (1.2–2.0)	1.7 (1.1–2.6)		
			p for trend	< 0.001	< 0.001		
			Pack–years				
			0–8	1.0 (0.8–1.3)	0.8 (0.5–1.3)		
			> 8–18	1.2 (1.1–1.4)	1.6 (1.2–2.1)		
			> 18–98	1.4 (1.2–1.6)	1.7 (1.4–2.2)		
			p for trend	< 0.001	< 0.001		
			Age at starting smoking				
			≥ 25 years	1.1 (1.0–1.3)	1.2 (0.9–1.6)		
			20–24 years	1.3 (1.1–1.5)	1.4 (1.1–1.7)		
			15–19 years	1.2 (1.1–1.4)	1.6 (1.3–1.9)		
			< 15	1.4 (1.2–1.8)	1.5 (1.0–2.2)		
			p for trend	< 0.001	0.006		

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
McLaughlin *et al*. (1995) USA 1954–80	US Veterans' Study 177 903 men (excluded 34 219 pipe/cigar smokers and 35924 with unknown smoking habits)	2596 colon and 735 rectal deaths	Former smoker	1.4 (1.2–1.5)	1.3 (1.0–1.5)		Age, calendar-year time-period. Relative risks were lower for 1954–69 than for 1970–80: colon cancer, 1.1 (95% CI, 1.0–1.3) and 1.4 (95% CI, 1.2–1.6), respectively; rectal cancer, 1.2 (95% CI, 1.0–1.5) and 2.0 (95% CI, 1.5–2.8), respectively.
			Current smoker	1.2 (1.1–1.4)	1.4 (1.2–1.7)		
			Ever-smoker	1.3 (1.2–1.4)	1.4 (1.2–1.6)		
			Cigarettes/day				
			1–9	1.1 (0.9–1.3)	1.3 (1.1–1.9)		
			10–20	1.2 (1.1–1.4)	1.3 (1.1–1.6)		
			31–39	1.3 (1.1–1.5)	1.6 (1.2–2.0)		
			≥ 40	1.7 (1.3–2.1)	1.5 (0.9–2.4)		
			p for trend	< 0.01	< 0.01		
Chyou *et al*. (1996) USA 1965–95	American Men of Japanese Ancestry Study 7945 men	330 colon and 123 rectal cancers	Former smoker	1.3 (1.0–1.7)	1.3 (0.8–2.2)		Age
			Current smoker	1.4 (1.1–1.9)	2.0 (1.3–3.0)		
			Pack–years				
			1–15	1.3 (0.9–1.9)	1.1 (0.4–2.1)		
			16–30	1.1 (0.8–1.5)	1.6 (0.9–2.7)		
			≥ 31	1.5 (1.1–1.9)	1.9 (1.2–3.0)		
			p for trend	0.0008	0.0034		
			Per 10 pack–years	1.1 (1.0–1.1)	1.1 (1.0–1.2)		Age, alcohol consumption, body-mass index, serum cholesterol, heart rate, intake of mono unsaturated fatty acid
Engeland *et al*. (1996) Norway 1966–93	Norwegian Cohort Study 11 863 men, 14 269 women	Colon (230 men, 300 women) and rectum (139 men, 141 women) cancers	*Men*				Age
			Former smoker	1.0 (0.6–1.5)	0.8 (0.4–1.6)		
			Current smoker	1.2 (0.8–1.6)	1.6 (1.0–2.6)		
			Women				
			Former smoker	1.3 (0.9–2.0)	1.3 (0.8–2.4)		
			Current smoker	1.1 (0.8–1.4)	0.8 (0.5–1.3)		

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Murata *et al*. (1996) Japan 1984–93	Chiba Center Association Study 17 200 men	61 colon, 43 rectum	*Cigarettes/day*				Crude 95% CI calculated by Working Group based on the data presented. No effect of smoking by levels of alcohol intake
			1–10	0.8 (0.3–2.2)	1.3 (0.3–6.0)		
			11–20	1.1 (0.5–2.4)	1.1 (0.5–2.7)		
			≥ 21	1.0 (0.3–2.8)	3.0 (0.7–13.4)		
			p for trend	0.98	0.37		
Nyrén *et al*. (1996) Sweden 1971–91	Swedish Construction Workers Cohort 134 985 men for colon, 135 009 men for rectum	713 colon, 505 incident rectal cancers	Former smoker	1.0 (0.8–1.2)	1.2 (1.0–1.5)		Body-mass index, height, normal and maximum pulse rate, marital status and asbestos exposure
			Current smoker	1.0 (0.8–1.2)	1.1 (0.9–1.4)		
			Cigarettes/day				
			1–4	0.9 (0.7–1.2)	1.1 (0.81–1.4)		
			5–14	0.8 (0.7–1.0)	0.8 (0.6–1.0)		
			15–24	1.1 (0.9–1.4)	1.2 (0.9–1.5)		
			≥ 25	1.1 (0.6–1.8)	1.1 (0.6–2.0)		
			Duration (years)				
			Former smoker				
			1–10	0.8 (0.4–1.1)	1.3 (0.9–1.9)		
			11–20	1.1 (0.9–1.5)	1.4 (1.0–1.9)		
			≥ 21	1.1 (0.8–1.4)	1.1 (0.8–1.5)		
			Current smoker				
			1–10	0.8 (0.4–1.3)	0.8 (0.4–1.7)		
			11–20	0.7 (0.5–1.1)	1.0 (0.7–1.6)		
			21–30	1.0 (0.8–1.3)	1.2 (0.8–1.6)		
			31–40	1.1 (0.8–1.3)	1.3 (1.0–1.7)		
			≥ 41	1.0 (0.7–1.4)	1.1 (0.7–1.6)		
Yuan *et al*. (1996) China 1986–93	Shanghai Men's Study 18 244 men	26 colon, 31 rectal cancers	Ever-smoker	1.1	0.6		Adjusted for age and alcohol consumption
			Cigarettes/day				
			< 20	1.5	0.5		
			≥ 20	0.7	0.7		
Chen *et al*. (1997) China 1972–93	Shanghai Factory Study 1696 men and women	22 colorectal cancers	*Cigarettes/day*				Adjusted for age, systolic blood pressure, serum cholesterol and regular alcohol drinking (yes/no)
			1–19			1.5 $p > 0.05$	
			≥ 20			2.6 $p > 0.05$	

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Kato *et al*. (1997) USA 1985–94	New York University Women's Health Study 14 727 women	73 colon and 27 rectum	Former smoker Current smoker			1.0 (0.6–1.6) 1.0 (0.5–1.9)	Age, place of enrolment
Liaw & Chen (1998) China, Province of Taiwan 1982–94	Taiwanese Study 17 538 men and women	42 colorectal cancers	Current smoker			0.8 (0.4–1.5)	Analysis for men only because of the small number of cases in women
Norlund *et al*. (1997) Sweden 1963–89	Swedish Census Study 26 032 women	559 incident colorectal cancers	Former smoker Current smoker *Cigarettes/day* 1–7 8–15 > 15 *Age at starting smoking (years)* 20–23 < 19 *p* for trend			1.2 (0.7–1.9) 0.9 (0.7–1.2) 0.9 (0.6–1.3) 0.7 (0.4–1.1) 1.4 (0.8–2.6) 1.2 (0.6–2.3) 1.0 (0.5–1.9) 0.95	Age, place of residence
Tulinius *et al*. (1997) Iceland 1968–95	Reykjavík Study 11 366 men, 11 580 women	Colorectal cancers (193 men, 145 women)	*Women* Former smoker *Cigarettes/day* 1–14 15–24 ≥ 25	 1.1 (0.7–1.9) 1.4 (0.9–2.1) 1.5 (1.0–2.5) 2.5 (1.0–6.2)			Age, glucose levels. Results for men were not presented: presumably not statistically significant

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Hsing *et al*. (1998) USA 1966–86	Lutheran Brotherhood Insurance Study 17 633 men	120 colon, 25 rectal deaths	Former smoker	1.5 (0.8–2.7)		1.1 (0.7–1.8)	Age, urban/rural residence, alcohol intake Occasional users smoked less than 1 cigarette, pipe or cigar per day
			Occasional smoker	1.4 (0.7–2.9)		1.1 (0.6–2.0)	
			Current smoker	1.4 (0.7–2.7)		1.0 (0.6–1.7)	
			Cigarettes/day				
			1–19	1.1 (0.5–2.5)		0.8 (0.4–1.6)	
			20–29	1.6 (0.7–3.4)		1.1 (0.5–2.1)	
			≥ 30	2.3 (0.9–5.7)		1.7 (0.7–3.8)	
			p for trend	0.3		0.5	
			Duration (years)				
			1–19	1.3 (0.2–9.7)		0.8 (0.1–6.0)	
			20–29	2.4 (1.0–5.3)		1.0 (0.7–3.2)	
			≥ 30	1.2 (0.6–2.4)		0.9 (0.5–1.6)	
			p for trend	0.8		0.8	
Knekt *et al*. (1998) Finland 1966–94	Mobile Health Clinic Study 56 973 men and women	241 colon and 216 incident rectal cancers	Former smoker	1.2 (0.8–1.9)	0.9 (0.6–1.4)	1.0 (0.7–1.4)	Sex, age, body-mass index, occupation, area, type of population, marital status
			Cigarettes/day				
			< 15	1.1 (0.7–1.7)	1.1 (0.7–1.7)	1.1 (0.8–1.5)	
			≥ 15	1.4 (0.8–2.1)	0.9 (0.5–1.4)	1.0 (0.7–1.5)	
			Smoker in 1966 and 1973	1.9 (1.1–3.5)	1.5 (0.8–2.9)	1.7 (1.1–2.7)	17 291 subjects in second health examination between 1973 and 1976
			Follow-up (years)			*Smokers*	
			< 10			1.0 (0.6–1.6)	
			11–20			1.6 (1.1–2.2)	
			> 20			0.8 (0.5–1.1)	
Singh & Fraser (1998) USA 1976–82	Adventists' Health Study 32 051 men and women	157 colon (135 colon, 22 recto-sigmoid)	Former smoker	1.1 (0.8–1.7)			Age, sex, parental history of colon cancer
			Current smoker	1.4 (0.5–3.8)			

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Chao *et al.* (2000) USA 1982–96	Cancer Prevention Study (CPS) II 312 332 men and 469 019 women	Colorectal deaths (2156 men, 2276 women)	*Men*				Age, race, body-mass index, education, family history of colorectal cancers, exercise, aspirin and multivitamin use, intake of alcohol, vegetables, high-fibre cereal products, and fatty meats; hormone replacement therapy in women; no. of colon and rectal cancers not specified
			Former smoker			1.2 (1.0–1.3)	
			Current smoker	1.3 (1.2–1.5)	1.2 (0.9–1.7)	1.3 (1.2–1.5)	
			Women				
			Former smoker			1.2 (1.1–1.4)	
			Current smoker	1.4 (1.3–1.6)	1.3 (1.0–1.8)	1.4 (1.3–1.6)	
			Men and women				
			Cigarettes/day				
			< 20			1.3 (1.2–1.5)	
			20			1.4 (1.2–1.6)	
			21–39			1.3 (1.1–1.6)	
			≥ 40			1.5 (1.3–1.8)	
			p for trend			0.03	
			Pack–years				
			< 20			1.3 (1.1–1.5)	
			20–39			1.3 (1.1–1.5)	
			40–59			1.4 (1.2–1.6)	
			≥ 60			1.5 (1.3–1.7)	
			p for trend			0.05	
			Duration (years)				
			< 20			1.1 (0.8–1.5)	
			20–29			1.3 (1.1–1.6)	
			30–39			1.4 (1.2–1.6)	
			≥ 40			1.4 (1.3–1.6)	
			p for trend			0.24	
			Age at starting smoking (years)				
			≥ 20			1.3 (1.2–1.5)	
			16–19			1.4 (1.3–1.6)	
			≤ 15			1.5 (1.3–1.7)	
			p for trend			0.02	

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
Chao *et al*. (2000) (contd)			*Former smokers*				Similar patterns of increased risk with years smoked and pack–years smoked among former smokers.
			Years since quitting				
			≤ 10			1.3 (1.2–1.5)	
			11–19			1.2 (1.1–1.4)	
			≥ 20			1.0 (0.9–1.2)	
			p for trend			0.0001	
			Age at quitting smoking				
			≤ 30			0.9 (0.8–1.1)	
			31–40			1.1 (1.0–2.3)	
			41–50			1.2 (1.0–1.3)	
			51–60			1.4 (1.2–1.6)	
			≥ 61			1.3 (1.1–1.6)	
			p for trend			0.0001	
Stürmer *et al*. (2000) USA 1982–95	Physicians' Health Study 22 071 men	351 colorectal cancers	Former smoker			1.5 (1.2–1.9)	Body-mass index, alcohol intake, exercise, use of vitamins and aspirin, and selected dietary factors
			Current smoker			1.8 (1.3–2.6)	
			p for trend			< 0.001	
			Former smoker				
			< 20 cigarettes/day			1.5 (1.1–2.1)	
			> 20 cigarettes/day			1.3 (1.0–1.7)	
			Current smoker				
			< 20 cigarettes/day			1.3 (0.7–2.4)	
			> 20 cigarettes/day			2.1 (1.5–3.1)	
			p for trend			0.002	
			Pack–years				
			0–≤ 10			1.5 (1.1–2.2)	
			10–≤ 20			1.6 (1.1–2.2)	
			20–≤ 40			1.2 (0.9–1.7)	
			> 40			1.7 (1.2–2.4)	
			p for trend			0.009	

Table 2.1.7.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. of deaths from cancer of colon or rectum/incident cancers	Smoking categories	Relative risks (95% CI or *p* value)			Adjustment factors/ comments
				Colon cancer	Rectal cancer	Colorectal cancer	
van Wayenburg *et al*. (2000) Netherlands 1974–96	Dutch Study 20 555 women	95 colorectal deaths	Ever-smoker			1.4 (0.9–2.2)	Age, age at first birth, use of oral contraceptives, natural or artificial menopause, social class, body-mass index
Terry *et al*. (2001) Sweden 1961–97	Swedish Twin Registry Study 10 945 pairs	318 colon, 180 rectal cancers	Former smoker	1.1 (0.8–1.5)	1.0 (0.6–1.6)	1.0 (0.8–1.4)	Age (5-year age groups), sex, body-mass index, physical activity
			Cigarette smoker				
			Light smoker	1.0 (0.7–1.5)	0.9 (0.6–1.7)	1.0 (0.7–1.3)	
			Moderate smoker	1.0 (0.6–1.8)	1.2 (0.6–2.4)	1.1 (0.7–1.7)	
			Heavy smoker	1.7 (0.4–7.0)	5.3 (1.9–15.0)	3.1 (1.4–7.1)	

CI, confidence interval

Table 2.1.7.3. Case–control studies on tobacco smoking and colorectal cancer: main characteristics of study design

Reference Country and years of study	No. of cases and controls	Comments
Williams & Horm (1977) USA Early 1960s	Men: 333 colon, 185 rectum; women: 389 colon, 154 rectum; and about 4700 controls	Data from the Third National Cancer Survey personal interviews Controls included patients with all other cancers, excluding 'tobacco-related cancers' (lung, larynx, oesophagus, bladder and oral cavity).
Dales *et al.* (1979) USA 1973–76	Men and women: 99 colorectum cases and 280 controls	Hospital-based study among African Americans in the San Francisco Bay Area Cases with colon cancer (72), rectosigmoid cancer (5) and rectal cancer (22); response rate, 40% Controls were hospital patients matched 2:1 (189) and from multiphasic health check-ups matched 1:1 (91), all matched on age, sex and ethnicity; response rate, 50%
Tuyns *et al.* (1982) France 1973–80	Men: 80 colon, 104 rectum and 923 controls; women: 62 colon, 94 rectum and 1053 controls	Population-based study in Calvados Controls represented a random sample of 2% of the total adult population, aged ≥ 20 years,; response rate, 75%
Vobecky *et al.* (1983) Canada 1965–76	Men: 103 colorectum and 103 controls; women: 104 colorectum and 104 controls	Population-based study in St Laurent River Area Cases had 93% response rate. Controls randomly selected in area, individually matched 1:1 by age and sex
Tajima & Tominaga (1985) Japan 1981–83	Men: 27 colon, 25 rectume and 111 controls; women: 15 colon, 26 rectum and 75 controls	Hospital-based study in Aichi Cancer Centre Cases aged 40–70 years Controls were non-cancer patients
Jarebinski *et al.* (1988, 1989) Yugoslavia 1984–86	1988: men: 97 colorectum and 97 controls; women: 87 colorectum and 87 controls; 1989: men: 56 rectum and 112 controls; women: 42 rectum and 84 controls	Population- and hospital-based study in Belgrade Controls from case's neighbourhood (98) and hospital (98), individually matched by sex and age
Ferraroni *et al.* (1989) Italy 1985–88	Men: 221 colon, 170 rectum and 1334 controls; women: 234 colon, 125 rectum and 610 controls	Hospital-based study in northern Italy Cases aged < 75 years Controls were cancer-free (all subjects included in D'Avanzo *et al.*, 1995)
Peters *et al.* (1989) USA 1974–82	Men: 106 colon, 41 rectum and 106 controls	Population-based study among young white men in Los Angeles County Cases aged 25–44 years; response rate, 63% Controls individually matched for neighbourhood, race, sex, date of birth; response rate, 63%

Table 2.1.7.3 (contd)

Reference Country and years of study	No. of cases and controls	Comments
Kato *et al*. (1990a) Japan 1986–90	Men: 79 colon, 60 rectum and 377 controls; women: 53 colon, 31 rectum and 201 controls	Population-based study in Aichi Cancer Centre among 1776 patients receiving colonoscopy; response rate for cases, 86% Controls from telephone directories matched by sex, age (5-year groups) and municipality; response rate, 91%
Kato *et al*. (1990b) Japan 1979–87	Men: 1716 colon, 1611 rectum and 16 600 controls	Hospital-based study in Aichi Cancer Centre among patients receiving colonoscopy Cases with cancer of the colon (445 proximal, 765 distal, 506 not specified), or rectum aged ≥ 20 years; response rate, 89% Controls with other cancers, excluding sites related to smoking (larynx, lung, pancreas, bladder) and alcohol consumption
Slattery *et al*. (1990) USA 1979–83	Men: 112 colon and 185 controls; women: 119 colon and 206 controls	Population-based study in Utah Cases of primary cancer, histologically confirmed, aged 40–79 years; response rate, 71% Controls selected by random-digit dialling; response rate, 74%
Choi & Kahyo (1991) Republic of Korea 1986–90	Men: 63 colon, 67 rectum, 189 controls for colon cases, 201 controls for rectal cases	Hospital-based study in Korea Cancer Centre Controls were cancer-free, matched 3:1 on birth years (± 5 years), sex and admission date.
Kune *et al*. (1992) Australia 1980–81	Men: 202 colon, 186 rectum; women: 190 colon, 137 rectum; and 727 controls	Population-based study in Melbourne Incident, histologically confirmed cases; response rate, 62% Controls from community, matched by age and sex; response rate, 71%
Hoshiyama *et al*. (1993) Japan 1984–90	Men: 37 colon, 61 rectum and 343 controls; women: 42 colon, 41 rectum and 310 controls	Population-based study in Saitama Prefecture Incident cases aged 40–69 years Controls from general population; response rate, 28%
Olsen & Kronborg (1993) Denmark 1986, 1988, 1990	Men: 21 colorectum and 156 controls; women 28 colorectum and 206 controls	Randomized control trial using Hemaoccult II as screening test for colorectal cancer 30 970 to screening and 30 968 to control group Cases tested positive for Hemaoccult II test and colonoscopy, aged 45–74 years (mean, 66.7 years) Controls tested negative for Hemaoccult II test, matched to cases on age and sex; mean age, 63.8 years

Table 2.1.7.3 (contd)

Reference Country and years of study	No. of cases and controls	Comments
Baron *et al*. (1994) Sweden 1986–88	Men and women: 352 colon, 217 rectum (262 men, 307 women) and 512 controls (236 men, 276 women)	Population-based study in Stockholm County All cases diagnosed in the area during that period identified through the regional cancer registry; age, 40–79 years; response rate, 79% Controls from population register; response rate, 82%
Boutron *et al*. (1995) France 1985	Men: 109 colorectum and 159 controls; women: 62 colorectum and 150 controls	Population-based study in a clinic in Côte d'Or Cases aged 30–79 years; response rate, 80% Controls selected from the 1975 census list; response rate, 54%
D'Avanzo *et al*. (1995) Italy 1985–91 (see also Ferraroni *et al*., 1989)	Men: 498 colon, 337 rectum and 1863 controls; women: 457 colon, 252 rectum and 1016 controls	Hospital-based study in northern Italy (Greater Milan and Pordenone Province) Cases aged 20–74 years; response rate, 95% Controls with a wide spectrum of acute non-malignant conditions, excluding diseases of the gastrointestinal tract or diseases related to coffee, alcohol or tobacco consumption; response rate, 95%
Inoue *et al*. (1995) Japan 1988–92	Men and women: 94 proximal and 137 distal colon, 201 rectum (257 men, 175 women) and 31 782 controls (8621 men, 23 161 women)	Hospital-based study in Aichi Cancer Centre; response rate for cases, 94% Controls were non-cancer outpatients on first hospital visit; response rate, 94%
Kotake *et al*. (1995) Japan 1992–94	Men and women: 187 colon, 176 rectum (214 men, 149 women) and 363 controls	Hospital-based study in 10 hospitals Controls included cancer (94), non-cancer (56) and screening controls (213) individually matched by age and sex
Newcomb *et al*. (1995) USA 1990–91	Women: 536 colon, 243 rectum and 2315 controls	Population-based study in Wisconsin Incident cases aged 30–74 years; response rate, 74% Controls randomly selected from driver's licences and Health Care Financing Administration listings; response rate, 90%
Siemiatycki *et al*. (1995) Canada 1979–85	Men: 505 colon, 256 rectum and 1492 controls	Study based in major hospitals in Montreal Cases aged 35–70 years; response rate, 82% (including next of kin) Controls selected among cancer patients (959) and from electoral lists (533); response rate, 72%
Le Marchand *et al*. (1997) USA 1987–92	Men: 698 colorectum and 698 controls; women: 494 colorectum and 494 controls	Population-based study among residents of Oahu, Hawaii Cases histologically confirmed, aged < 85 years; response rate, 66% Controls individually matched on sex, ethnicity and age; response rate, 71%

Table 2.1.7.3 (contd)

Reference Country and years of study	No. of cases and controls	Comments
Slattery *et al.* (1997) USA 1991–94	Men: 1097 colon and 1290 controls; women: 892 colon and 1220 controls	Population-based study in northern California, Utah and Minnesota Cases with first primary cancer, excluding rectosigmoid junction or rectum, aged 30–79 years; response rate, 76% Controls selected by random-digit dialling, Health Care Financing Administration and drivers' licence listings; response rate, 64%
Yamada *et al.* (1997) Japan 1991–93	Men: 108 cancers *in situ*, 55 colorectum; women: 21 cancers *in situ*, 11 colorectum; and 390 controls	Study based on a multiphasic health check-up in Tokyo Cases and controls selected among 79 082 persons receiving a faecal occult blood test Controls with no history of colorectal cancer or inflammatory bowel disease, matched 2:1 on sex, age and history of prior health check-up
Ghadirian *et al.* (1998) Canada 1989–93	Men: 200 colon and 239 controls; women: 202 colon and 429 controls	Population-based study in Greater Montreal Cases selected from five teaching hospitals, aged 35–79; response rate, 60% Controls selected by random-digit dialling, matched by age, sex, place of residence and language; response rate, 50%
Tavani *et al.* (1998) Italy 1991–96	Men: 688 colon, 437 rectum and 2073 controls; women: 537 colon, 219 rectum and 2081 controls	Hospital-based study in six centres in northern Italy Cases aged < 75 years Controls were non–cancer patients Response rate for cases and controls, > 95%
Nusko *et al.* (2000) Germany 1993–96	Men: 126 colorectum and 100 controls; women: 76 colorectum and 134 controls	Hospital-based study among patients undergoing colonoscopy Cases aged ≥ 40 years Controls were polyp-free patients
Chiu *et al.* (2001) USA 1986–89	Men: 317 colon, 362 rectum and 1503 controls; women: 338 colon, 267 rectum and 833 controls	Population-based study in Iowa Incident cases, histologically confirmed; aged 40–85 years; response rate, 86% Controls selected from driver's licence and Health Care Financing Administration listings, frequency-matched by sex and age; response rate, 80%
Lam *et al.* (2001) Hong Kong SAR 1997–99	Men: 636 colorectum; women: 563 colorectum; and 13 054 controls	Mortality study among 27 507 cancer deaths Cases aged ≥ 35 years; information retrieved from next of kin; response rate, 81% Controls were relatives of cases or other informants.

Table 2.1.7.4. Case–control studies on tobacco smoking and colorectal cancer

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Williams & Horm (1977) USA Early 1960s	Pack–years				Age, race
	Men				
	< 20	0.7 ($p < 0.05$)	1.6 ($p < 0.05$)		
	20–40	0.7	1.5		
	> 40	0.8	0.8		
	Women				
	< 20	1.2	0.8		
	20–40	0.9	0.7		
	> 40	0.7	0.9		
Dales *et al.* (1979) USA 1973–76	Ever-smoker			58% cases versus 58% controls	Crude percentages
Tuyns *et al.* (1982) France 1973–80	Current smoker	1.0 (0.4–2.7)	1.1 (0.4–2.6)		Age, sex. Risks were non-significantly increased with alcohol intake; 44% of controls were younger than cases.
Vobecky *et al.* (1983) Canada 1965–76	*Men*				Age, sex, city. Alcohol was not a risk factor for colon cancer but was for rectal cancer in men (not significant); information and selection bias
	Former smoker	0.5 (p >0.05)	0.2 ($p = 0.03$)		
	Current smoker	2.0 ($p > 0.05$)	1.4 ($p > 0.05$)		
	Women				
	Former smoker	Not available	Not available		
	Current smoker	1.3 ($p > 0.05$)	1.0 ($p > 0.05$)		

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)					Variables adjusted for and other comments
		Colon	Rectum		Colorectum		
Tajima & Tominaga (1985) Japan 1981–83	Ever-smoker	0.6	1.0				Age, education. All odds ratios were non–significant
	Pack–years						
	< 30	0.3	1.1				
	30	0.8	0.9				
	Age at starting smoking (years)						
	< 20	0.2	0.8				
	> 20	0.7	1.2				
Jarebinski *et al.* (1988, 1989) Yugoslavia 1984–86	*Cigarettes/day (current smokers only)*		N[†]	H[†]	N	H	Age, sex. Adjusted for cigarettes/day and duration, respectively. Extent of overlap of subjects unknown [†]N, neighbourhood controls; H, hospital controls
	1–14		0.7	1.0	0.6	0.7	
	15–24		1.3	1.0	1.1	1.2	
	≥ 25		1.3	1.8	1.5	1.3	
	Duration (years) (former + current smokers)						
	1–30		1.0	1.0	1.0	1.0	
	≥ 31		2.7	2.3	2.0	1.5	
			All $p > 0.05$		All $p > 0.05$		
Ferraroni *et al.* (1989) (see also D'Avanzo *et al.* 1995) Italy 1985–88	Former smoker	0.7	0.9				Age, sex,education, marital status, coffee and alcohol consumption
	Cigarettes/day						
	< 15	0.7	0.7				
	15–24	0.8	0.8				
	≥ 25	0.8	1.1				
	p for trend	> 0.05	> 0.05				
Peters *et al.* (1989) USA 1974–82	Former smoker	0.6 (0.3–1.3)	0.7 (0.3–1.8)		0.7 (0.4–1.4)		Age and education. Effect for alcohol consumption only with ≥ 70 g/day
	Pack/day						
	≤ 1	0.4 (0.2–1.0)	0.9 (0.3–2.5)		0.7 (0.3–1.4)		
	≥ 2	1.1 (0.5–2.1)	0.5 (0.2–1.5)		0.9 (0.4–1.8)		

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Kato *et al*. (1990a) Japan 1986–90	Former smoker Current smoker	1.1 (0.6–2.1) 0.6 (0.3–1.1)	1.5 (0.7–3.4) 1.4 (0.7–3.0)		Sex, age, residence; not adjusted for alcohol. Increased risk for colon and rectal cancer with former, but not current drinking
Kato *et al*. (1990b) Japan 1979–87	Current smoker	*Proximal* 0.7 (0.6–0.9) *Distal* 0.8 (0.7–1.0) All 0.8 (0.7–0.9)	0.9 (0.8–1.1)		Age Approximately 50% of control subjects had stomach cancer.
Slattery *et al*. (1990) USA 1979–83	*Men*				No adjustments No effect of alcohol, but an effect of coffee intake
	Any tobacco	1.7 (1.0–2.8)			
	Cigarettes/day				
	1–16	1.2 (0.6–2.4)			
	17–20	1.4 (0.8–2.6)			
	> 20	2.0 (1.0–3.9)			
	p for trend	0.04			
	Women				
	Current smoker	1.2 (0.7–2.2)			
	Cigarettes/day				
	1–16	0.8 (0.3–1.8)			
	17–20	2.0 (0.8–4.7)			
	> 20	1.5 (0.5–4.8)			
	p for trend	0.24			
	Men				Age, body-mass index, calories, crude fibre intake
	Cigarette smoker	1.3 (0.8–2.3)			

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Choi & Kahyo (1991) Republic of Korea 1986–90	Former smoker	0.6 (0.2–1.7)	1.4 (0.5–3.3)		Age, marital status, education, diet, alcohol intake
	Current smoker	0.8 (0.4–1.6)	0.7 (0.4–1.5)		
	Cigarettes/day				
	1–20	0.7 (0.3–1.3)	0.7 (0.3–1.4)		
	21–40	1.4 (0.5–4.0)	1.3 (0.5–3.1)		
	> 40	–	0.4 (0.1–3.8)		
	Duration (years)				
	1–19	1.1 (0.4–3.3)	1.2 (0.5–2.9)		
	20–39	0.7 (0.3–1.6)	0.7 (0.3–1.4)		
	≥ 40	0.6 (0.3–1.6)	1.0 (0.4–2.8)		
	Age at starting smoking (years)				
	≥ 25	1.0 (0.4–2.5)	1.6 (0.7–3.9)		
	18–24	0.8 (0.4–1.6)	0.6 (0.2–1.3)		
	<18	0.6 (0.2–1.7)	1.2 (0.4–3.5)		
	Years of cessation				
	1–4	1.1 (0.2–5.9)	2.8 (0.9–9.1)		
	5–9	–	1.3 (0.3–5.3)		
	≥ 10	1.6 (0.5–4.9)	1.6 (0.5–5.7)		
Kune *et al*. (1992) Australia 1980–81	*Men*				Age, alcohol, dietary factors. Only significant increased risk with combination of hand-rolled and ready-made cigarettes. No significant association with pack–years or cigarettes/day
	Former smoker	1.0	1.2	1.1	
	Ever-smoker	0.9	1.1	1.0	
	Current smoker	0.7	1.0	0.9	
	Women				
	Former smoker	0.7	0.6	0.7	
	Ever-smoker	0.7	0.7	0.8	
	Current smoker	0.8	0.9	0.8	

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Hoshiyama *et al.* (1993) Japan 1984–90	Current smoker	0.3 (0.1–0.8)	1.4 (0.6–3.1)		Sex and age
	Cigarettes/day				
	1–29	0.3 (0.1–0.7)	1.7 (0.9–3.4)		
	≥ 30	0.3 (0.1–1.0)	(0.3–2.6)		
	Pack–years				
	≤ 40	0.3 (0.1–0.7)	1.6 (0.8–3.0)		
	> 40	0.2 (0.0–0.7)	1.5 (0.6–3.6)		
	p for trend	< 0.01	0.31		
Olsen & Kronborg (1993) Denmark 1986, 1988, 1990	Former smoker			1.2 (0.5–3.1)	Age, sex, dietary fibre and coffee intake. Controls were younger (mean age, 63.8 versus 66.7 for colorectal cases)
	Current smoker			0.9 (0.4–2.1)	
	Duration (years)				
	1–19			2.8 (0.9–8.7)	
	20–39			0.7 (0.3–1.9)	
	≥ 40			0.7 (0.3–1.7)	
Baron *et al.* (1994) Sweden 1986–88	Former smoker	0.9 (0.7–1.3)	0.9 (0.6–1.3)	0.9 (0.7–1.3)	Age, gender, fat and fibre consumption, body-mass index, exercise [†]Questions on smoking starting from 1950
	Current smoker	0.9 (0.6–1.3)	0.8 (0.6–1.3)	0.9 (0.7–1.2)	
	Cigarettes/day				
	1–10	1.1 (0.7–1.7)	1.0 (0.6–1.7)	1.1 (0.7–1.6)	
	≥ 11	0.8 (0.5–1.2)	0.7 (0.4–1.2)	0.8 (0.5–1.1)	
	Duration (years)[†]				
	< 20	1.0 (0.7–1.5)	1.0 (0.6–1.6)	1.0 (0.7–1.4)	
	25–35	0.9 (0.6–1.3)	0.8 (0.5–1.4)	0.9 (0.6–1.3)	
	≥ 40	0.9 (0.6–1.3)	0.8 (0.5–1.3)	0.9 (0.6–1.2)	
	Pack–years[†]				
	< 11.05	0.8 (0.5–1.2)	0.9 (0.6–1.5)	0.9 (0.6–1.2)	
	11.05–< 22.74	1.0 (0.7–1.6)	0.9 (0.5–1.3)	1.0 (0.7–1.4)	
	≥ 22.74	0.9 (0.6–1.4)	0.8 (0.5–1.3)	0.9 (0.6–1.3)	

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Boutron *et al.* (1995) France 1985	Pack–years				Age; not clear if alcohol was adjusted for. Smoking was a risk factor for polyps
	Men				
	1–20			1.4 (0.7–2.8)	
	> 20			1.5 (0.8–2.9)	
	Women				
	1–20			0.2 (0.03–2.0)	
	> 20			0.6 (0.2–1.9)	
D'Avanzo *et al.* (1995) (see also Ferraroni *et al.*, 1989) Italy 1985–91	Former smoker	1.1 (0.8–1.3)	0.8 (0.6–1.0)	0.9 (0.8–1.1)	Age, sex, education, area of residence, food score, fat intake, calorie intake, meat and alcohol, family history of cancer. Results similar in men and women
	Current smoker	0.7 (0.5– 0.8)	0.7 (0.6–0.9)	0.7 (0.6–0.8)	
	Cigarettes/day				
	< 15	0.6 (0.5–0.8)	0.7 (0.6–0.9)	0.7 (0.5–0.8)	
	15–24	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.7 (0.6–0.9)	
	≥ 25	0.6 (0.4–0.9)	0.9 (0.6–1.2)	0.8 (0.6–1.0)	
	Duration (years)				
	< 10	0.9 (0.6–1.2)	0.7 (0.5–1.1)	0.8 (0.7–1.1)	
	10–19	0.7 (0.6–1.0)	0.8 (0.6–1.1)	0.7 (0.6–0.9)	
	20–29	0.9 (0.7–1.1)	0.7 (0.5–0.9)	0.8 (0.6–1.0)	
	≥ 30	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.7 (0.6–0.9)	
	Time since starting (years)				
	< 30	0.7 (0.6–0.9)	0.7 (0.5–1.0)	0.7 (0.6–0.9)	
	> 30	0.8 (0.7–1.0)	0.7 (0.6–0.9)	0.8 (0.7–0.9)	
	Time since quitting (years)				
	< 10	0.9 (0.7–1.2)	0.9 (0.6–1.2)	1.1 (0.8–1.4)	
	> 10	1.2 (0.9–1.6)	0.7 (0.6–0.9)	0.7 (0.6–0.8)	
	Pack–years				
	1–9	0.9 (0.7–1.3)	0.9 (0.6–1.2)	0.9 (0.7–1.2)	
	10–19	0.9 (0.7–1.4)	0.7 (0.5–1.0)	0.8 (0.6–1.0)	
	20–29	0.7 (0.5–1.0)	0.5 (0.3–0.7)	0.6 (0.5–0.8)	
	30–39	0.7 (0.5–1.0)	0.6 (0.4–0.9)	0.7 (0.5–0.9)	
	≥ 40	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.8 (0.6–1.0)	

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Inoue *et al*. (1995) Japan 1988–92	Nonsmoker versus ever-smoker	*Proximal*			Age. No association with alcohol consumption
	Men	0.7 (0.4–1.4)	1.9 (1.1–3.2)		
	Women	0.9 (0.4–2.4)	1.7 (1.0–3.1)		
		Distal			
	Men	1.0 (0.6–1.7)			
	Women	1.1 (0.6–2.3)			
Kotake *et al*. (1995) Japan 1992–94	Current smoker	1.3 (0.3–5.2)	1.4 (0.3–6.8)		Age, sex. Potential for selection bias of control groups
	> 20 pack–years	0.8 (0.2–2.8)	2.7 (0.9–8.3)		
Newcomb *et al*. (1995) USA 1990–91	Former smoker	1.2 (1.0–1.6)	1.3 (0.9–1.8)		Age, body-mass index, consumption of beer, wine and spirits, family history of cancer, sigmoidoscopy biopsy. Trends for amount smoked, age at start or time since cessation not significant after adjusting for duration. Increased risk mainly for cancer of left colon and not right colon
	Ever-smoker	1.3 (1.0–1.6)	1.4 (1.1–1.9)		
	Current smoker	1.3 (1.0–1.8)	1.7 (1.2–2.4)		
	Cigarettes/day				
	≤ 10	1.2 (0.9–1.5)	1.3 (0.9–1.9)		
	11–20	1.4 (1.0–1.8)	1.6 (1.1–2.3)		
	21–30	1.2 (0.7–2.1)	1.3 (0.6–2.7)		
	> 30	1.7 (1.0–2.8)	1.6 (0.8–3.2)		
	p for trend	0.01	0.02		
	Duration (years)				
	1–20	1.1 (0.8–1.5)	1.1 (0.7–1.7)		
	21–30	1.1 (0.7–1.6)	1.0 (0.6–1.8)		
	31–40	1.7 (1.2–2.3)	1.5 (0.9–2.3)		
	> 40	1.4 (0.9–1.9)	2.2 (1.4–3.5)		
	p for trend	0.005	< 0.001		

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Newcomb *et al.* (1995) (contd)	*Age at starting smoking (years)*				
	> 30	1.4 (0.9–2.2)	0.6 (0.4–1.5)		
	26–30	0.8 (0.5–1.5)	1.1 (0.6–2.0)		
	21–25	1.3 (1.0–1.9)	1.9 (1.3–2.9)		
	≤ 20	1.4 (1.0–1.8)	1.5 (1.1–2.2)		
	p for trend	0.02	0.002		
	Years of cessation				
	> 20	1.1 (0.8–1.7)	1.3 (0.8–2.2)		
	11–20	1.3 (0.9–1.9)	1.0 (0.5–1.8)		
	1–10	1.3 (0.9–1.9)	1.4 (0.9–2.3)		
	Current smoker	1.3 (1.0–1.8)	1.7 (1.2–2.4)		
	p for trend	0.02	0.004		
Siemiatycki *et al.* (1995) Canada 1979–85	Ever-smoker	1.0 (0.8–1.4)	1.1 (0.7–1.6)		Age, ethnic group, social class, blue collar/white collar dirtiness score, consumption of coffee, alcohol and β-carotene
	Cigarette–years				
	1–500	1.2 (0.8–1.8)	1.1 (0.7–1.8)		
	501–1000	1.1 (0.8–1.6)	1.1 (0.7–1.8)		
	1001–1500	0.9 (0.6–1.3)	0.9 (0.5–1.4)		
	≥ 1501	0.9 (0.6–1.5)	1.1 (0.6–1.9)		
Le Marchand *et al.* (1997) USA 1987–92		Right colon	Left colon	Rectum	Age, family history of colorectal cancer, alcohol, physical activity, body-mass index, intake of eggs, dietary fibre, calcium, calories. Tertile cuts differed for men and women. Interquartile range was 0–39 pack–years in men and 0–28 in women.
	Men	(*n* = 197)	(*n* = 270)	(*n* = 221)	
	Former smoker	1.0 (0.5–1.9)	1.4 (0.9–2.4)	1.4 (0.8–2.3)	
	Current smoker	0.7 (0.3–1.6)	0.9 (0.4–1.9)	0.8 (0.4–1.8)	
	Pack–years				
	Tertile 1	1.0	1.0	1.0	
	Tertile 2	1.1 (0.6–2.2)	0.9 (0.5–1.6)	1.2 (0.7–2.1)	
	Tertile 3	0.8 (0.4–1.6)	2.0 (1.1–3.5)	1.3 (0.7–2.5)	
			p = 0.006	*p* = 0.41	
	Women	(*n* = 164)	(*n* = 194)	(*n* = 129)	
	Former smoker	2.4 (1.0–5.6)	1.1 (0.6–2.0)	1.6 (0.7–3.4)	
	Current smoker	1.1 (0.4–2.6)	0.7 (0.3–1.5)	1.4 (0.5– 3.7)	

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Le Marchand *et al*. (1997) (contd)	*Pack–years*				
	Tertile 1	1.0	1.0	1.0	
	Tertile 2	2.1 (0.9–5.1)	0.5 (0.3–1.2)	1.5 (0.5–4.4)	
	Tertile 3	1.6 (0.7–3.6)	1.3 (0.7–2.5)	1.5 (0.7–3.0)	
		p = 0.47	*p* = 0.41	*p* = 0.35	
Slattery *et al*. (1997) USA 1991–94	**Men**				Age, body-mass index, activity, intake of energy, fibre and calcium, family history of cancer, non-steroidal anti-inflammatory drugs. Cigarettes/day and years smoked were mutually adjusted. No consistent differences between colon subsites. [Identical values of relative risk and confidence intervals for pack–years in men and women]
	Ever-smoker	1.3 (1.1–1.5)			
	Cigarettes/day				
	≤ 10	1.0 (0.8–1.4)			
	11–20	1.2 (0.9–1.7)			
	> 20	1.5 (1.1–1.8)			
	Duration (years)				
	< 15	0.8 (0.6–1.1)			
	15–34	1.1 (0.9–1.5)			
	≥ 35	0.9 (0.7–1.2)			
	Pack–years				
	≤ 20	1.1 (0.9–1.4)			
	21–35	1.3 (1.0–1.7)			
	>35	1.4 (1.1–1.7)			
	Age at starting smoking (years)				
	≤ 16	1.3 (1.0–1.6)			
	17–20	1.4 (1.1–1.7)			
	> 20	1.1 (0.8–1.5)			
	Years of cessation				
	≥ 15	1.3 (1.0–1.6)			
	11–14	1.4 (1.0–2.1)			
	5–10	1.3 (1.0–1.8)			
	Current smoker	1.2 (0.9–1.5)			
	Women				
	Ever-smoker	1.1 (0.9–1.3)			

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Slattery *et al.* (1997) (contd)	*Cigarettes/day*				
	≤ 10	1.1 (0.7–1.5)			
	11–20	1.0 (0.7–1.6)			
	> 20	1.5 (0.9–2.4)			
	Duration (years)				
	< 15	0.9 (0.6–1.2)			
	15–34	0.9 (0.7–1.3)			
	≥ 35	0.9 (0.6–1.3)			
	Pack–years				
	≤ 20	1.1 (0.9–1.4)			
	21–35	1.3 (1.0–1.7)			
	> 35	1.4 (1.1–1.7)			
	Age at starting smoking (years)				
	≤ 16	1.2 (0.9–1.7)			
	17–20	1.1 (0.8–1.3)			
	> 20	1.1 (0.8–1.5)			
	Years of cessation				
	≥ 15	1.0 (0.7–1.2)			
	11–14	1.4 (0.8–2.3)			
	5–10	1.5 (1.0–2.1)			
	Current smoker	1.1 (0.8–1.4)			

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Yamada *et al.* (1997) Japan 1991–93	*Pack–years*		**Cancer *in situ***	**Cancer**	Gender, age, body mass index, cumulative alcohol consumption. Current alcohol intake associated with small increased risk for colorectal cancer (*p* for trend = 0.09), but not for cancer *in situ*
	1–20		1.4 (0.7–2.7)	0.8 (0.3–2.2)	
	21–40		2.8 (1.4–5.4)	1.2 (0.5–3.0)	
	> 41		2.5 (1.3–5.1)	2.6 (0.9–7.1)	
	p for trend		0.006	0.02	
	Cigarettes/day				
	Past		1.0 (0.5–1.9)	1.8 (0.7–4.4)	
	Current: 1–15		2.2 (1.0–4.6)	1.2 (0.4–3.8)	
	16–30		2.6 (1.3–5.1)	0.8 (0.3–2.1)	
	≥ 31		3.1 (1.3–7.5)	2.4 (0.7–8.6)	
	p for trend		0.006	0.8	
	Pack–years				
	Within past 20 years				
	1–15		1.3 (0.7–2.4)	1.1(0.5–2.7)	
	16–30		2.2 (1.2–4.1)	1.2 (0.5–2.9)	
	≥ 31		3.7 (1.6–8.5)	2.9 (0.9–9.4)	
	p for trend		0.0003	0.1	
	Until 20 years ago				
	1–15		1.2 (0.7–2.0)	1.0 (0.4–2.4)	
	16–30		2.1 (1.0–4.0)	3.4 (1.2–9.2)	
	≥ 31		0.7 (0.3–2.0)	5.0 (1.3–18.3)	
	p for trend		0.9	0.005	
Ghadirian *et al.* (1998) Canada 1989–93	*Ever-smoker*				Age, sex, marital status, family history of colon cancer. Matching not clearly reported
	Any tobacco	1.0 (0.7–1.3)			
	Cigarettes	1.0 (0.7–1.3)			

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Tavani *et al.* (1998) Italy 1991–96	Former smoker	1.0 (0.9–1.2)	1.1 (0.9–1.4)		Centre, age, sex, education, body-mass index, alcohol and energy intake, consumption of vegetables and coffee, meals/day, physical activity, family history of cancer. No association in analysis by colon subsites
	Current smoker	0.8 (0.7–1.0)	0.7 (0.6–0.9)		
	Cigarettes/day				
	< 15	0.8 (0.6–1.0)	0.6 (0.5–0.9)		
	15–24	0.8 (0.6–1.0)	0.8 (0.6–1.1)		
	≥ 25	0.9 (0.6–1.3)	0.9 (0.6–1.4)		
	Duration (years)				
	< 20	1.1 (0.8–1.3)	1.1 (0.8–1.4)		
	20–29	0.9 (0.8–1.2)	0.8 (0.6–1.0)		
	30–39	0.9 (0.7–1.1)	0.9 (0.7–1.1)		
	≥ 40	0.8 (0.6–1.0)	0.9 (0.7–1.1)		
	p for trend	< 0.05	> 0.05		
	Pack–years				
	< 20	0.9 (0.8–1.1)	0.9 (0.7–1.1)		
	20–39	0.9 (0.7–1.1)	1.0 (0.8–1.2)		
	≥ 40	0.9 (0.7–1.2)	0.9 (0.7–1.2)		
	Age at starting smoking (years)				
	< 18	1.0 (0.8–1.3)	1.0 (0.8–1.3)		
	18–20	0.9 (0.7–1.1)	0.9 (0.7–1.1)		
	≥ 21	0.8 (0.6–1.0)	0.8 (0.6–1.1)		
	Years since starting				
	< 30	0.9 (0.7–1.1)	0.7 (0.5–1.0)		
	30–39	0.9 (0.7–1.1)	0.8 (0.6–1.1)		
	≥ 40	0.9 (0.8–1.1)	1.1 (0.8–1.3)		
	Years since cessation				
	< 10	1.0 (0.8–1.3)	1.1 (0.8–1.5)		
	> 10	1.0 (0.8–1.3)	1.1 (0.9–1.4)		

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Nusko *et al.* (2000) Germany 1993–96	Smoker			1.5 (1.0–2.1)	Crude Definition of smoker not given. Cases were older, higher percentage of men; no adjustment for age, sex or other relevant covariates
Chiu *et al.* (2001) USA 1986–89	Men				Age, total energy, farming, fibre intake, colitis, no. of first degree relatives with colorectal cancer, body-mass index at age 20 years
	Former smoker	1.5 (1.1–2.0)	1.4 (1.1–1.8)		
	Ever-smoker	1.3 (1.0–1.8)	1.3 (1.0–1.8)		
	Current smoker	1.0 (0.7–1.5)	1.3 (0.9–1.9)		
	Cigarettes/day				
	≤ 10	1.5 (1.0–2.4)	1.5 (1.0–2.2)		
	11–20	1.3 (0.9–1.8)	1.3 (1.0–1.8)		
	21–40	1.3 (0.9–1.9)	1.2 (0.9–1.8)		
	> 40	1.3 (0.7–2.3)	1.2 (0.7–2.0)		
	Duration (years)				
	≤ 20	1.5 (1.0–2.3)	1.2 (0.8–1.8)		
	21–40	1.1 (1.0–1.4)	1.1 (1.0–1.4)		
	> 40	1.1 (1.0–1.2)	1.1 (1.0–1.2)		
	Pack–years				
	≤ 20	1.5 (1.0–2.2)	1.4 (1.0–2.0)		
	21–40	1.6 (1.1–2.3)	1.5 (1.1–2.1)		
	> 40	1.1 (0.8–1.6)	1.2 (0.9–1.7)		
	Women				
	Former smoker	1.6 (1.1–2.2)	1.2 (0.8–1.8)		
	Ever-smoker	1.3 (0.9–1.7)	1.0 (0.7–1.3)		
	Current smoker	1.0 (0.7–1.4)	0.7 (0.5–1.1)		
	Cigarettes/day				
	≤ 10	1.1 (0.7–1.6)	1.0 (0.6–1.6)		
	11–20	1.3 (0.9–1.9)	1.2 (0.8–1.8)		
	21–40	1.2 (0.7–2.0)	0.5 (0.2–0.9)		
	> 40	1.5 (0.7–9.9)	1.2 (0.2–9.7)		

Table 2.1.7.4 (contd)

Reference Country and years of study	Smoking variables	Odds ratio (95% CI or *p* value)			Variables adjusted for and other comments
		Colon	Rectum	Colorectum	
Chiu *et al*. (2001) (contd)	*Duration (years)*				
	≤ 20	1.3 (0.7–2.4)	1.4 (0.8–2.6)		
	21–40	1.1 (0.9–1.4)	0.9 (0.8–1.2)		
	> 40	1.1 (0.9–1.2)	0.9 (0.8–1.1)		
	Pack–years				
	≤ 20	1.4 (0.9–2.1)	1.3 (0.8–2.0)		
	21–40	1.1 (0.7–1.8)	0.9 (0.6–1.5)		
	> 40	1.2 (0.8–1.9)	0.7 (0.4–1.1)		
Lam *et al*. (2001) Hong Kong SAR 1997–99	*Ever-smoker*				Age, education
	Men aged 35–69 years			0.8 (0.6–1.1)	
	Men aged ≥ 70 years			1.2 (0.9–1.5)	
	Women aged 35–69 years			1.0 (0.6–1.7)	
	Women aged ≥ 70 years			1.1 (0.8–1.4)	
				Men *Women*	
	Cigarettes/day			Aged ≥ 70 years	
	1–14			1.1 1.1	
	15–24			1.2 0.9	
	≥ 25			1.7 1.3	
	p for trend			< 0.05 0.63	
				Aged 35–69 years	
	1–14			0.9 1.1	
	15–24			0.7 0.5	
	≥ 25			1.2 2.5	
	p for trend			0.29 0.98	

CI, confidence interval

Table 2.1.7.5. Tobacco smoking and risk of colorectal polyps

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Hoff *et al.* (1987) Norway	400 individuals randomly selected from population registry, aged 50–59 years; 324 (81%) underwent sigmoi-doscopy.	90 (55 M, 35 F) adenomas and/or hyperplastic polyps 71 (50 M, 21 F) adenomas and/or hyperplastic polyps	69 (32 M, 37 F) 38 (23 M, 15 F)	*Duration (years)* Men Women *Age at start (years)* Men Women	Cases vs non-cases 31.3 ± 1.7 vs 17.3 ± 2.8; $p < 0.01$ 17.6 ± 2.8 vs 8.9 ± 2.2; $p < 0.05$ 17.9 ± 0.6 vs 19.0 ± 1.2; $p > 0.05$ 23.1 ± 1.9 vs 27.7 ± 2.3; $p > 0.05$	Crude analysis. No significant differences in risk according to amount smoked daily
Demers *et al.* (1988) USA 1981–85	1380 male aerospace workers screened for colorectal cancer by sigmoidoscopy	246 polyps, including 94 adenomatous polyps	1134	Ever-smoker Adenomatous polyps Any polyp	 1.7 (1.3–2.3) 1.5 (1.2–1.8)	Adjusted for age
Stemmermann *et al.* (1988) USA 1966–83	American Men of Japanese Ancestry Study 163 deaths with detailed autopsy of the colon	79 adenomatous polyps	84	 Ever-smoker Current smoker	Cases vs non-cases 32.1 vs 30.7; $p = 0.74$ 13.2 vs 12.3; $p = 0.70$	
Kikendall *et al.* (1989) USA 1984–87	204 patients referred for colonoscopy; 185 with complete colonoscopy, adequate biopsy and smoking history	98 adenomas or adenocarcinomas	87	*Cigarettes/day* 1–19 ≥ 20 *Pack–years* 1–19 20–39 ≥ 40 *Years since quitting* > 2 < 2	 2.0 (1.3–3.2) 4.2 (1.7–10.3) 1.5 (1.1–2.0) 2.2 (1.3–3.9) 3.3 (1.4–7.8) 1.2 2.8	Adjusted for age, sex and beer consumption [number of cases and non-cases not clear; sex distribution not reported]

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Kato *et al.* (1990b) Japan 1986–90	2052 patients undergoing colonoscopy; 1776 (87%) responded to postal questionnaire.	525 adenomas[†] 163 proximal (124 M, 39 F) 351 distal (219 M, 132 F) 118 rectum (80 M, 38 F)	578 (377 M, 201 F) selected through telephone directories; 91% responded to postal questionnaire		Proximal colon	Adjusted for age, sex and residence [†]Inconsistency between total number of adenomas and numbers at specific sites
				Former smoker	1.03 (0.6–1.9)	
				Current smoker	0.8 (0.4–1.3)	
					Distal colon	
				Former smoker	0.9 (0.6–1.5)	
				Current smoker	0.8 (0.6–1.3)	
					Rectum	
				Former smoker	0.95 (0.5–1.9)	
				Current smoker	1.1 (0.6–2.0)	
Kono *et al.* (1990) Japan 1986–88	1348 male self-defence officials aged 49–56 years, undergoing colonoscopy for health check-up	86 adenomatous polyps of sigmoid colon	1184	*Pack–years*		Adjusted for rank, alcohol and rice consumption
				< 20	0.8 (0.4–1.6)	
				≥ 20–< 40	0.9 (0.5–1.6)	
				≥ 40	0.8 (0.4–1.7)	
Cope *et al.* (1991) UK	152 patients undergoing routine colonoscopy	66 (36 M, 30 F) adenomatous polyps	86 (38 M, 48 F)	Nonsmoker/non-drinker	1.0	Adjusted for age and sex; categories refer to current alcohol drinkers and/or smokers.
				Smoker/non-drinker	2.1 (0.5–8.3)	
				Nonsmoker/drinker	3.0 (1.1–8.2)	
				Smoker/drinker	12.7 (3.0–53.4)	

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Monnet *et al.* (1991) France 1983–87	302 male inpatients or outpatients referred for colonoscopy; 211 (70%) responded to survey by phone or post.	103 adenomas	108	Former smoker	2.7 (1.3–5.7)	Adjusted for age; diagnosis of adenoma confirmed by biopsy
				Ever-smoker	2.2 (1.1–4.4)	
				Current smoker	1.9 (0.9–4.0)	
				Cigarettes/day		
				1–9	1.5 (0.6–3.9)	
				10–19	2.0 (1.0–4.3)	
				> 19	3.4 (1.5–7.9)	
				p for trend	< 0.02	
				Duration (years)		
				1–19	1.3 (0.5–3.6)	
				> 19	2.5 (1.3–4.9)	
				p for trend	< 0.02	
				Pack–years		
				1–19	1.4 (0.6–3.0)	
				> 19	3.0 (1.5–6.1)	
				p for trend	< 0.004	
				Years of cessation		
				> 10	2.2 (0.9–5.3)	
				< 10	3.2 (1.3–7.7)	

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)		Adjustment factors, comments
Zahm *et al.* (1991) USA 1981–83	1465 white male pattern makers examined by flexible sigmoidoscopy; 48% completed questionnaire; 549 with smoking history	76 polyps (adenomatous, hyperplastic or other not specified)	470	Former smoker	1.4 (0.8–2.5)		Adjusted for age and alcohol consumption; relative risks available for former smokers by number of cigarettes per day, years of smoking and pack–years, and for former and current smokers according to duration of employment
				Ever-smoker	1.7 (1.0–2.9)		
				Current smoker	2.2 (1.2–4.1)		
				Cigarettes/day			
				≤ 19	5.5 (2.5–12.1)		
				20–39	1.5 (0.7–3.3)		
				≥ 40	5.7 (2.6–12.9)		
				p for trend	0.0035		
				Duration (years)			
				≤ 10	Not available		
				11–25	3.3 (1.3-8.3)		
				≥ 26	2.8 (1.4-5.5)		
				p for trend	0.0006		
				Pack–years			
				≤ 20	2.4 (0.9–6.4)		
				21–40	4.5 (2.2–9.4)		
				≥ 41	2.1 (1.0–4.5)		
				p for trend	0.0014		
Honjo *et al.* (1992) Japan 1989–90	1296 male self-defence officials aged 48–54 years; 1203 received routine colonoscopy.	116 adenomatous polyps in sigmoid colon	930	Former smoker	2.2 (1.1–4.3)		Adjusted for alcohol drinking, official rank and body-mass index
				Current smoker			
				Cigarettes/day			
				< 25	3.3 (1.8–6.3)		
				≥ 25	2.8 (1.3–5.9)		
				Pack–years			
				< 20	2.3 (1.1–4.6)		
				20–< 40	2.9 (1.5–5.4)		
				≥ 40	3.2 (1.6–6.5)		
Kono *et al.* (1990); Honjo *et al.* (1992) Japan	Combined data from both studies 202 polyps with information on size	Adenomas 86 small (< 5mm) 72 large (≥ 5 mm)	2114	*Pack–years*	Small	Large	Adjusted for alcohol intake, official rank and body-mass index
				< 20	1.5 (0.7–3.3)	1.7 (0.8–3.8)	
				20–< 40	2.1 (1.1–4.1)	1.7 (0.8–3.4)	
				≥ 40	2.5 (1.2–5.3)	1.4 (0.6–3.3)	

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Lee *et al.* (1993) USA 1986–88	2879 patients referred for colonoscopy beyond splenic flexure, aged 35–84 years; 1892 (81%) interviewed	303 polyps 271 (153 M, 118 F) with smoking data	509 457 (202 M, 255 F) with smoking data	*Pack–years* ≤ 10 > 10–≤ 40 > 40 *p* for trend *Pack–years* ≤ 7.5 > 7.5–≤ 30 > 30 *p* for trend	Men 1.0 (0.5–1.9) 1.8 (0.3–3.3) 2.2 (1.2–3.8) 0.002 Women 0.9 (0.5–1.8) 1.2 (0.6–2.1) 1.4 (0.8–2.5) > 0.05	Adjusted for age. Significant trend by intensity of smoking for right side colon, severe atypia, multiplicity and polyps ≥ 10 mm
Olsen & Kronborg (1993) Denmark 1986	20 672 individuals randomly selected for Haemoccult II screening test; 397 (85%) with positive test had complete colonoscopy.	171 polyps (57 M, 114 F)	362 (157 M, 205 F)	Former smoker Current smoker *Duration (years)* 1–19 20–39 ≥ 40	2.1 (1.1–3.9) 2.0 (1.1–3.5) 2.1 (0.8–5.6) 2.0 (1.1–3.6) 2.7 (1.6–4.7)	Adjusted for age, sex and consumption of dietary fibre, coffee, tea and alcohol. Controls were participants with negative screening test result.
Sandler *et al.* (1993) USA 1988–91	2094 patients undergoing colonoscopy, aged ≥ 30 years; 645 eligible with reliable interviews	236 (105 M, 131 F) adenomatous polyps, including 39 adenomatous and hyperplastic polyps	409 (165 M, 244 F), including 46 with hyper-plastic polyps	Ever-smoker Ever-smoker[†] *Cigarettes/day* 1–10 11–20 ≥ 21 *Pack–years* 1–20 21–40 ≥ 41	1.1 (0.8–1.6) 1.2 (0.9–1.7) 1.3 (0.8–2.1) 1.00 (0.6–1.6) 0.96 (0.6–1.7) 1.2 (0.8–1.9) 0.9 (0.5–1.4) 1.4 (0.8–2.4)	Adjusted for age and sex. [†]Excluding controls with hyperplastic polyps. Similar results in men and women. Little change in results after adjusting for alcohol consumption. No difference between cases and controls for age at start, mean number of cigarettes per day, mean years of smoking and mean pack–years by sex. No difference between ever-smoker, former smoker and current smoker

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)		Adjustment factors, comments
Giovannucci *et al.* (1994a) USA 1980–90 (see also Kearney *et al.*, 1995)	Nurses' Health Study 12 143 women undergoing endoscopy (primarily sigmoido- scopy)	564 prevalent and incident adenomatous polyps of distal colon and rectum		Current smoker *Pack–years* 1–9 10–19 20–29 30–39 ≥ 40 *p* for trend	2.1 (1.7–2.6) 1.2 (0.9–1.7) 1.5 (1.1–2.0) 1.3 (0.9–1.8) 2.2 (1.6–3.1) 2.4 (1.8–3.1) < 0.0001		Adjusted for age, intake of dietary fat, fibre, folate and alcohol, body-mass index and family history of colorectal cancer. Diagnosis confirmed with histopathological reports. Significant trend for large (≥ 1 cm) adenomas with total pack–years (*p* < 0.0001), pack–years smoked before age 30 years (*p* = 0.05) and pack–years smoked after age 30 years (*p* < 0.0001) Significant trend for small (< 1 cm) adenomas with total pack–years (*p* < 0.0001) and pack–years smoked after age 30 years (*p* < 0.0001)
Giovannucci *et al.* (1994b) USA 1986–92 (see also Kearney *et al.*, 1995)	Health Professionals Follow-up Study 12 854 men undergoing endoscopy (primarily sigmoidoscopy)	499 prevalent adenomatous polyps of distal colon and rectum		Current smoker *Pack–years* 1–9 10–19 20–29 30–39 ≥ 40 *p* for trend	1.6 (1.2–2.1) 1.5 (1.1–2.0) 1.3 (0.9–1.7) 1.4 (0.99–1.9) 1.9 (1.4–2.7) 1.7 (1.3–2.2) < 0.0001		Adjusted for age, family history of colorectal cancer, body-mass index and intake of fat, fibre, folate and alcohol. Diagnosis confirmed by histopathological reports Significant trend for small (*p* = 0.05) and large (*p* = 0.0002) polyps by total pack–years
				Pack–years ≥ 20 years ago 1–4 5–9 10–15 ≥ 16 *p* for trend	Large 1.9 (0.9–3.8) 1.3 (0.8–2.4) 1.4 (0.7–2.7) 2.4 (1.6–3.6) 0.004	Small 1.7 (1.03–2.9) 1.2 (0.8–1.9) 0.8 (0.5–1.5) 0.96 (0.7–1.4) 0.95	

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)		Adjustment factors, comments
Giovannucci *et al.* (1994b) (contd)					Large	Small	
				Pack–years < 20 years ago			
				1–9	0.9 (0.5–1.6)	1.2 (0.8–1.9)	
				10–19	0.9 (0.5–1.6)	1.2 (0.7–2.0)	
				20–34	1.3 (0.8–2.2)	1.3 (0.8–2.2)	
				≥ 35	0.5 (0.1–1.9)	3.0 (1.5–6.0)	
				p for trend	0.56	0.04	
				Pack–years before 30 years			
				1–4	1.9 (0.9–3.9)	1.4 (0.8–2.5)	
				5–10	1.6 (0.9–2.9)	1.2 (0.8–2.0)	
				11–15	1.8 (1.1–3.1)	1.0 (0.7–1.6)	
				≥ 16	2.3 (1.2–4.2)	0.97 (0.6–1.7)	
				p for trend	0.02	0.56	
				Pack–years after 30 years			
				1–9	0.8 (0.4–1.6)	0.99 (0.6–1.7)	
				10–19	1.1 (0.6–1.9)	0.9 (0.6–1.5)	
				20–34	1.2 (0.7–2.1)	1.1 (0.7–1.9)	
				≥ 35	1.1 (0.6–2.1)	1.6 (0.96–2.7)	
				p for trend	0.23	0.03	
Jacobson *et al.* (1994) USA 1986–88	3008 patients with self-reported history of polypectomy, undergoing colonoscopy for adenoma recurrence, aged 35–84 years	186 (130 M, 56 F) recurrent adenomas	330 (187 M, 143 F)	*Pack–years*	Men		Adjusted for age, time since previous polypectomy, body-mass index, alcohol intake and percentage of fat/calories consumed
				1–12	1.3 (0.7–2.6)		
				13–40	2.4 (1.3–4.4)		
				> 40	1.9 (1.0–3.7)		
				p for trend	0.03		
				Pack–years	Women		
				1–7	0.5 (0.1–1.7)		
				8–30	1.7 (0.6–4.5)		
				> 30	2.8 (1.2–6.5)		
				p for trend	0.005		

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Boutron *et al.* (1995) France	1232 patients undergoing colono-scopy, aged 30–79 years	208 (129 M, 79 F) large adenomas (≥ 10 mm) 154 (85 M, 69 F) small adenomas (< 10 mm)	427 (182 M, 245 F)	**Small adenomas**		Small adenomas: adjusted for age; large adenomas: adjusted for age and alcohol intake; data available for men only
				Pack–years	Men	
				1–20	1.9 (0.9–4.1)	
				> 20	3.6 (1.8–7.3)	
				p for trend	< 0.0001	
				Pack–years	Women	
				1–5	1.3 (0.5–3.1)	
				> 5	1.4 (0.6–3.2)	
				p for trend	> 0.1	
				Large adenomas		
				Pack–years	Men	
				1–20	2.3 (1.2–4.5)	
				> 20	2.1 (1.1–4.2)	
				p for trend	< 0.01	
Honjo *et al.* (1995) Japan 1986–92	4981 male self-defence officials undergoing sigmoidoscopy or colonoscopy, aged 48–56 years	429 sigmoid adenomas, 75 rectal adenomas	3101	*Pack–years*	Sigmoid adenoma	Adjusted for body-mass index, official rank, hospital, study period and alcohol consumption. Seventeen patients had both sigmoid and rectal adenomas and were included in both groups.
				≤ 22.5	1.7 (1.2–2.3)	
				> 22.5–≤ 33	2.3 (1.7–3.2)	
				> 33	2.3 (1.6–3.2)	
				p for trend	< 0.01	
				Pack–years	Rectal adenoma	
				≤ 22.5	0.6 (0.3–1.2)	
				> 22.5–≤ 33	1.7 (0.9–3.2)	
				> 33	1.0 (0.5–2.0)	
				p for trend	0.28	

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Kearney *et al.* (1995) USA 1986–92 (see also Giovannucci *et al.*, 1994a,b)	Health Professionals Follow-up Study 12 922 men undergoing endoscopy	219 hyperplastic polyps of the distal colon and rectum		 Former smoker Current smoker *Cigarettes/day* 1–14 ≥ 15	Men 1.1 (0.9–1.5) 2.5 (1.6–3.8) 2.3 (1.2–4.4) 2.1 (1.3–3.6)	Adjusted for age, energy intake, family history of colorectal cancer, previous endoscopy; [discrepancies in relative risks between text and table]
1980–90	Nurses' Health Study 15 984 women undergoing endoscopy	175 hyperplastic polyps of the distal colon and rectum		 Former smoker Current smoker *Cigarettes/day* 1–14 ≥ 15 *p* for trend	Women 1.3 (0.9–2.0) 2.0 (1.2–2.9) 2.2 (1.3–3.7) 2.4 (1.6–3.7) < 0.0001	
Martínez *et al.* (1995) USA 1991–93	4698 patients undergoing colonoscopy or sigmoidoscopy, identified by medical records; 200 eligible cases, 673 eligible controls (aged > 35 years)	157 (98 M, 59 F) adenomatous polyps	480 (229 M, 251 F)	Former smoker Current smoker *Pack–years* 1–10 11–20 > 20 *p* for trend	1.6 (1.03–2.5) 2.3 (1.3–4.1) 1.7 (0.5–5.7) 2.1 (0.6–6.5) 2.6 (1.3–5.1) = 0.008	Adjusted for age, sex, race, intake of dietary fibre, vitamin C and alcohol, body-mass index, family history of colorectal cancer, physical activity and non-steroidal anti-inflammatory drugs. Relative risks available for interaction with alcohol
Nelson *et al.* (1995) USA 1984–87 (see also Kikendall *et al.*, 1989)	Patients undergoing colonoscopy, aged 26–87 years [number not specified]	137 (109 M, 28 F) adenomas	136 (86 M, 50 F)	Smoker	2.0 (1.1–3.8)	Adjusted for age, sex, family history of cancer, race, alcohol consumption, serum ferritin, β-carotene, α-toco- pheral and selenium. Controls included patients with hyperplastic polyps.

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Longnecker *et al*. (1996) USA 1991–93	1317 patients undergoing sigmoidoscopy, aged 50–74 years; 488 matched pairs with complete smoking and diet data	488 (325 M, 163 F) (response rate, 84%)	488 matched by age, sex, date of sigmoidoscopy and medical centre (response rate, 82%)	Former smoker Current smoker *Ever-smoker* *(pack–years)* Total 1–9 10–29 ≥ 30 *p* for trend *≤ 20 years ago* 1–9 10–30 > 30 *p* for trend *> 20 years ago* 1–9 10–30 > 30 *p* for trend	1.2 (0.9–1.7) 2.4 (1.6–3.8) 1.2 (0.8–1.8) 1.3 (0.9–1.9) 1.8 (1.2–2.5) 0.002 1.5 (1.00–2.3) 2.3 (1.4–3.7) 2.4 (1.02–5.6) 0.0007 1.2 (0.7–1.8) 0.7 (0.5–1.2) 1.1 (0.6–1.9) 0.65	Adjusted for race, alcohol intake, body-mass index, vigorous leisure-time activity, intake of energy, saturated fat and fruits and vegetables. Results by period of tobacco consumption similar for small (< 1 cm) and large (≥ 1cm) polyps 55% of cases and 54% of controls were whites.
Manus *et al.* (1997) Germany 1990–91	1166 patients in clinical rehabilitation centre, aged 50–60 years; 665 (57%) underwent sigmoidoscopy.	146 (97 M, 49 F) adenomatous polyps	519 (308 M, 211 F)	Ever-smoker	Cases vs non-cases 33.6% vs 24.1% ($p = 0.03$)	Large number of subjects with diabetes or hypertension
Martínez *et al.* (1997) USA 1991–93 (see also Martínez *et al.*, 1995)	4698 patients undergoing colonoscopy or sigmoidoscopy, identified by medical records; 113 eligible cases, 719 eligible controls (aged > 35 years)	81 (44 M, 37 F) hyperplastic polyps	480 (229 M, 251 F)	Former smoker Current smoker *Pack–years* ≤ 10 11–20 > 20	1.3 (0.8–2.3) 2.5 (1.2–5.0) 1.2 (0.6–2.3) 1.7 (0.8–3.7) 2.0 (1.02–3.8)	Adjusted for age, sex, race, intake of dietary fibre, energy and alcohol, body-mass index, physical activity and non-steroidal anti-inflammatory drugs

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Baron *et al.* (1998) USA 4 years	864 participants in an ongoing clinical trial with prior history of colorectal polypectomy; 751 subjects had colonoscopy 1 and 4 years after the excision	260 (212 M, 48 F) recurrent adenomas	449 (344 M, 105 F)	Former smoker Current smoker *Cigarettes/day* ≤ 20 21–40 > 40 *Duration (years)* ≤ 20 > 20–≤ 30 > 30– ≤ 40 > 40	1.1 (0.8–1.6) 0.95 (0.6–1.5) 1.2 (0.8–1.8) 0.8 (0.5–1.2) 1.6 (0.9–2.7) 1.5 (0.9–2.5) 0.7 (0.4–1.2) 1.1 (0.7–1.7) 0.97 (0.6–1.6)	Adjusted for age, sex, clinical centre, intake of fat, total dietary fibre, energy intake and colonoscopy interval. Similar results for polyp recurrence in right and left colon
Kahn *et al.* (1998) USA 1982–92	Cancer Prevention Study II 72 868 men and 81 356 women without polyps at baseline, aged 40–64 years	12 615 (7504 M, 5111 F) polyps		 Former smoker Current smoker *(cigarettes/day)* 1–20 ≥ 21 Former smoker Current smoker *(cigarettes/day)* 1–20 ≥ 21	Men 1.25 (1.17–1.34) 1.30 (1.18–1.43) 1.34 (1.21–1.47) Women 1.21 (1.13–1.30) 1.37 (1.25–1.50) 1.50 (1.32–1.70)	Adjusted for age, education, race, gallbladder status, body-mass index, exercise, alcohol and coffee consumption, aspirin use, multivitamin use, family history of colorectal cancer, diet change, diet (intake of eggs, vegetables, meat, fibre, chicken, fish), and for women, parity, estrogen replacement therapy and menopausal status
Terry & Neugut (1998) USA 1986–88	3008 subjects undergoing complete colonoscopy beyond splenic flexure, aged 35–84 years; 2443 (81%) eligible; 2001 interviewed	269 (155 M, 114 F) polyps	508 (225 M, 283 F)	Ever-smoker *Pack–years* 1–19 20–39 ≥ 40	1.3 (0.97–1.8) 1.2 (0.8–1.8) 1.2 (0.7–1.9) 1.6 (1.1–2.4)	Adjusted for gender, age and Quetelet index. Study investigated the hypothesis that control groups in many studies on tobacco smoking and colorectal cancer included a high proportion of individuals with adenomatous polyps.

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Nagata *et al.* (1999) Japan 1993–95	14 427 M, 17 125 F residents of Takayama, aged ≥ 35 years; 593 underwent colonoscopy	259 (181 M, 78 F) histologically proven adenomas			Men	Adjusted for age
				Former smoker	1.2 (0.8–2.0)	
				Current smoker	1.4 (0.9–2.3)	
				Cigarettes/day		
				1–19	1.4 (0.9–2.2)	
				≥ 20	1.3 (0.8–2.2)	
				Duration (years)		
				1–29	1.1 (0.7–1.8)	
				≥ 30	1.6 (1.02–2.6) $p = 0.02$	
				Pack–years		
				1–19	1.1 (0.7–1.9)	
				≥ 20	1.5 (0.97–2.5)	
				p for trend	0.04	
					Women	
				Ever-smoker	2.2 (1.2–3.7)	
				Cigarettes/day		
				1–4	2.4 (1.2–4.5)	
				≥ 5	2.1 (0.9–4.5)	
				Duration (years)		
				1–29	1.5 (0.7–2.9)	
				≥ 30	4.5 (2.0–9.1)	
				p for trend	0.0002	
				Pack–years		
				1–14	2.1 (1.00–3.8)	
				≥ 15	2.9 (1.2–6.0)	
				p for trend	0.002	

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Almendingen *et al.* (2000) Norway 3 years	116 subjects with polyps at baseline participating in a 3-year follow-up intervention study, aged 50–76 years	87 histologically confirmed adenomas	35 hospital outpatients with abdominal pain; 35 healthy controls; both groups matched by age and sex		*Healthy controls*	Adjusted for body-mass index, familial colonic cancer, energy, fat, fibre, dietary vitamin C, cruciferous vegetables, coffee and alcohol
				Former smoker	1.4 (0.4–4.4)	
				Current smoker	3.8 (0.9–14.4)	
				Duration (years)		
				0.1–15	1.7 (0.4–7.3)	
				16–25	1.4 (0.3–6.6)	
				≥ 26	2.7 (0.8–9.0)	
				p for trend	0.1	
				Pack–years[†]		[†]Referent category included former smokers.
				0.1–15	1.1 (0.2–5.9)	
				> 15	5.5 (1.3–24.3)	
				p for trend	0.03	
					Hospital controls	
				Former smoker	1.4 (0.5–3.9)	
				Current smoker	3.6 (1.1–12.6)	
				Duration (years)		
				0.1–15	0.9 (0.3–3.4)	
				16–25	2.1 (0.5–9.4)	
				≥ 26	2.8 (0.9–8.4)	
				p for trend	0.05	
				Pack–years[†]		
				0.1–15	1.6 (0.3–9.0)	
				> 15	4.1 (1.1–15.9)	
				p for trend	0.04	

Table 2.1.7.5 (contd)

Reference Country and years of study	Initial study population	Case patients (M, F)	Polyp-free patients (M, F)	Smoking categories	Relative risk (95% CI)	Adjustment factors, comments
Breuer-Katschinski *et al.* (2000) Germany 1993–95	Patients undergoing colonoscopy at 5 major hospitals in Essen	182 (94 M, 88 F) polyps; response rate, 69%	178 (88 M, 90 F) hospital controls; response rate, 50% 182 (92 M, 90 F) population controls; response rate, 66%	 Former smoker Current smoker *Cigarettes/day* 1–10 11–20 > 20 Former smoker Current smoker Ever-smoker *Cigarettes/day* 1–10 11–20 > 20	*Population controls* 0.9 (0.5–1.4) 0.97 (0.5–1.8) 0.8 (0.4–1.4) 1.2 (0.6–2.1) 0.7 (0.4–1.4) *Hospital controls* 1.0 (0.6–1.7) 2.3 (1.1–4.6) 1.3 (0.9–2.1) 1.2 (0.7–2.3) 1.5 (0.8–2.8) 1.1 (0.6–2.2)	Adjusted for age, sex, social class, intake of fat, fibre and energy, relative weight, consumption of red meat, vitamin A, carotene and folate Data available for men and women separately, and for large and small polyps separately with each control group

M, men; F, women; CI, confidence interval

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2.1.8 *Cancer of the liver*

(*a*) *Overall risk*

An association between cigarette smoking and liver cancer was reported in two cohort studies, one in Japan and one in the USA, and in four case–control studies on the topic (IARC, 1986). In one of the cohort studies (Hirayama, 1981), the relative risks associated with smoking were statistically significant in each alcohol-specific stratum; in another (Trichopoulos *et al.*, 1980), a relative risk of 5.5 remained among hepatitis B surface antigen (HBsAg)-positive individuals who smoked > 20 cigarettes/day after adjustment for alcohol consumption. At the time, however, it was thought that the available data did not convincingly exclude residual confounding.

Twenty-eight additional cohort studies have been published since or after 1985, including 10 from Japan (Kono *et al.*, 1987; Akiba & Hirayama, 1990; Hiyama *et al.*, 1990; Shibata *et al.*, 1990; Kato *et al.*, 1992; Goodman *et al.*, 1995; Chiba *et al.*, 1996; Murata *et al.*, 1996; Mizoue *et al.*, 2000; Mori *et al.*, 2000), nine from China (Tu *et al.*, 1985; Ross *et al.*, 1992; London *et al.*, 1995; Yuan *et al.*, 1996; Chen *et al.*, 1997; Lam *et al.*, 1997; Gao *et al.*, 1999; Sun *et al.*, 1999; Evans *et al.*, 2002), four from China, Province of Taiwan (Yu & Chen, 1993; Chang *et al.*, 1994; Liaw & Chen, 1998; Yang *et al.*, 2002), two each from the USA (Hsing *et al.*, 1990; McLaughlin *et al.*, 1995) and Sweden (Carstensen *et al.*, 1987; Nordlund *et al.*, 1997) and one from the United Kingdom (Doll *et al.*, 1994). In some studies, the cohort included patients with decompensated cirrhosis or post-transfusional hepatitis (Kato *et al.*, 1992), persons with chronic hepatitis or cirrhosis (Chiba *et al.*, 1996) or HBsAg-positive healthy patients (Hiyama *et al.*, 1990). The design of these cohort studies is described in Tables 2.1 and 2.1.8.1, and the results are summarized in Table 2.1.8.2.

Most of the new cohort studies show an increased relative risk among current smokers.

Twenty-six additional case–control studies (Tables 2.1.8.3 and 2.1.8.4) published after 1985 provide information on smoking and liver cancer: six were conducted in Japan (Hiyama *et al.*, 1990; Tsukuma *et al.*, 1990; Tanaka *et al.*, 1992; Pyong *et al.*, 1994; Tanaka *et al.*, 1995; Mukaiya *et al.*, 1998), three each in Africa (Kew *et al.*, 1990; Olubuyide & Bamgboye, 1990; Mohamed *et al.*, 1992), China or Hong Kong SAR (Lin *et al.*, 1991; Liu *et al.*, 1998; Lam *et al.*, 2001) and the USA (Austin *et al.*, 1986; Yu, M.C. *et al.*, 1991; Chen *et al.*, 2003), two each in Greece (Tzonou *et al.*, 1991; Kuper *et al.*, 2000), Italy (La Vecchia *et al.*, 1988; Ferraroni *et al.*, 1989), the Republic of Korea (Choi & Kahyo, 1991; Shin *et al.*, 1996) and China, Province of Taiwan (Chen *et al.*, 1991; Yu, M.W. *et al.*, 1991) and one each in Canada (Siemiatycki *et al.*, 1995), Germany (Peters *et al.*, 1994) and Spain (Vall Mayans *et al.*, 1990). The majority of these studies used hospital controls. Five studies included community controls; two large Chinese studies (Liu *et al.*, 1998; Lam *et al.*, 2001) include controls who had died of causes other than neoplastic respiratory or vascular diseases. Risks in current smokers that were higher than those in never-smokers were found in 17 studies and attained statistical significance in 10 studies. An association between smoking and increased risk of liver cancer is thus consistently demonstrated in nearly all cohort studies and in a number of case–control studies, particularly the largest ones from Asia, Greece and the USA. These studies used different approaches to consider other established risk factors for liver cancer such as infection with hepatitis B virus (HBV) and with hepatitis C virus (HCV) infection and alcohol consumption.

(i) *Confounding and effect modification*

Covariates that may potentially confound and/or modify the relationship between smoking and liver cancer include chronic infection with HBV and HCV (IARC, 1994) and heavy alcohol consumption (IARC, 1988). Consideration of each of these factors presents a challenge, however, because analyses that adjust for alcohol consumption may over-control for cigarette smoking, and stratification on hepatitis infection status rather than adjustment may be the preferred approach for differentiating confounding from effect modification by HBV or HCV infection.

Heavy, although not moderate, intake of alcoholic beverages is associated with an increased risk for liver cancer (IARC, 1988). The excess of liver cancer in populations where drinking alcohol is common could thus reflect an insufficient adjustment for drinking habits (Doll *et al*., 1994; McLaughlin *et al*., 1995). However, several recent case–control and cohort studies have found an association between smoking and liver cancer after controlling for alcohol consumption (Yu, M.C. *et al*., 1991; Yuan *et al*., 1996; Chen *et al*., 1997; Liaw & Chen, 1998; Mizoue *et al*., 2000) and among persons who reported no alcohol consumption. Chen *et al.* (1991) showed that subjects who consumed no alcohol, but smoked 20 cigarettes or more daily had a relative risk of 2.7 of developing liver cancer relative to nonsmokers who drank no alcohol. Those who both drank and smoked heavily had a relative risk of 11.7. Further supportive evidence is provided by the association between smoking and liver cancer observed among Chinese women (Liu *et al*., 1998) and Japanese women (Tanaka *et al*., 1995), in whom heavy alcohol drinking is extremely rare.

Infection with HBV is the main cause of liver cancer worldwide, whereas HCV infection causes a large fraction of liver cancer in Japan, northern Africa and southern Europe (IARC, 1994). Infection with HCV is increasing in many countries. To distinguish the strong effect of infection with HBV and HCV (relative risks of the order of 20; IARC, 1994) from the association with smoking, stratification and/or adjustment for HBsAg and anti-HCV have been made in some studies (Yu, M.C. *et al*., 1991; Yu, M.W. *et al*., 1991; Liaw & Chen, 1998; Kuper *et al*., 2000). The association between smoking and liver cancer was not generally weakened by adjustment for HBV and HCV. Infection with HBV was less frequent among smokers than nonsmokers in a large population survey in China (Evans *et al*., 2002). The possibility that tobacco smoking may potentiate the progression of chronic HBV and HCV infections to liver cirrhosis (Yu *et al.*, 1997) and/or liver cancer (Tsukuma *et al.*, 1993) has been examined in relatively few studies. The increase in risk for liver cancer associated with cigarette smoking appears to be greater among HBV carriers than among uninfected persons in some studies (Tu *et al.*, 1985), but not in others (Kuper *et al*., 2000).

No information on confounding from exposure to aflatoxin was available.

(ii) *Bias*

The most frequent bias that can arise in studies of associations between smoking and cancer are described in the General Remarks. Many of the case–control studies that have not found an association between smoking and liver cancer are hospital-based, so that the control series may include tobacco-related diseases. Morbidity and symptoms resulting from prevalent liver cirrhosis or undiagnosed liver cancer can lead to lifestyle changes, including a reduction in number of cigarettes smoked per day or cessation of smoking. This phenomenon would lead to underestimation of the relative risk for current smokers and to overestimation of the relative risk for former smokers. It can also distort the association of liver cancer with the number of cigarettes smoked per day. The detection of liver cancer in a cirrhotic liver presents substantial difficulties of under- or over-diagnosis in cohort studies. Differential ascertainment of liver cancer according to smoking status, however, is unlikely.

A varying, but often substantial, proportion of liver cancer cases in the studies considered in this section was not pathologically confirmed. Liver cancer is a common site for metastases. If a high proportion of liver cancer for which pathological confirmation was not acquired were in reality metastases from smoking-related cancers (e.g. of the lung, oesophagus or stomach), the association between smoking and liver cancer in some studies would be overestimated. In the vast majority of the examined studies, however, diagnosis of liver cancer was confirmed by cytological findings or by the combined presence of elevated concentrations of α-fetoprotein (> 400 ng/mL) and at least one positive image obtained by angiography, sonography, liver scan or computerize tomography scan.

(*b*) *Factors affecting risk*

(i) *Duration and intensity*

The US Veterans Study (Hsing *et al.*, 1990) found a substantial increase in the association with increased smoking duration. A clear trend of increasing risk of liver cancer with the increase in pack–years was reported by Chiba *et al.* (1996). Many more studies reported relative risk by number of cigarettes smoked per day. An increased risk in heavy smokers relative to light smokers was shown in several studies (Hiyama *et al.*, 1990; Hsing *et al.*, 1990; Chen *et al.*, 1991; Tzonou *et al.*, 1991; Yu, M.W. *et al.*, 1991; Tanaka *et al.*, 1992; Chiba *et al.*, 1996; Liu *et al.*, 1998; Kuper *et al.*, 2000). In other studies, especially those from Asia, however, the relative risk among smokers did not vary by category of cigarettes smoked per day. The reasons for this are unknown but they may include the relatively low power of most studies to detect small relative risks, and the inclusion of persons who smoke up to 25 cigarettes per day in the referent group. Hsing *et al.* (1990) showed higher relative risk among smokers who started smoking earlier (generally before age 20 years) than in those who started at age 25 years or older.

(ii) *Smoking cessation*

Nine cohort and 10 case–control studies provided information on the relative risk for former smokers. Most studies showed a lower risk for liver cancer among former smokers than in current smokers. In four studies, however, the relative risk for former smokers was of similar magnitude or even higher than the relative risk for current smokers (Ferraroni *et al*., 1989; Tanaka *et al.*, 1992, 1995; Kuper *et al*., 2000). The only study that examined relative risks by number of years since quitting showed a decrease in risk with time since cessation (Goodman *et al*., 1995).

(iii) *Type of cigarettes*

No data were available to the Working Group.

(*c*) *Population characteristics*

(i) *Sex*

The absolute risk of liver disease (hepatitis, cirrhosis, and cancer) is substantially greater in men than women in all populations. The data available suggest, however, that the association between smoking and liver cancer is similar in men and women (Liu *et al*., 1998; Kuper *et al*., 2000), after taking into account different levels of smoking in the two sexes.

(ii) *Ethnicity*

Some disparities have been described in the relative risks observed in different racial and ethnic populations. [Such variations may reflect factors other than race such as different smoking and alcohol drinking patterns, variations in prevalence of HBV and HCV infection, and the greater probability of residual confounding from alcohol drinking in populations from Europe and North America.]

Table 2.1.8.1. Additional cohort studies on tobacco smoking and liver cancer

Reference Country and years of study	Hepatitis B virus (HBV) status	Cohort sample	Cases/deaths identification	Comments
Basa *et al.* (1977) Philippines 1968–73	HBV/HCV status unknown	16 492 cancer cases registered at the Central Tumour Registry of the Philippines	Registry	Retrospective study
Tu *et al*. (1985) China 1980–82	16% HBV-positive Stratified data	Male residents of Chongming Island, aged ≥ 40 years	Deaths ascertained by local Anti-Epidemic Station	
Hiyama *et a*l. (1990) Japan 1969–85	Unknown status	Male patients admitted to mental hospitals for alcoholism [age range not reported]	Deaths	
1972–92	All HBsAg-positive	8646 men who donated blood in 1972–75		Nested case–control study
Shibata *et al*. (1990) Japan 1958–86 1960–86	Status unknown	Men aged 40–69 years from: Farming areas (cohort I) Fishing areas (cohort II)	Deaths ascertained with resident's cards and other materials at municipal offices	
Kato *et al*. (1992) Japan 1987–90	Status known No adjustment No stratification	Patients with decompensated liver cirrhosis, 343 with post- transfusion hepatitis, aged ≥ 16 years	Cases	
Ross *et al.* (1992) China 1986–90	HBsAg-positive: 55% cases, 11% controls	All men aged 45–64 years living in 4 defined areas of metropolitan Shanghai	Cases of primary liver cancer identified through Shanghai municipality and Shanghai Cancer Registry	Nested case–control study; adjustment for HBsAg status in a multivariate regression model
Yu & Chen (1993) China, Province of Taiwan 1984–90	HBsAg-positive: 57% cases, 55% controls Anti-HCV: 20% cases, 3% controls No stratification	Men aged 30–85 years	Cases	Nested case–control study, adjustment for HBsAg and anti- HCV status in multivariate regression model

Table 2.1.8.1. (contd)

Reference Country and years of study	Hepatitis B virus (HBV) status	Cohort sample	Cases/deaths identification	Comments
Chang *et al*. (1994) China, Province of Taiwan 1984–92	HBsAg-positive: 63% cases, 7% controls Anti-HCV: 13% cases, 3% controls	Men aged 30–85 years	Cases	Same cohort as Yu & Chen (1993). Nested case–control study without adjustment for HBsAg or anti-HCV status
London *et al*. (1995); Evans *et al*. (2002) China 1992–2000	81% HBsAg-positive 11–15% HBsAg-positive, 1.5% HCV-positive No adjustment, no stratification	Residents of Haimen City, the world highest incidence area for hepatocellular carcinoma; aged 30–64 years	Deaths certificates confirmed by hospital records	London *et al.* (1995) conducted a nested case–control study with matching for HBV status.
Chiba *et al*. (1996) Japan 1977–93	HBsAg-negative, anti-HCV-positive	412 patients with chronic liver disease, including 232 chronic hepatitis and 180 cirrhosis	Cases ascertained by medical follow-up	
Sun *et al*. (1999) China 1987–98	16% HBsAg-positive, 7% HCV-positive	Men with chronic hepatitis B (72% of all men with hepatitis B in two townships)	Cases identified by twice-yearly examinations	
Mori *et al*. (2000) Japan 1992–97	1.8% HBsAg-positive 22% HCVAb-positive	Baseline survey during liver disorder screening	Cases	
Yang *et al*. (2002) China, Province of Taiwan 1991–2000	Known HBV and HCV status	Men aged 30–65 years	Cases ascertained by yearly mass screening	Nested case–control study

HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen

Table 2.1.8.2. Cohort studies on tobacco smoking and liver cancer

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)		Adjustment factors/ comments
Hammond (1966) USA 1959–63	Cancer Prevention Study (CPS) I 440 558 men, 562 671 women		Ever-smoker Aged 45–64 years Aged 65–79 years	**Mortality ratio** 2.8 1.3		Mortality ratio of age-standardized death rates. Study based on examination of death certificates on which secondary liver cancers may have been included in the category 'liver cancer' (many smoking-related cancers metastasize to the liver).
Basa *et al*. (1977) Philippines 1968–73	16 492 cancer cases (6771 men, 9721 women)	541 men, 213 women	 Ever-smoker Current smoker	**Men** 1.5 ($p = 0.01$) 1.3	**Women** 2.6 ($p = 0.001$) 1.9 ($p = 0.01$)	Adjusted for age
Hirayama (1981) Japan 1965–78	Six-prefecture Study 265 118 men and women	865 deaths	*Lifelong no. of cigarettes smoked* None 1–190 000 200 000–390 000 400 000	**Alcohol use** *Occasional, rare, none* 26.5 38.8 39.9 45.2	 *Daily* 24.0 49.4 45.8 66.9	Standardized mortality ratios
Tu *et al*. (1985) China 1980–82	12 222 men	70 deaths	*HBV carrier* Nonsmoker Current smoker ≤ 19 cigs/day ≥ 20 cigs/day *HBV non-carrier* Nonsmoker Current smoker ≤ 19 cigs/day ≥ 20 cigs/day	**Mortality rate** 332.8 737.9 660.1 1519 ($p < 0.05$) 115.1 99.9 96.3 145.2		Adjusted for age and alcohol consumption

Table 2.1.8.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)		Adjustment factors/ comments
Carstensen	Swedish Census	54 deaths	Former smoker	1.7		Relative death rates
et al. (1987)	Study		Current smoker	3.0		Categories in grams of any tobacco/day
Sweden	25 129 men		*Cigarettes/day*			combined: 1 cigarette = 1 g; 1 small
1963–79			1–7	1.6		cigar = 3 g; 1 large cigar = 5 g
			8–15	3.3		
			> 15	4.1		
Kono *et al*.	Japanese	51 deaths	1–19 cigarettes/day	1.1 (0.6–2.2)		Adjusted for age and alcohol
(1987)	Physicians' Study		≥ 20 cigarettes/day	1.0 (0.5–2.2)		
Japan	5130 men					
1965–83						
Akiba &	Six-prefecture	1060 deaths	Current smoker	1.5 (1.2–1.9)		Adjusted for prefecture, occupation, age
Hirayama	Study	(662 men,	*Cigarettes/day*			and observation period. No trend
(1990)	122 261 men,	398 women)	**Men**			observed in the relative risk in relation
Japan	142 857 women		1–4	1.1 (0.5–2.0)		to calendar period. Unclear whether
1965–81	~3 975 000 person–		5–14	1.6 (1.3–2.0)		former smokers were included in
	years		15–24	1.4 (1.2–1.8)		analysis or not
			25–34	1.6 (1.1–2.4)		
			≥ 35	1.9 (1.1–3.2) [*p* for trend = 0.002]		
			Women			
			1–4	1.4 (0.7–2.5)		
			5–14	1.4 (1.0–2.0)		
			≥ 15	2.5 (1.3–4.1) [*p* for trend = 0.001]		
Hiyama *et al*.	13 171 men	93 cases		*Ratio observed/expected*		
(1990)				1.4 (1.1–1.7)		
Japan						
1969–85						
1972–92	8646 men	22 cases,		*Crude odds*	*Adjusted for*	Nested case–control study; controls
		44 controls	*Cigarettes/day*	*ratio*	*alcohol*	matched by age
			10–29	1.7 (0.4–6.4)	1.2	
			≥ 30	5.8 (1–34.2)	6.3	

Table 2.1.8.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)	Adjustment factors/ comments
Hsing *et al*.	US Veterans' Study	289 deaths	Former smoker	1.9 (1.2–2.9)	Adjusted for age and calendar period
(1990)	293 916 men		Current smoker	2.4 (1.6–3.5)	
USA			*Cigarettes/day*		
1954–80			< 10	2.2 (1.2–3.8)	
			10–20	2.0 (1.3–3.0)	
			21–39	2.9 (1.8–4.5)	
			> 39	3.8 (1.9–8.0)	
			Duration (years)		
			< 35	0.9 (0.4–2.1)	
			35–39	2.6 (1.4–4.9)	
			> 39	2.7 (1.5–4.9)	
			Age at starting smoking (years)		
			< 20	2.9 (1.6–5.3)	
			20–24	2.3 (1.2–4.3)	
			> 24	1.0 (0.4–2.3)	
Shibata *et al*.	Cohort I	11 deaths	Current smoker	1.1 (0.2–4.7)	Adjusted for age. Calculations based on
(1990)	639 men		*Cigarettes/day*		small number of liver cancer cases. No
Japan	17 480 person–		1–9	0.6 (0.1–3.7)	information on HBV/HCV
1958–86 (I)	years		≥ 10	1.2 (0.2–5.7) [*p* for trend ~0.6]	
1960–86 (II)	Cohort II	22 deaths	Former smoker	2.9 (0.3–29.0)	
	677 men		Current smoker	3.6 (0.6–22.3)	
	17 172 person–		*Cigarettes/day*		
	years		1–9	11.9 (1.5–96.8)	
			10–19	1.1 (0.1–10.6)	
			20–29	2.7 (0.4–19.2)	
			≥ 30	3.2 (0.4–23.7) [*p* for trend ~0.5]	
			1–19	2.1 (0.4–10.0)	Adjusted for age and alcohol
			≥ 20	1.9 (0.4–9.4)	

Table 2.1.8.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)	Adjustment factors/ comments
Kato *et al*. (1992) Japan 1987–90	1441 patients with decompensated liver cirrhosis, 343 with post-transfusion hepatitis 4386 person–years	122 cases	Former smoker	0.9 (0.4–2.0)	Adjusted for sex and age. Record linkage study. Patients at high risk for development of hepatocellular carcinoma
			Current smoker	1.0 (0.5–1.8)	
			Pack–years		
			< 30	0.8 (0.4–1.7)	
			≥ 30	0.9 (0.5–1.9) *p* for trend = 0.824	
Ross *et al*. (1992) China 1986–89	18 244 men 35 299 person–years	22 cases, 140 controls	Ever-smoker	2.6 (0.9–7.2)	No adjustment; nested case–control study. Population-based controls matched on age, sample collection and residence
			Cigarettes/day		
			1–19	3.1 (1.0–10.3)	
			≥ 20	2.1 (0.6–6.9)	
			Duration (years)		
			1–29	2.6 (0.7–9.4)	
			≥ 30	2.5 (0.9–7.6)	
			Ever-smoker	1.8 (0.6–5.6)	Adjusted for HBV, alcohol consumption, aflatoxin exposure and education
Yu & Chen (1993) China, Province of Taiwan 1987–90	9691 men	35 cases, 140 controls	Current smoker	1.2 (0.4–3.1)	Nested case–control study; controls matched by age, date of interview and residence. Adjusted for testosterone, alcohol consumption, HCV status, HBsAg status, vegetable consumption and history of liver disease
Chang *et al*. (1994) China, Province of Taiwan 1984–92	9775 men	38 cases, 152 controls	Ever-smoker	1.2 (0.6–2.7)	Nested case–control study; controls matched for age, residence and date of recruitment. Cases confirmed pathologically or α-fetoprotein ≥ 400 mg/mL and ultrasound

Table 2.1.8.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)	Adjustment factors/ comments
Doll *et al*. (1994) UK 1951–91	British Doctors' Study 34 439 men	76 deaths		**Mortality rate**	Annual mortality rate per 100 000 men
			Never-smoker	7	
			Former smoker	9	
			Current smoker	11	
			Cigarettes/day		
			1–14	17	
			15–24	3	
			≥ 25	15 [*p* for trend = 0.7]	
Goodman *et al*. (1995) Japan 1980–89	Life Span Study 36 133 men and women 311 086 person–years	252 cases (156 men, 86 women)	**Men**		Adjusted for city, age at time of bombing and radiation dose to liver. Relative risk among non-drinkers of alcohol for ever smoking, 1.9 (95% CI, 1.2–2.9); among men, 7.2 (95% CI, 1.0–53.3); among women, 1.3 (95% CI, 1.0–1.7). [CIs calculated by the Working Group]
			Former smoker	4.2 (2.0–10.7)	
			Current smoker	4.3 (1.9–9.7)	
			Ever-smoker	4.4 (1.9–9.9)	
			Pack–years		
			< 23	6.5 (2.7–15.3)	
			23–40	4.4 (1.9–10.5)	
			> 40	3.1 (1.3–7.3)	
			Years since quitting		
			≥ 24	4.0 (1.5–10.6)	
			14–23	4.1 (1.6–10.7)	
			< 14	5.6 (2.2–14.6)	
			Women		
			Former smoker	1.7 (0.8–3.6)	
			Current smoker	1.6 (0.9–2.9)	
			Ever-smoker	1.6 (1.0–2.7)	
			Pack–years		
			< 16	1.8 (0.9–3.8)	
			≥ 16	1.5 (0.7–3.2)	
			Years since quitting		
			≥ 25	2.3 (0.7–7.4)	
			10–24	1.0 (0.3–4.2)	
			< 10	10.4 (2.5–43.5)	

Table 2.1.8.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)	Adjustment factors/ comments
London *et al*. (1995) China 1992–95	60 984 men	183 cases (2% histolo- gically verified), 868 controls	Current smoker	0.7 (0.5–1.0)	Nested case–control study; controls matched 5:1 by age, area of residence and HBV status; strong inverse association between recent hepatitis and current smoking
McLaughlin *et al*. (1995) USA 1954–80	US Veterans' Study 248 046 men 3 252 983 person–years	363 deaths	Former smoker Current smoker *Cigarettes/day* 1–9 10–20 21–30 ≥ 40	1.5 (1.4–2.3) 1.8 (1.4–2.3) 1.8 (1.1–2.8) 1.4 (1.1–2.0) 2.3 (1.6–3.1) 2.6 (1.4–4.6) p for trend < 0.01	Adjusted for age and calendar-year time-period
Chiba *et al*. (1996) Japan 1977–93	249 men, 163 women ~2000 person–years	63 cases (54 men, 9 women)	*Pack–years* < 20 ≥ 20	 1.7 (0.8–3.7) 2.5 (1.1–5.5)	Adjusted for age, sex, alcohol consumption, clinical stage of liver disease, serum α-fetoprotein value, antibodies against HBV, history of blood transfusion, history of surgical procedures and family history of liver cancer
Murata *et al*. (1996) Japan 1983–94	Chiba Cancer Association Study 17 200 men	Cases 8 26 3	*Cigarettes/day* 1–10 11–20 ≥ 21	 1.4 2.0 $p < 0.05$ 0.4	
Yuan *et al*. (1996) China 1986–93	Shanghai Men's Study 18 244 men 98 267 person–years	79 cases	Ever-smoker *Cigarettes/day* < 20 ≥ 20	1.8 $p < 0.05$ 1.8 1.8	Adjusted for age and alcohol consumption

Table 2.1.8.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)	Adjustment factors/ comments
Chen *et al*.	Shanghai Factory	66 deaths	Current smoker	2.0 $p < 0.05$	Adjusted for age, blood pressure,
(1997)	Study		*Cigarettes/day*		cholesterol and alcohol at baseline
China	6494 men, 2857		1–19	2.1	
1972–93	women		≥ 20	2.1	
	149 616 person–		*p* for trend	0.07	
	years				
Lam *et al*.	Xi'an Factory Study	17 deaths	Ever-smoker	1.1 (0.4–2.9)	Adjusted for age, marital status,
(1997)	1124 men, 572				occupation, blood pressure,
China	women				triglycerides and total cholesterol
1976–96	32 428 person–				
	years				
Nordlund *et al*.	Swedish Census	41 cases	Current smoker	0.7 (0.2–2.0)	Adjusted for age and place of residence
(1997)	Study				
Sweden	26 000 women				
1963–89	600 000 person–				
	years				
Liaw & Chen	Taiwanese Study	128 deaths	Current smoker	2.2 (1.4–3.6)	Adjusted for age, HBV status and
(1998)	11 096 men, 3301	(110 men,	**Men**		alcohol
China, Province	women	18 women)	*Cigarettes/day*		
of Taiwan	140 493 person–		≤ 10	2.1 (1.2–3.5)	
1982–94	years		11–20	1.9 (1.2–3.2)	
			> 20	1.8 (1.2–3.5) *p* for trend = 0.02	
			Duration (years)		
			≤ 20	1.6 (0.8–3.2)	
			21–30	1.0 (0.5–2.1)	
			> 30	2.5 (1.6–4.1	

Table 2.1.8.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)	Adjustment factors/ comments
Liaw & Chen (1998) (contd)			*Age at starting smoking (years)*		
			> 24	1.4 (0.8–2.6)	
			21–24	2.3 (1.2–4.2)	
			≤ 20	2.2 (1.4–3.7) p for trend < 0.01	
			Pack–years		
			< 20	1.7 (1.0–2.9)	
			20–40	2.1 (1.2–3.5)	
			≥ 41	2.5 (1.3–4.6)	
Gao *et al.* (1999) China 1983–94	Shanghai Residential Study 213 800 men and women		**Men**		[†]CI does not include 1.0. p for trend < 0.05 for intensity of smoking for men and women and for age at starting smoking for men only
			Urban	1.5[†]	
			Suburban	1.4	
			Rural	1.5[†]	
			Women (urban)	2.4[†]	
Sun *et al.* (1999) China 1987–98	145 men	22 cases, 45% histolo-gically confirmed		**Incidence rate**	Rate per 100 person–years
			Never-smoker	2.3	
			Current smoker	1.6 $p = 0.5$	
Mizoue *et al.* (2000) Japan 1986–96	Fukuoka Study 4050 men 35 785 person–years	59 deaths	Former smoker	2.9 (1.0–8.4)	Adjusted for age, alcohol consumption and area of residence
			Current smoker	3.3 (1.2–9.5)	
			Cigarettes/day		
			1–24	3.5 (1.2–10.2)	
			≥ 25	2.8 (0.8–9.6)	
Mori *et al.* (2000) Japan 1992–97	974 men, 2078 women 13 984 person–years	22 (14 men, 8 women)	Former smoker	2.1 (0.6–7.2)	Adjusted for age and sex
			Pack–years		
			< 10	3.3 (0.4–28.2)	
			≥ 10	2.0 (0.6–6.9) p for trend = 0.3	

Table 2.1.8.2 (contd)

Reference Country and years of study	Cohort No. of subjects	No. deaths/ incident cancers	Smoking categories and other variables	Relative risk (95% CI)	Adjustment factors/ comments
Evans *et al*. (2002) China 1992–2000	48 454 men, 25 430 women	977 deaths (900 men, 77 women)	*Current smoker* Men Women	 0.9 (0.8–1.1) 2.0 (0.9–4.2)	Smoking was not significantly associated with liver cancer as assessed by present consumption, duration of smoking or pack–years
Yang *et al*. (2002) China, Province of Taiwan 1991–2000	11 83 men 92 359 person– years	111 cases, 222 controls	Current smoker	1.5 (1.0–2.2)	Nested case–control study; population-based controls matched on age, date of enrolment and township. Adjusted for HBV and HCV status, age and alcohol consumption

HBV, hepatitis B virus; HCV, hepatitis C virus

Table 2.1.8.3. Case–control studies on tobacco smoking and liver cancer: main characteristics of study design

Reference Country and years of study	No. of cases and controls	Source of cases and controls
Williams & Horm (1977) USA 1969–71	Men: 31 cases and 1739 controls; women: 14 cases and 3164 controls	Study with the Third National Survey Cases and controls aged ≥ 35 years; response rate, 57% Controls were patients with other cancers, excluding lung, larynx, oral cavity, oesophagus and bladder
Trichopoulos *et al*. (1980) Greece 1976–77	Men: 35 cases and 169 controls; women: 5 cases and 35 controls	Hospital-based study among HBsAg-negative Cases histologically confirmed (58%); mean age, 62 years Controls matched on age and sex
Lam *et al*. (1982) Hong Kong SAR 1977–80	Men: 17 cases and 94 controls; women: 2 cases and 13 controls	Hospital-based study among HBsAg-negative patients Cases histologically confirmed (99%); mean age, 50 years Controls matched on age and sex
Stemhagen *et al*. (1983) USA 1975–80	Men: 178 cases and 356 controls; women: 87 cases and 174 controls	Hospital-based study Cases histologically confirmed; mean age, 64 years Controls matched on age, race, sex and area of residence
Yu *et al*. (1983) USA 1975–79	Men and women: 78 cases and controls	Population-based study among black and white non-Asians Incident cases histologically confirmed (70.6%); aged ≥ 70 years Controls matched on age, sex, race and neighbourhood
Hardell *et al*. (1984) Sweden 1974–81	Men: 98 cases and 200 controls	Population-based study Deceased cases of hepatocellular carcinoma (83) or cholangiocarcinoma (15), 100% histologically confirmed; aged 25–80 years Controls randomly selected from population
Austin *et al*. (1986) Cuba, USA (years of study not specified)	Men: 60 cases; women: 26 cases; 172 controls	Hospital-based study Cases confirmed histologically (93%); aged 19–84 years Controls matched by age, sex and race
La Vecchia *et al*. (1988) Italy 1984–87	Men: 115 cases and 776 controls; women: 36 cases and 275 controls	Hospital-based study Cases aged 24–74 years Controls with acute conditions excluding malignant disorders, digestive tract diseases and conditions related to tobacco or alcohol; aged 22–74 years
Ferraroni *et al*. (1989) Italy 1983–88	Men: 115 cases and 1334 controls; women: 36 cases and 610 controls	Hospital-based study Cases histologically confirmed (100%); aged < 75 years Controls with no cancer, digestive tract disorders or conditions related to coffee, alcohol and tobacco consumption; comparable catchment areas

Table 2.1.8.3 (contd)

Reference Country and years of study	No. of cases and controls	Source of cases and controls
Hiyama *et al*. (1990) Japan 1984–87	Men: 192 cases and 192 controls; women: 37 cases and 74 controls	Population-based study (in Japanese)
Kew *et al*. (1990) South Africa (years of study not specified)	Women: 46 cases and 92 controls	Hospital-based study Cases aged 19–54 years Controls with various medical disorders, excluding diseases related to contraceptive steroids, matched on sex, race, exact tribe, place of birth (rural/urban), migration, hospital and ward
Vall Mayans *et al*. (1990) Spain 1986–88	Men: 67 cases and 133 controls; women: 29 cases and 57 controls	Hospital-based study Cases histologically confirmed (77%) Controls were diagnosed with 76 different conditions (including other cancers, AIDS, liver disease, stomach ulcer, pancreatitis), all unrelated to study exposure, matched on age and sex
Olubuyide & Bamgboye (1990) Nigeria 1987–88	Men: 85 cases and 85 controls; women: 15 cases and 15 controls	Hospital-based study Cases of primary hepatocellular carcinoma, 100% histologically confirmed; aged 42–55 years Controls were patients admitted to orthopaedic clinic, matched for sex and age
Tsukuma *et al*. (1990) Japan 1983–87	Men: 192 cases and 192 controls; women: 37 cases and 74 controls	Hospital-based study Cases histologically confirmed (38%); aged < 74 years Controls from gastroenterology department, excluding liver disease and smoking- or alcohol-related diseases
Chen *et al*. (1991) China, Province of Taiwan 1985–87	Men: 200 cases and 200 controls	Population-based study Cases recruited at teaching hospitals Controls selected from household registration offices, with no history of hepatocellular carcinoma, matched on age, sex, ethnic group and area of residence
Choi & Kahyo (1991) Republic of Korea 1986–90	Men: 216 cases and 648 controls	Hospital-based study Cases; average age, 49 years Controls matched on age and date of admission to hospital
Lin *et al*. (1991) China 1984–86	Men: 200 cases and 200 controls	Hospital-based study in a polyclinic Cases with primary hepatoma; aged ≥ 20 years Controls were patients with conditions unrelated to smoking

Table 2.1.8.3 (contd)

Reference Country and years of study	No. of cases and controls	Source of cases and controls
Tzonou *et al*. (1991) Greece 1976–84	Men: 166 cases and 381 controls; women: 19 cases and 51 controls	Hospital-based study in nine major hospitals Cases histologically confirmed (58%) Controls were patients without cancer or liver disease
Yu, M.C. *et al*. (1991b) USA 1984–90	Men: 49 cases and 104 controls; women: 25 cases and 58 controls	Population-based study Cases histologically confirmed (100%); aged 18–74 years Controls from neighbourhood, matched by age, sex and race
Yu, M.W. *et al*. (1991) China, Province of Taiwan 1986–87	Men: 121 cases and 121 controls; women: 6 cases and 6 controls	Population-based study Cases histologically confirmed (80%); aged 38–62 years Health community controls from household registration offices, individually matched for sex, age, ethnicity and area of residence
Mohamed *et al*. (1992) South Africa (years of study not specified)	Men: 77 cases and 77 controls; women: 24 cases and 24 controls	Hospital-based study in a major teaching hospital Cases histologically confirmed (95%); aged 20–87 years Controls with conditions unrelated to alcohol consumption, matched for age, sex and ethnicity
Tanaka *et al*. (1992) Japan 1985–89	Men: 168 cases and 291 controls; women: 36 cases and 119 controls	Hospital-based study Cases histologically confirmed (40%); aged 40–69 years
Peters *et al*. (1994) Germany 1986–93	Men: 72 cases and 72 controls; women: 14 ccases, and 14 controls	Hospital-based study Cases histologically confirmed (74%) Controls with cirrhosis, matched on age and sex (mean age: men, 62.8 years; women 65.0 years)
Pyong *et al*. (1994) Japan 1989–92	Men: 68 cases and 109 controls; women: 22 cases and 140 controls	Study among Koreans Cases aged 40–89 years Controls matched by age
Siemiatycki *et al*. (1995) Canada 1979–86	Men: 48 cases and 2238 controls	Hospital-based study Cases histologically confirmed (100%); aged 35–70 years Controls were hospital controls with other cancers (1705) and population controls (533)
Tanaka *et al*. (1995) Japan 1983–89	Women: 120 cases and 257 controls	Hospital-based study Cases aged 35–74 years

Table 2.1.8.3 (contd)

Reference Country and years of study	No. of cases and controls	Source of cases and controls
Shin *et al*. (1996) Republic of Korea 1990–93	Men: 159 cases and 318 controls; women: 44 cases and 88 controls	Hospital-based study Cases histologically confirmed (53%) Controls were healthy patients from check-up at hospital (159 men, 44 women) and in-patients (159 men, 44 women), individually matched for sex and age
Liu *et al*. (1998) China 1989–91	Men and women: 28 187 cases and 87 315 controls	Population-based study in rural and urban areas of China Cases: 17 523 (13 478 men, 4045 women) from urban and 10 664 (7979 men, 2685 women) from rural areas Controls: 51 880 (30 709 men, 21 171 women) from urban and 35 435 (22 046 men, 13 389 women) from rural areas
Mukaiya *et al*. (1998) Japan 1991–93	Men: 104 cases and 104 controls	Hospital-based study Cases with chronic liver disease; aged 51–69 years Controls with chronic disease but no hepatocellular carcinoma, matched for age
Kuper *et al*. (2000) Greece 1995–98	Men: 283 cases and 298 controls; women: 50 cases and 62 controls	Hospital-based study Cases histologically confirmed (47%) Non-cancer controls with injuries, eye/ear/nose/throat conditions, unrelated to smoking, alcohol or coffee consumption
Lam *et al*. (2001) Hong Kong SAR 1998	Men: 15 296 cases and 3918 controls; women: 12 211 cases and 9136 controls	Population-based study among ethnic Chinese Cases from death registries; aged ≥ 35 years Controls were spouses or relatives; aged ≥ 60 years
Chen *et al*. (2003) China 1986–88	Men: 26 294 cases and 11 321 controls; women: 9642 cases and 5619 controls	Retrospective population-based study in 24 cities and 74 rural counties Cases aged ≥ 35 years Controls with cirrhosis

Table 2.1.8.4. Case–control studies on tobacco smoking and liver cancer

Reference Country and years of study	No. of cases and controls	Smoking categories	Relative risk (95% CI)		Adjustment/comments
Williams & Horm (1977) USA 1969–71	40/204	*Pack–years* < 20 20–39 ≥ 40	Men 0.6 2.3 3.1	Women 0.3 – 1.6	Adjusted for age and sex. Non-significant odds ratios
Trichopoulos *et al*. (1980) Greece 1976–77	19/107	*Cigarettes/day* 1–10 11–20 21–30 ≥ 31	 1.3 2.5† 3.7† 8.4†		Persistence of effect after adjusting for alcohol consumption †significantly higher than 1
Lam *et al*. (1982) Hong Kong 1977–80	265/530	≥ 20 cigarettes/day	3.3 (1.0–13.4)		Overall, no significant association between alcohol consumption and liver cancer. Peanuts not considered as important source of aflatoxin
Stemhagen *et al*. (1983) USA 1975–80	78/78	Ever-smoker	Men 0.7 (0.5–1.1)	Women 1.0 (0.6–1.7)	No difference when adjusted for alcohol consumption. No dose–response
Yu *et al*. (1983) USA 1975–79		Former smoker ≤ 20 cigarettes/day > 20 cigarettes/day	1.1 (0.3–4.0) 1.2 (0.6–2.5) 2.6 (1.0–6.7)		Adjusted for alcohol. Nonsmokers and former smokers combined. [The Working Group considered that because only 4 controls drank ≥ 80 g/day ethanol, there were insufficient data to study the effect of smoking among heavy drinkers. Among lighter drinkers, the effect does not reach significance, is lower in magnitude that the unstratified effect and may be influenced by residual confounding.]
Hardell *et al*. (1984) Sweden 1974–81	98/200				The small positive association between HCC and smoking disappeared after controlling for alcohol consumption. Strong association between smoking and cholangiocarcinoma

Table 2.1.8.4 (contd)

Reference Country and years of study	No. of cases and controls	Smoking categories	Relative risk (95% CI)	Adjustment/comments
Austin *et al*.	86/172	Ever-smoker	1.3 (NS)	Unadjusted
(1986)		Current smoker	1.5 (0.7–3.7)	
USA		Former smoker	0.9 (NS)	Adjusted for alcohol consumption
		Ever-smoker	1.0 (0.5–1.8)	
		Current smoker	1.1 (0.5–2.4)	
		Pack–years		Adjusted for HBsAg status and alcohol consumption
		1–24	0.9 (NS)	
		25–49	2.6 (NS)	
		≥ 50	0.8 (NS)	
La Vecchia *et al*. (1988) Italy 1984–87	151/1051	Former smoker Current smoker	0.7 (0.4–1.0) 0.9 (0.6–1.5)	Adjusted for age, sex, geographical area, hepatitis, cirrhosis and alcohol consumption
Ferraroni *et al*.	151/1944	Former smoker	0.9	Adjusted for age, sex, alcohol, education, marital status and coffee consumption. No difference when adjusted for age and sex only
(1989)		*Cigarettes/day*		
Italy		< 15	0.9 (NS)	
1983–88		15–24	0.7 (NS)	
		≥ 25	0.8 (NS)	
Hiyama *et al*.	229/266	*Pack–years*		Adjusted for HBsAg status, age, sex, alcohol consumption and family history of liver cancer
(1990)		< 20	1.0 (baseline)	
Japan		20–39	1.9 (1.1–3.3)	
1984–87		40–59	2.0 (1.1–3.6)	
		≥ 60	1.0 (0.5–1.9)	
Kew *et al*.	46/92	Current smoker	2.2 (0.8–6.1)	
(1990)		*Cigarettes/day*		
South Africa		< 10	2.1 (0.8–7.1)	
		≥ 10	2.1 (0.4–10.7)	
Vall Mayans	96/190	*Cigarettes/day*		χ^2 for trend = 0.01. No difference after adjustment for HBV or alcohol consumption
et al. (1990)		1–20	1.4	
Spain		> 20	1.1	
1986–88				

Table 2.1.8.4 (contd)

Reference Country and years of study	No. of cases and controls	Smoking categories	Relative risk (95% CI)			Adjustment/comments
Olubuyide & Bamgboye (1990) Nigeria 1987–88	100/100	*Current smoker*				
		All	1.7 (0.9–3.1) $p < 0.1$			
		Men	1.5 (0.8–2.8)			
		Women	7.1 (0.7–26.5)			
Tsukuma *et al.* (1990) Japan 1983–87	229/266	**Men and women**				Adjusted for age and sex
		Former smoker	0.7			
		Current smoker	2.5 (1.4–4.5)			
		Cigarettes/day				
		1–19	4.2			
		20–39	2.2			
		≥ 40	1.1			
		Pack–years	*All*	*Men*	*Women*	
		0–19	1.0	1.0	1.0	
		20–39	1.7 (1.0–2.8)	1.6 (0.9–2.8)	[2.4]	
		40–50	1.8 (1.0–3.1)	1.9 (1.1–3.4)		
		≥ 50	1.0 (0.5–1.8)	0.9 (0.5–1.7)	[1.6]	
		Men				Adjusted for age
		Former smoker	0.8			
		Current smoker	2.3 (1.1–4.8)			
		Cigarettes/day				
		1–19	3.4			
		20–39	2.5			
		≥ 40	1.0			
		Women				Crude risk estimates
		Current smoker	2.9 (1.1–7.9)			
		Cigarettes/day				
		1–19	[6.1]			
		≥ 20	[1.1]			

Table 2.1.8.4 (contd)

Reference Country and years of study	No. of cases and controls	Smoking categories	Relative risk (95% CI)	Adjustment/comments
Chen *et al*. (1991) China, Province of Taiwan 1985–87	200/200	*Cigarettes/day* 1–10 11–20 ≥ 21	 1.1 (0.6–2.0) 1.9 (1.2–3.1) 3.0 (1.5–5.8)	Matched univariate analysis
Choi & Kahyo (1991) Republic of Korea 1986–90	216/648	Former smoker Current smoker *Cigarettes/day* 1–20 21–40 ≥ 41 *Duration (years)* 1–19 20–39 ≥ 40	0.7 (0.4–1.2) 1.0 (0.7–1.6) 1.2 (0.8–1.8) 0.6 (0.3–1.2) 0.5 (0.1–2.6) 0.7 (0.4–1.3) 1.0 (0.6–1.6) 1.9 (0.4–1.8)	Adjusted for HBV status, age, alcohol consumption, education and marital status
Lin *et al*. (1991) China 1984–86	200/200	Current smoker	2.1 (1.3–3.2)	Adjusted for age; study in an aflatoxin-endemic region of China
Tzonou *et al*. (1991) Greece 1976–84	185/432	HCC cases with cirrhosis	2.3 (0.9–5.9)	Adjusted for age and sex
		HCC cases without cirrhosis	2.1 (1.1–4.0)	Adjusted for HBsAg and HCV status
		HBsAg-positive cases and controls	1.7 (0.5–5.6)	Adjusted for age and sex
		HBsAg-negative cases and controls	2.4 (1.2–4.7)	Adjusted for HCV status [Crude odds ratio, 1.7 (95% CI, 1.1–2.6)]

Table 2.1.8.4 (contd)

Reference Country and years of study	No. of cases and controls	Smoking categories	Relative risk (95% CI)			Adjustment/comments
Yu, M.W. *et al.* (1991) China, Province of Taiwan 1986–87	127 pairs of cases and controls	*Cigarettes/day*				Matched odds ratio
		1–10	1.1 (0.5–2.2)			
		11–20	1.8 (1.0–3.4)			
		> 20	1.7 (0.7–4.5)			
		1–10	0.4 (0.1–1.9)			Adjusted for HBV and HCV status, alcohol and peanut consumption
		11–20	1.3 (0.4–4.2)			
		> 20	2.1 (0.3–13.5)			
Yu, M.C. *et al.* (1991) USA 1984–90	74/162		*All*	*Men*	*Women*	Unadjusted
		Former smoker	1.6 (0.7–3.5)	1.8 (0.7–4.8)	1.4 (0.3–6.5)	
		Current smoker	2.5 (1.2–5.0)	2.8 (1.0–7.9)	2.4 (0.8–6.9)	
		Cigarettes/day				
		≤ 19	2.8 (1.2–6.9)	3.7 (1.0–13.3)	2.1 (0.6–7.7)	
		≥ 20	2.2 (1.0–5.0)	2.4 (0.8–7.4)	2.9 (0.7–11.7)	
		Former smoker	1.1 (0.4–2.6)	1.1 (0.4–3.3)	0.8 (0.1–8.9)	Adjusted for alcohol consumption
		Current smoker	2.1 (1.1–4.3)	2.2 (0.8–6.0)	2.4 (0.9–6.7)	
		Current smoker				Adjusted for age, sex and ethnicity
		HBV/HCV-positive	1.8 (0.5–6.2)			
		HBV/HCV-negative	3.4 (0.9–12.5)			
Mohamed *et al.* (1992) South Africa	101/101	*Cigarettes/day*	*Men*	*Women*		Adjusted for alcohol, age and HBV status
		0–19	1.3 (0.5–3.4)	2.2 (0.3–6.3)		
		≥ 20	0.7 (0.2–2.5)	–		
Tanaka *et al.* (1992) Japan 1985–89	204/410		*All*	*Men*	*Women*	Adjusted for age and sex. Subjects with chronic hepatitis and cirrhosis exluded from control group. Histologically confirmed cases (82) did not differ from the remaining cases of liver cancer in their smoking habits.
		Former smoker	1.6 (0.9–2.8)	1.8 (0.9–3.5)	1.7 (0.4–7.1)	
		Current smoker	1.5 (0.5–2.5)	1.7 (0.9–3.2)	1.0 (0.3–3.2)	
		Pack–years				
		< 10.9	1			
		11–26.2	1.4 (0.8–2.3)			
		26.3–35.9	1.2 (0.7–2.1)			
		≥ 36	1.4 (0.8–2.4)			

Table 2.1.8.4 (contd)

Reference Country and years of study	No. of cases and controls	Smoking categories	Relative risk (95% CI)	Adjustment/comments
Peters *et al*. (1994) Germany 1986–93	86/86	Current smoker of > 40 pack–years	1.2 (0.5–2.9)	Adjusted for alcohol and HBV and HCV status
Pyong *et al*. (1994) Japan 1989–92	90/249	*Cigarettes/day*		Adjusted for age, sex, HBV and HCV status, transfusion and alcohol consumption
		1–20	0.7 (0.2–2.4)	
		> 20	0.4 (0.1–1.6)	
Siemiatycki *et al*. (1995) Canada 1979–86	48/2238	Ever-smoker	0.9 (0.4–2.1)	Adjusted for age; cancer control group had cancer at sites not previously associated with cigarette smoking
		Pack–years		
		< 25	1.4 (0.5–3.8)	
		25–49	0.7 (0.3–1.9)	
		50–74	0.7 (0.2–2.2)	
		≥ 75	0.8 (0.3–2.7)	
Tanaka *et al*. (1995) Japan 1983–89	120/257	Former smoker	2.2 (1.2–4.1)	Adjusted for age, study category (except for ever-smokers), HBV, history of transfusion, family history of liver cancer and alcohol consumption. Combined analysis of 3 studies; partial overlap with Tanaka *et al*. (1992)
		Current smoker	2.8 (1.1–6.9)	
		Male ever-smoker	1.9 (1.2–2.8)	
		Pack–years		
		0.1–12.9	2.4 (1.1–4.9)	
		≥ 13.0	1.8 (0.8–3.7)	
Shin *et al*. (1996) Republic of Korea 1990–93	203/406	*Current smoker*		Adjusted for HBV/HCV status, *Clonorchis sinensis*, history of hepatitis, liver, alcohol consumption and socioeconomic status
		Moderate	2.3 (0.4–11.7)	
		High (> 20 cigs/day for > 10 years)	1.1 (0.3–2.5)	

Table 2.1.8.4 (contd)

Reference Country and years of study	No. of cases and controls	Smoking categories	Relative risk (95% CI)		Adjustment/comments
Liu *et al*. (1998) China 1989–91	29 187/ 87 215	*Ever-smoker*[†]	*Men*	*Women*	Adjusted for age and study area (county or city). Retrospective proportional mortality study. Latency, 6–8 years. [†]Values in parentheses are standard errors.
		Urban	1.4 (0.03)	1.5 (0.06)	
		Rural	1.4 (0.04)	1.1 (0.08)	
		All China weighted	1.4 (0.03)	1.2 (0.06)	
		Current smoker	*Urban men*	*Rural men*	
		Cigarettes/day			
		1–19	1.4 (0.03)	1.5 (0.05)	
		20	1.5 (0.04)	1.6 (0.06)	
		> 20	1.6 (0.07)	1.8 (0.12)	
		Age at starting smoking (years)			
		< 20	1.4 (0.04)	1.4 (0.06)	
		20–24	1.4 (0.03)	1.4 (0.04)	
		≥ 25	1.4 (0.04)	1.4 (0.05)	
Mukaiya *et al*. (1998) Japan 1991–93	104/104	≥ 5 years vs < 5 years	3.3 (1.3–8.3)		
		≥ 10 pack/years vs < 10 pack–years	3.3 (1.3–8.3)		
Kuper *et al*. (2000) Greece 1995–98	333/360		*< 40 cigarettes/day*	*≥ 40 cigarettes/day*	
		Former smoker	1.2 (0.7–1.9)	1.5 (0.7–3.0)	Adjusted for age and sex
		Current smoker	1.2 (0.8–1.9)	1.6 (0.9–2.9)	
		Ever-smoker	1.6 (0.8–2.9)	2.5 (1.1–5.5)	Adjusted for age, sex and HBV and HCV status
		Current smoker			Adjusted for age, sex, education and HBV and HCV status
		HBV- and HCV-negative	1.8 (0.9–3.6)	2.8 (1.1–6.9)	
		HBV- and/or HCV-positive	1.3 (0.3–5.6)	2.1 (0.3–17.1)	
		All, adjusted for HBV/HCV	1.6 (0.8–2.9)	2.5 (1.1–5.5)	

Table 2.1.8.4 (contd)

Reference Country and years of study	No. of cases and controls	Smoking categories	Relative risk (95% CI)		Adjustment/comments
Lam *et al*. (2001) Hong Kong SAR 1998	27 507/ 13 054	*Ever-smoker*	*Men*	*Women*	Adjusted for age and education
		Aged 35–59	1.6 (1.3–1.9)	1.4 (0.8–2.4)	
		Aged ≥ 70	1.2 (0.9–1.5)	1.4 (0.9–2.0)	
Chen *et al*. (2003) USA 1986–88	36 000 cases/ 17 000 controls with cirrhosis		*Men*	*Women*	Adjusted for age and locality. Relative risk independent of age, urban/rural status or age at start of smoking
		Ever-smoker	1.4 (1.3–1.4)	1.2 (1.1–1.3)	
		Cigarettes/day (approx.)			
		10	1.3	1.1 (0.9–1.3)	
		20	1.5	1.5 (1.2–1.8)	
		30	1.6	–	
		p for trend	< 0.001		

CI, confidence interval; NS, not significant; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

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2.1.9 *Breast cancer*

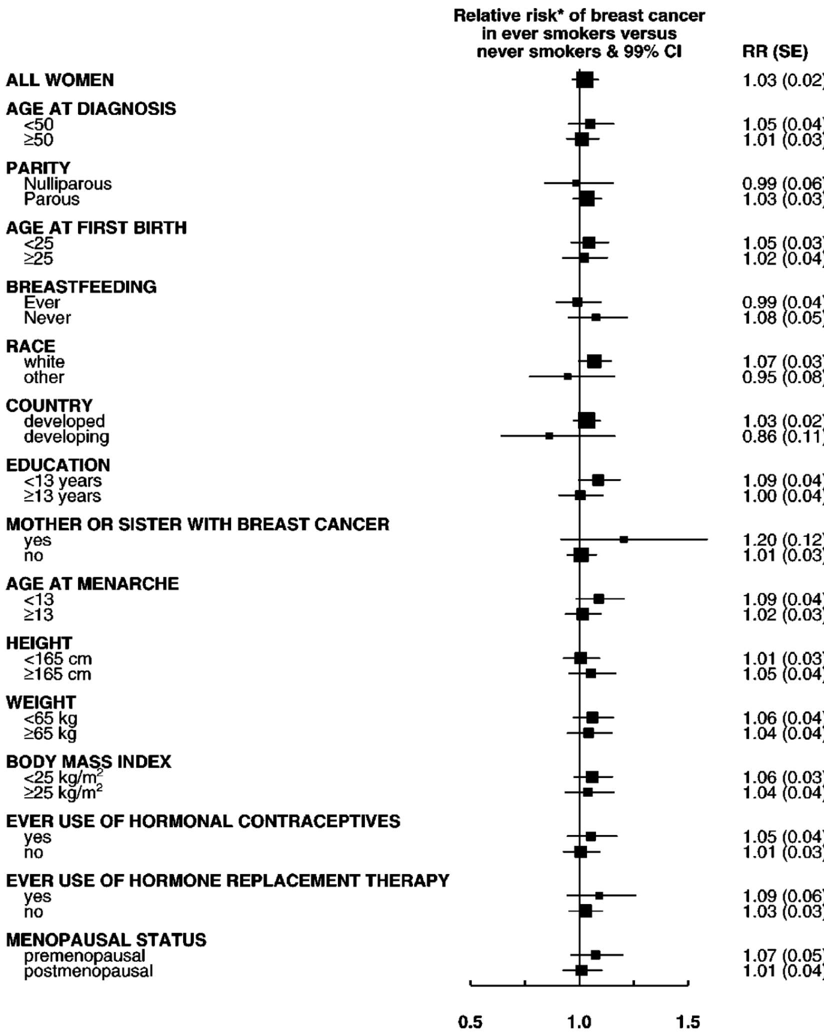
Indirect evidence suggests that smoking could conceivably reduce the risk for breast cancer. It is recognized that high levels of estrogens, particularly of estrone and estradiol, contribute to an increased risk for breast cancer and smoking is thought to have an anti-estrogenic effect. The occurrence of menopause at an earlier age among smokers than among nonsmokers is also well established, and late age at menopause has been consistently related to an increased risk for breast cancer. Conversely, cigarette smoke contains carcinogens that could plausibly affect the breast (US Department of Health and Human Services, 2001). Research is in progress to determine whether some population groups are placed genetically at a higher risk for breast cancer associated with smoking (see Section 4).

A total of 18 case–control and cohort studies that addressed the association of tobacco smoke with breast cancer were reviewed by the IARC Working Group on Tobacco Smoke in 1986 (IARC, 1986). A suggestion of a decreased risk was noted, but the reported relative risks were distributed on both sides of unity, ranging from 0.7 to 1.4. While the epidemiological evidence was consistent with a decrease in risk, it could not be concluded that this had been demonstrated.

Thirty-six case–control studies and eight cohort studies as well as one large pooled analysis of data from 10 cohort and 29 case–control studies from the Collaborative Group on Hormonal Factors in Breast Cancer Study (2002) were examined to assess the relationship between smoking and breast cancer risk. The characteristics of the case–control studies and the principal findings relative to the association with smoking are shown in Tables 2.1.9.1 and 2.1.9.2, respectively. Descriptions of all cohort studies are presented at the beginning of Section 2 and in Tables 2.1 and 2.1.9.3, and the results for breast cancer are given in Table 2.1.9.4. The studies included in the analysis by the Oxford Collaboration and the results of the pooled analysis are shown in Table 2.1.9.5 and Figure 2.1.9.1 (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

The Oxford Collaborative Study included over 80% of the worldwide epidemiological data on breast cancer and on alcohol and tobacco consumption. Overall, the analyses for tobacco exposure included 58 515 women with invasive breast cancer and 95 067 controls from 53 studies, in which individual data on both alcohol and tobacco consumption had been recorded. Case–control and cohort studies were eligible for the collaborative analysis if they included at least 100 women with incident invasive breast cancer and had information on reproductive factors and on use of hormonal therapies. Cohort studies were included using a nested case–control design, in which four controls were selected at random, matched on follow-up to the age of the case at diagnosis and, where appropriate, matched on broad geographical region. Only active smoking was considered and no attention was given to the reported associations with passive exposures, nor was information obtained on the age when women started or stopped smoking, or the amount smoked. Relative risks of breast cancer were estimated, after stratifying by study, age, parity and, when indicated, women's age at time of first birth and their consumption of alcohol and tobacco.

Figure 2.1.9.1. Relative risk of breast cancer in relation to tobacco consumption in various subgroups of women



*Stratified by study, age, parity and age at first birth; analyses restricted to women who reported drinking no alcohol
RR, relative risk; SE, standard error

The collaborative analysis examined the relationship between smoking and breast cancer and found it to be substantially confounded by the effect of alcohol consumption. When the analyses were restricted to 22 255 cases and 40 832 controls reported to drink no alcohol, smoking was not associated with breast cancer (compared with never-smokers, the relative risk for ever-smokers was 1.03 (95% CI, 0.98–1.07) and the relative risk for current smokers was 0.99 (95% CI, 0.92–1.05)). The findings for tobacco were not substantially confounded by any other factors, including family history of breast cancer, race, height, weight, age at menarche, menopause or use of hormonal preparations. Furthermore, the results for tobacco exposure and breast cancer did not vary substantially between studies, study designs or by the 15 personal characteristics of the women that were examined (Figure 2.1.9.1).

Among women who reported drinking alcohol, it was difficult to distinguish the independent effects of smoking (Collaborative Group on Hormonal Factors in Breast Cancer Study, 2002). For example, when ever-smokers were compared with never-smokers, the relative risk for breast cancer was 1.09 before stratification by alcohol consumption and was reduced to 1.05 after stratification. Moreover, the corresponding χ^2 (Chi squared) value declined by 75% from 23.4 to 6.4. Among ever-smokers in the 48 studies that gave information on current and past smoking, 54% were current smokers and 46% were past smokers. Compared with never-smokers, the relative risk for breast cancer was 0.99 for current smokers and 1.07 for past smokers.

Eleven studies, comprising a total of 4781 cases and 12 713 controls, contributed data on tobacco consumption for each woman, but no data on alcohol consumption, and were not included in the pooled analysis. The relative risk for breast cancer in ever-smokers compared with never-smokers in this subset of 11 studies was 1.05.

The results of some individual studies, particularly hospital-based case–control studies, must be interpreted cautiously (see General Remarks). Furthermore, questions have been raised about the results of some studies of women who participated in breast cancer screening programmes because the extent to which early detection methods are used may be correlated with smoking behaviour. Population-based case–control studies are generally believed to provide the most valid results.

Confounding

The most serious constraint in the interpretation of results from most studies that have attempted to evaluate the association of exposure to tobacco smoking with breast cancer risk results from the strong correlation of alcohol consumption, an established risk factor for breast cancer, with smoking behaviour, and the imprecision in estimates of the amount of alcohol consumed, especially those based on self-reports. The Oxford Collaborative analysis addressed this constraint by limiting the analysis of the association of breast cancer with tobacco consumption to study subjects who reported never drinking alcohol.

Table 2.1.9.1. Case–control studies on tobacco smoking and breast cancer: main characteristics of study design

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Rosenberg *et al.* (1984) USA and Canada 1976–82	2160 cases diagnosed in the last 6 months, and 717 controls, aged 30–69 years	Case–control surveillance programme in medical centers Controls admitted for cancers unrelated to smoking and to age at menopause (e.g. endometrium)
Smith *et al.* (1984) USA 1980–82	429 cases and 612 controls, aged 20–54 years, matched by age	National population-based study conducted by the CDC Cases histologically confirmed Controls with no previous cancer of the breast, endometrium and ovary 95% response rate for both cases and controls
Schechter *et al.* (1985) Canada Up to 1982	123 cases and 369 controls, aged 40–59 years, matched by age group and screening center	Multicenter randomized controlled trial (National Breast Screening Study) Criteria for eligibility: no history of breast cancer, not pregnant, no mammogram in the last 12 months Cases histologically confirmed Controls selected among women allocated to mammography
Brinton *et al.* (1986) USA 1973–1980	1547 cases and 1930 controls, matched by center, ethnicity, age group, time of entry and length of participation in the programme	Multicenter screening programme (Breast Cancer Detection Demonstration Project) Controls selected among women not having received a biopsy 74% response rate for cases and 90% for controls
McTiernan *et al.* (1986) USA 1981–82	329 cases and 332 controls, aged 25–54 years, matched by age	Population-based study (CDC Cancer and Steroid Hormone Study) Controls selected among women of the county by Waxberg's random-digit dialling method 79% response rate for cases and 87% for controls
O'Connell *et al.* (1987) USA 1977–78	276 cases and 1519 controls, aged 30 years or older	Population-based study Cases (patients admitted to North Carolina hospitals) histologically confirmed Controls selected from a stratified sample of households within the catchment area of the hospitals where the cases were identified 93% response rate for cases and 88% for controls
Stockwell & Lyman (1987) USA 1981	5246 cases and 3921 controls	Population-based study Controls were residents of the state of Florida diagnosed with colon or rectal cancers, or melanoma, or endocrine neoplasms

Table 2.1.9.1 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Stanford *et al.* (1987) USA 1980–82	458 cases and 568 controls, aged 20–54 years, matched by age group	Population-based study (Cancer and Steroid Hormone Study) Cases histologically confirmed Controls selected by random-digit dialling in the same geographical area as cases 85% response rate for cases and 90% for controls
Adami *et al.* (1988) Sweden & Norway 1984–85	422 cases and 527 controls, aged less than 45 years (Sweden) and less than 40 years (Norway), matched by age (Sweden) and day and year of birth (Norway)	Population-based study Cases histologically confirmed Controls with no history of cancer selected from population registers 89% response rate for cases and 81% for controls
Brownson *et al.* (1988) USA 1979–86	456 cases (88% prevalent) and 1693 controls, matched by age group and county of residence	Screening programme (Columbia Women's Cancer Control Programme) Cases histologically confirmed Controls randomly selected from participants to the programme Near 100% response rates for cases [controls not specified]
Cooper *et al.* (1989); Rohan & Baron (1989) Australia 1982–84	451 case–control pairs, aged 20–74 years, matched by age	Population-based study Cases histologically confirmed Controls randomly selected from the electoral roll of the Adelaide area 81% response rate for cases; 648 controls approached to achieve a final number of 451
Kato *et al.* (1989) Japan 1980–86	1740 cases and 8920 controls, aged 20 years and older	No detailed information on study design Cases selected from cancer registry Controls with cancers of known primary site, unrelated to alcohol
Meara *et al.* (1989) UK 1980–84	998 cases (hospital study) and 118 cases (screening), aged 25–59 years (hospital study) and 45–69 years (screening), and 998 controls matched by age group	Hospital-based study and mammographic screening Controls selected among patients from the same hospital with conditions unrelated to breast cancer or contraceptive practice, and among normal screenees Near 100% response rates in both studies for cases and controls
Schechter *et al.* (1989) Canada 1982–85 (prevalence study) 1981–87 (incidence study)	254 prevalent cases and 762 controls; 317 incident cases and 951 controls; age 40–59 years	Multicentre randomized controlled trial (National Breast Screening Study) Criteria for eligibility: no history of breast cancer, not pregnant, no mammogram in the last 12 months Cases histologically confirmed Controls selected among women allocated to mammography

Table 2.1.9.1 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Chu *et al.* (1990) USA 1980–82	4720 cases and 4682 controls, aged 20–54 years, matched by age group and geographic location	Population-based study (CDC Cancer and Steroid Hormone Study) Controls selected among women of the county by Waxberg's random-digit dialling method 80% response rate for cases and 88% for controls
Ewertz (1990) Denmark 1983–84	1480 cases and 1332 controls, aged less than 70 years, matched by age	Population-based study Controls with no history of breast cancer identified from the Central Population Register 87% response rate for cases and 78% for controls
Palmer *et al.* (1991) Canada and USA 1982–86	**Canada** 607 cases and 1214 controls under age 70, matched by age and neighbourhood **USA** 1955 cases and 805 controls, aged 30–69 years	**Population-based study in Canada** English-speaking women with no history of cancer were eligible Controls identified from tax assessment rolls 76% response rate for cases and 65% for controls **Hospital-based study in the USA** Controls admitted to hospital for cancers unrelated to smoking (colon, rectum, melanoma, lymphoma, bone or connective tissues) diagnosed in the last 6 months and having no previous history of cancer
Field *et al.* (1992) USA 1982–84	1617 case–control pairs aged 20–79 years, matched by year of birth and county of residence	Population-based study Cases histologically confirmed Controls selected using state driver's licence files 79% response for cases and 72% for controls
Smith *et al.* (1994) UK 1984–88	755 case–control pairs (cases under age 36 at date of diagnosis), matched by date of birth (within 6 months)	Population-based study Cases diagnosed in 1982–85 Controls randomly chosen from each case's general practioner list of patients 72% response rate for cases and 89% for controls
Ranstam & Olsson (1995) Sweden 1981–84	177 premenopausal and 216 postmenopausal cases; 195 premenopausal and 254 postmenopausal controls	Population-based study Controls randomly selected from the national population register 90% response rate for cases and 80% for controls
Baron *et al.* (1996) USA 1988–91	6888 cases and 9529 controls, aged less than 75 years	Population-based study Controls randomly selected from state driver's licence lists (aged < 65 years) and among women enrolled in Medicare in the participating state (aged 65–74 years) 81% response rate for cases and 84% for controls

Table 2.1.9.1 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Braga *et al.* (1996) Italy 1991–94	2569 cases and 2588 controls, aged 23–74 years (cases) and 20–74 years (controls)	Multicentre hospital-based study in six Italian areas Cases histologically confirmed Controls with no history of cancer admitted to hospitals for acute, non-neoplastic, non-hormonal, non-gynaecological diseases, smoking-related conditions excluded > 96% response rate for both cases and controls
Haile *et al.* (1996) Canada and USA 1970–89 (Los Angeles) 1975–89 (Quebec) 1935–89 (Connecticut)	144 cases and 232 controls, aged less than 50 years	Population-based study Cases histologically confirmed Controls were cases' sister(s) who were alive in 1989 (≥ 1 sister by case) and unaffected by breast cancer ~70% response rate for cases and controls combined
Morabia *et al.* (1996) Switzerland 1992–93	244 cases and 1032 controls, aged less than 75 years	Population-based study Cases histologically confirmed Controls were residents of Geneva, aged 30–74 years 71% response rate for cases and 70% for controls
Yoo *et al.* (1997) Japan 1988–92	1154 cases and 21714 controls, aged 25 years or older	Hospital-based study Cases histologically confirmed Controls were cancer-free hospital patients with no history of cancer
Brunet *et al.* (1998) Canada and USA [years of study not specified]	186 case–control pairs, mean age 49.7 years, matched by age and mutation in the same BRCA gene	Study involving genetic counselling centers Cases with past diagnosis of invasive breast cancer and no previous diagnosis of ovarian cancer Controls: women with no history of breast cancer, carriers of BRCA1 or BRCA2 mutations
Ghadirian *et al.* (1998) Canada 1989–93	414 cases and 429 controls, aged 35–79 years, matched by age and residence	Population-based study in the Francophone Community of greater Montreal Cases histologically confirmed Controls selected by random-digit dialling 77% response rate for cases
Gammon *et al.* (1998) USA 1990–92	2199 cases and 2009 controls, under 45 years, matched by age group and geographic area	Population-based study (Women's Interview Study of Health) Controls identified by random-digit dialling 86% response rate for cases and 71% for controls

Table 2.1.9.1 (contd)

Reference Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Millikan *et al.* (1998) USA 1993–96	498 cases and 473 controls	Population-based study (Carolina Breast Cancer Study) Cases histologically confirmed Controls selected from lists from the North Carolina Division of Motor Vehicles (aged 20–64 years) and the Health Care Financing Administration (aged 65–74 years) Randomized recruitment among cases and controls to have equivalent numbers of white and African Americans as well as < 50 and ≥ 50 years of age 77% response rate for cases and 68% for controls
Gammon *et al.* (1999) USA 1990–92	378 cases (168 TP53-positive and 210 TP53-negative) and 462 controls, under the age of 45 years, matched by age group	Multicentre population-based study Cases histologically confirmed Controls identified by random-digit dialling 83% response rate for cases and 77% for controls
Lash & Aschengrau (1999) USA 1983–86	265 cases and 763 controls	Population-based study Controls identified by random-digit dialling (aged < 65 years); from the Health Care Financing Administration lists (aged ≥ 65 years); and from the Massachusets Department of Vital Statistics lists (deceased subjects 1983–89) 79% response rate for cases and 77% for controls
Johnson *et al.* (2000) Canada 1994–97	2617 cases (805 premenopausal and 1512 postmenopausal) and 2438 controls, aged 25–74 years	Population-based study Cases histologically confirmed Controls randomly selected from provincial health insurance plans; or random-digit dialling; or population research laboratory 77% response rate for cases and 71% for controls
Marcus *et al.* (2000) USA 1993–96	864 cases and 790 controls, aged 20–74 years	Population-based study (Carolina Breast Cancer Study) see Millikan *et al.* (1998) 77% response rate for cases and 68% for controls
Innes & Byers (2001) USA 1989–95	319 cases and 768 controls, aged 26–45 years	Record-linkage study Cases had completed a first pregnancy after 1987 Primiparous controls who resided and delivered in the same county as the case and were not subsequently diagnosed with breast or endometrial cancer were identified from infants' birth records
Kropp & Chang-Claude (2002) Germany 1992–95 and 1999–2000	468 mostly premenopausal cases and 1093 controls, matched by age and region	Population-based study Cases histologically confirmed Controls selected from regional population registries 70% response rate for cases and 61% for controls

Table 2.1.9.2. Case–control studies on tobacco smoking and breast cancer

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Rosenberg *et al.* (1984) USA Canada 1976–82	Former smoker	1.1 (0.8–1.3)	Adjusted for all identified potential confounders
	Cigarettes/day		
	1–14	1.3 (0.9–1.8)	
	15–24	1.0 (0.8–1.4)	
	≥ 25	1.1 (0.8–1.7)	
Smith *et al.* (1984) USA 1980–82	Occasional smoker	0.9 (0.7–1.3)	Continuous smokers
	Current smoker	1.2 (0.9–1.6)	
Schechter *et al.* (1985) Canada Up to 1982	*All*		
	Former smoker	1.0 (0.6–1.7)	
	Ever-smoker	1.4 (0.9–2.1)	
	Current smoker	1.9 (1.2–3.1)	
	Premenopausal		
	Former smoker	1.0 (0.5–2.7)	
	Ever-smoker	2.1 (1.1–4.0)	
	Current smoker	3.6 (1.7–7.7)	
	Postmenopausal		
	Former smoker	1.0 (0.5–2.0)	
	Ever-smoker	1.1 (0.6–1.9)	
	Current smoker	1.3 (0.7–2.4)	
Brinton *et al.* (1986) USA 1973–80	Former smoker	1.2 (1.0–1.5)	Adjusted for age
	Ever-smoker	1.2 (1.0–1.4)	
	Current smoker	1.2 (0.9–1.4)	
	Cigarettes/day		
	< 10	1.2 (0.9–1.4)	*p* for trend = 0.2
	10–19	1.4 (1.1–1.8)	
	20–29	1.2 (0.9–1.4)	
	30–39	1.2 (0.9–1.8)	
	≥ 40	1.2 (0.8–1.6)	
	Duration (years)		
	< 10	1.4 (1.0–1.9)	*p* for trend = 0.02
	10–19	1.2 (0.9–1.5)	
	20–29	1.2 (0.9–1.4)	
	30–39	1.1 (0.9–1.4)	
	≥ 40	1.3 (0.9–1.7)	
	Age at starting smoking (years)		
	≥ 23	1.1 (0.9–1.4)	
	20–22	1.1 (0.9–1.5)	
	17–19	1.3 (1.0–1.6)	
	< 17	1.3 (1.0–1.6)	

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
McTiernan *et al.* (1986) USA 1981–82	*Estrogen receptor-positive cases* (*n* = 143)		Cases identified via population-based cancer registry, aged 25–54 years at diagnosis. Part of CASH study. Adjusted for age and use of alcohol
	Former smoker	0.96 (0.6–1.6)	
	Current smoker	1.1 (0.7–1.8)	
	Estrogen receptor-negative cases (*n* = 97)		
	Former smoker	0.8 (0.5–1.6)	
	Current smoker	0.8 (0.4–1.3)	
	Estrogen receptor status unknown (*n* = 89)		
	Former smoker	0.8 (0.5–1.5)	
	Current smoker	0.8 (0.5–1.5)	
O'Connell *et al.* (1987) USA 1977–78	Former smoker	1.2 (0.8–1.7)	Adjusted for age, race, estrogen use, oral contraceptive use and alcohol consumption
	Cigarettes/day		
	1–20	0.8 (0.5–1.1)	
	> 20	0.6 (0.3–1.1)	
Stockwell & Lyman (1987) USA 1981	Former smoker	1.0 (0.8–1.1)	Adjusted for age, race and marital status
	Cigarettes/day		
	> 20	1.3 (1.1–1.5)	
	20–40	1.2 (1.0–1.5)	
	> 40	1.3 (1.0–1.8)	
Stanford *et al.* (1987) USA 1980–82	Estrogen receptor-positive ever-smoker (*n* = 204)	1.03 (0.7–1.4)	Women aged 20–54 years. Part of CASH study. Ever-smoker defined as having smoked ≥ 100 cigarettes/lifetime
	Estrogen receptor-negative ever-smoker (*n* = 254)	1.00 (0.7–1.4)	Adjusted for age
Adami *et al.* (1988) Sweden, Norway 1984–85	*Cigarettes/day*		Adjusted for age, education, alcohol consumption and reproductive factors
	1–4	1.1 (0.5–2.1)	
	5–9	1.3 (0.8–2.0)	
	10–14	1.0 (0.6–1.5)	
	15–19	0.7 (0.4–1.2)	
	≥ 20	1.1 (0.7–1.8)	
	Duration (years)		
	0–4	1.2 (0.6–2.3)	
	5–9	0.7 (0.3–1.3)	
	10–14	1.0 (0.6–1.8)	
	15–19	1.1 (0.7–1.7)	
	≥ 20	1.2 (0.8–1.7)	
	Age at starting smoking (years)		
	≥ 25	1.6 (0.8–3.3)	
	20–24	0.8 (0.5–1.3)	
	15–19	1.0 (0.7–1.5)	
	< 15	1.3 (0.7–2.5)	

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Brownson *et al.* (1988) USA 1979–86	Former smoker	0.9 (0.6–1.2)	Adjusted for age, age at first pregnancy, parity, age at menarche, ever being married, family history of breast cancer and oral contraceptive use
	Ever-smoker	1.1 (0.9–1.4)	
	Current smoker	1.4 (1.01–1.9)	
Cooper *et al.* (1989); Rohan & Baron (1989) Australia 1982–84	*Estrogen receptor-positive* (*n* = 238)		Cigarette smoking associated with increased risk of estrogen receptor-negative cancer; women aged 20–74 years; adjusted for menopausal status
	Former smoker	0.9 (0.6–1.4)	
	Ever-smoker	0.95 (0.7–1.4)	
	Current smoker	1.3 (0.8–2.0)	
	Estrogen receptor-negative (*n* = 119)		
	Former smoker	1.9 (0.99–3.6)	
	Ever-smoker	1.6 (1.00–2.7)	
	Current smoker	1.3 (0.7–2.5)	
	Former smoker	1.04 (0.7–1.5)	Adjusted for family history of breast cancer, practice of breast self-examination, history of benign breast disease, obesity, menopausal status and alcohol consumption
	Ever-smoker	1.2 (0.9–1.5)	
	Current smoker	1.4 (0.95–2.0)	
	Cigarettes/day		
	1–15	1.2 (0.7–1.9)	
	> 15	1.6 (0.99–2.6)	
	Pack–years		
	1–< 5	0.99 (0.6–1.6)	
	5–< 14	1.1 (0.7–1.8)	
	14–< 25	1.1 (0.7–1.8)	
	≥ 25	1.6 (0.99–2.5)	*p* for trend = 0.088
Kato *et al.* (1989) Japan 1980–86	Ever-smoker	0.9 (0.7–1.02)	Adjusted for age, alcohol use, marital status, residence, occupation and family history of breast cancer
Meara *et al.* (1989) United Kingdom 1980–84	25–44 years		Adjusted for menopausal status, age at first full-term pregnancy, age at menarche, family history of breast cancer in first-degree relatives, duration of oral contraceptive use, alcohol use, Quetelet index and socioeconomic status
	Former smoker	0.9 (0.6–1.5)	
	Current smoker		
	1–14 cigarettes/day	0.6 (0.3–0.95)	
	≥ 15 cigarettes/day	1.2 (0.7–1.8)	
	45–69 years		
	Former smoker	0.95 (0.7–1.3)	
	Current smoker		
	1–14 cigarettes/day	0.8 (0.6–1.2)	
	≥ 15 cigarettes/day	0.8 (0.6–1.1)	
	Former smoker	0.99 (0.4–2.3)	
	Current smoker		
	1–14 cigarettes/day	1.8 (0.7–4.7)	
	≥ 15 cigarettes/day	2.9 (1.2–7.3)	*p* for trend < 0.05

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Schechter *et al.* (1989) Canada 1982–85 (prevalence) 1981–87 (incidence)	**Prevalent cases**		Adjusted for age at menarche, age at first live birth, parity, age at menopause, family history of breast cancer, history of benign breast disease, breast symptoms, oral contraceptive use, estrogen replacement, height, weight, skinfold thickness, ethnicity, marital status, education, centre, age, use of breast self-examination and number of previous mammograms
	Ever-smoker	1.1 (0.9–1.5)	
	Pack–years		
	1–10	1.0 (0.6–1.5)	
	> 10–25	1.1 (0.7–1.7)	
	> 25	1.2 (0.8–1.7)	
	Incident cases		
	Ever-smoker	1.2 (0.9–1.6)	
	Pack–years		
	1–10	1.2 (0.9–1.8)	
	> 10–25	1.1 (0.8–1.7)	
	> 25	1.3 (0.9–1.9)	
Chu *et al.* (1990) USA 1980–82	Former smoker	1.1 (1.0–1.3)	Adjusted for age, parity, menopausal status, age at first birth, age at menarche, family history of breast cancer, history of benign breast disease and estrogen replacement therapy
	Ever-smoker	1.2 (1.1–1.3)	
	Current smoker	1.2 (1.1–1.3)	
	Cigarettes/day		
	< 15	1.1 (1.0–1.3)	
	15–24	1.2 (1.0–1.3)	
	≥ 25	1.2 (1.1–1.4)	
	Duration (years)		
	< 10	1.1 (0.9–1.2)	
	10–19	1.3 (1.1–1.4)	
	20–29	1.2 (1.1–1.4)	
	≥ 30	1.1 (0.9–1.3)	
	Age at starting smoking (years)		
	≥ 23	1.3 (1.1–1.5)	
	20–22	1.2 (1.0–1.4)	
	17–19	1.2 (1.1–1.4)	
	< 17	1.1 (1.0–1.2)	
	Pack–years		
	< 10	1.1 (1.0–1.3)	
	10–19	1.1 (1.0–1.3)	
	20–29	1.1 (1.0–1.3)	
	30–39	1.3 (1.1–1.6)	
	≥ 40	1.1 (0.9–1.4)	
	Years since quitting		
	0–1	1.2 (1.1–1.3)	
	2–5	1.2 (1.0–1.5)	
	6–9	1.3 (1.0–1.7)	
	≥ 10	1.1 (0.9–1.3)	

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Ewertz (1990)	Former smoker	1.0 (0.8–1.2)	Adjusted for age and place of residence
Denmark	Current smoker	0.9 (0.8–1.1)	
1983–84	*Cigarettes/day*		
	1–4	0.9 (0.7–1.3)	
	5–9	1.05 (0.8–1.4)	
	10–14	1.02 (0.8–1.3)	
	15–19	1.01 (0.8–1.4)	
	≥ 20	0.8 (0.6–1.00)	
	Duration (years)		
	< 10	0.8 (0.6–1.1)	
	10–19	0.9 (0.7–1.2)	
	20–29	0.99 (0.8–1.3)	
	30–39	0.99 (0.8–1.2)	
	≥ 40	0.95 (0.7–1.3)	
	Age at starting smoking (years)		
	≥ 30	0.8 (0.6–1.1)	
	25–29	0.97 (0.7–1.4)	
	20–24	0.9 (0.7–1.1)	
	15–19	0.99 (0.8–1.2)	
	< 15	1.1 (0.8–1.6)	
	Pack–years		
	1–< 5	0.8 (0.6–1.1)	
	5–< 14	1.1 (0.9–1.4)	
	14–< 25	0.9 (0.8–1.2)	
	≥ 25	0.9 (0.7–1.2)	
Palmer *et al*. (1991)	Former smoker	1.0 (0.7–1.3)	Adjusted for age, age at menopause, age at menarche, age at first birth, parity, family history of breast cancer, history of fibrocystic breast disease, body-mass index, oral contraceptive use, alcohol use, years of education and geographical area
	Ever-smoker	1.0 (0.8–1.3)	
Canada	Current smoker	1.1 (0.9–1.4)	
	Cigarettes/day		
	< 25	1.0 (0.8–1.2)	
	25–34	1.1 (0.8–1.5)	
	≥ 35	1.5 (0.9–2.5)	
USA	Former smoker	1.1 (0.9–1.4)	
	Ever-smoker	1.2 (1.0–1.5)	
1982–86	Current smoker	1.3 (1.1–1.6)	
	Cigarettes/day		
	< 25	1.2 (1.0–1.5)	
	25–34	1.2 (0.8–1.9)	
	≥ 35	1.2 (0.9–1.8)	

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Field *et al.* (1992) USA 1982–84	Ever-smoker	1.03 (0.9–1.2)	Age-adjusted for birth-year and county of residence
	Cigarettes/day (approx.)		
	1–9	0.9 (0.7–1.1)	
	10–20	1.2 (1.00–1.4)	
	30	0.9 (0.7–1.1)	
	40	0.98 (0.7–1.4)	
	> 40	1.2 (0.7–2.0)	
	Duration (years)		
	1–9	1.00 (0.8–1.3)	
	10–19	1.2 (0.9–1.5)	
	20–29	0.9 (0.7–1.1)	
	30–39	1.04 (0.9–1.3)	
	≥ 40	1.04 (0.8–1.3)	
	Age at starting smoking (years)		
	≥ 30	0.9 (0.6–1.2)	
	20–29	1.1 (0.9–1.4)	
	< 20	1.00 (0.9–1.2)	
	Age at quitting (years)		
	< 30	1.05 (0.8–1.4)	
	30–39	1.2 (0.9–1.5)	
	40–49	0.98 (0.8–1.2)	
	50–59	1.03 (0.8–1.3)	
	≥ 60	0.9 (0.7–1.1)	
Smith *et al.* (1994) UK 1984–88	Ever-smoker	1.01 (0.8–1.3)	Adjusted for age at menarche, nulliparity, age at first full-term pregnancy, breastfeeding (ever/never), family history of breast cancer, total oral contraceptive use, biopsy for benign breast disease and total alcohol consumption at age 18
	Cigarettes/day		
	≤ 15	0.95 (0.7–1.2)	
	≥ 16	1.1 (0.8–1.5)	
	Duration (years)		
	1–9	1.1 (0.8–1.5)	
	≥ 10	0.97 (0.8–1.3)	
	Pack–years		
	< 1–10	1.00 (0.8–1.3)	
	≥ 10	1.02 (0.8–1.4)	
	Age at starting smoking (years)		
	≥ 17	0.9 (0.7–1.2)	
	≤ 16	1.1 (0.8–1.4)	
Ranstam & Olsson (1995) Sweden 1981–84	**Premenopausal**		Adjusted for age, age at menarche, age at first full-term pregnancy, parity and age at menopause
	Ever-smoker	1.0 (0.6–1.5)	
	Cigarettes/day		
	1–10	0.7 (0.3–1.4)	
	> 11	1.2 (0.7–2.1)	
	Postmenopausal		
	Ever-smoker	0.7 (0.4–1.2)	
	Cigarettes/day		
	1–10	0.7 (0.4–1.3)	
	> 11	0.8 (0.4–1.6)	

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Baron *et al.* (1996) USA 1988–91	Former smoker	1.1 (1.01–1.2)	Adjusted for age at menarche, age at first term birth, parity, history of lactation, family history of breast cancer, history of benign breast disease, alcohol intake and menopausal status
	Current smoker	1.0 (0.9–1.1)	
	Cigarettes/day		
	≤ 10	1.04 (0.95–1.1)	
	10–20	1.1 (0.98–1.2)	
	21–30	1.1 (0.9–1.2)	
	31–40	1.04 (0.9–1.2)	
	> 40	1.1 (0.8–1.5)	
	trend/10 cigarettes	0.99 (0.96–1.04)	
	Duration (years)		
	≤ 10	0.96 (0.8–1.1)	
	11–20	1.02 (0.9–1.2)	
	21–30	1.1 (1.00–1.3)	
	31–40	1.1 (1.00–1.3)	
	41–50	1.01 (0.9–1.2)	
	> 50	1.1 (0.8–1.4)	
	trend/10 years	1.03 (0.99–1.08)	
	Years since quitting		
	> 30	0.9 (0.8–1.1)	
	21–30	0.9 (0.8–1.1)	
	11–20	1.1 (0.95–1.2)	
	3–10	1.2 (1.1–1.4)	
	≤ 3	1.4 (1.1–1.7)	
	trend/10 years	0.9 (0.9–0.96)	
Braga *et al.* (1996) Italy 1991–94	Former smoker	1.1 (0.9–1.4)	Adjusted for age, centre, education, parity, body-mass index and reproductive factors
	Ever-smoker	0.9 (0.8–1.1)	
	Current smoker	0.8 (0.7–1.0)	
	Cigarettes/day		
	< 5	1.02 (0.8–1.3)	
	5–14	0.99 (0.8–1.2)	
	15–24	0.8 (0.6–1.0)	
	≥ 25	1.2 (0.8–1.7)	
	Duration (years)		
	< 20	0.97 (0.8–1.2)	
	20–29	0.9 (0.7–1.0)	
	≥ 30	0.99 (0.8–1.2)	
	Age at starting smoking (years)		
	≥ 25	0.95 (0.8–1.1)	
	19–24	0.9 (0.8–1.1)	
	16–18	0.9 (0.7–1.1)	
	< 16	0.97 (0.7–1.3)	
	Years since quitting		
	≥ 16	0.7 (0.5–1.1)	
	7–15	1.1 (0.9–1.6)	
	3–6	1.8 (1.3–2.5)	
	< 3	1.5 (0.9–2.3)	

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Haile *et al.* (1996) USA, Canada Up to 1989	1–20 pack–years	0.9 (0.5–1.6)	Cases of premenopausal bilateral breast cancer at < 50 years of age. Results adjusted for age, alcohol, oral contraceptive use, body-mass index and education
	> 20 pack–years	1.0 (0.5–2.1)	
	*Family history of breast cancer (*n *= 63)*		
	1–20 pack–years	0.9 (0.3–2.2)	
	> 20 pack–years	2.3 (0.7–8.1)	
	*No family history (*n *= 78)*		
	1–20 pack–years	0.8 (0.3–2.0)	
	> 20 pack–years	0.4 (0.1–1.4)	
Morabia *et al.* (1996) Switzerland 1992–93	*Former smoker (cig/day)*		Reference group comprised subjects not exposed to active or passive smoking.
	1–9	3.3 (1.4–7.6)	
	10–19	3.6 (1.6–8.1)	
	≥ 20	3.7 (1.5–8.8)	
	Ever-smoker (cig/day)		
	1–9	2.2 (1.0–4.4)	
	10–19	2.7 (1.4–5.4)	
	≥ 20	4.6 (2.2–9.7)	
	Current smoker (cig/day)		
	1–9	1.5 (0.6–3.9)	
	10–19	2.1 (0.9–4.8)	
	≥ 20	5.1 (2.1–12.6)	
	Pack–years		
	< 20	2.1 (1.0–4.5)	
	≥ 20	2.9 (1.4–6.0)	
Yoo *et al.* (1997) Japan 1988–92	*Ever-smoker*		Results presented for progesterone receptor status were similar to estrogen receptor status. Adjusted for age at diagnosis, current occupation, family history of breast cancer among first-degree relatives, menstrual regularity, menopausal status, history of full-term pregnancy, alcohol use, age at menarche, age at menopause, age at first full-term pregnancy, number of full-term pregnancies and average months of breastfeeding per child.
	All	1.3 (1.1–1.5)	
	Estrogen receptor-positive	1.4 (1.0–1.9)	
	Estrogen receptor-negative	1.3 (0.9–2.0)	
Brunet *et al.* (1998) USA, Canada NS	Ever-smoker	0.5 (0.3–0.8)	Adjusted for parity, age at first birth, age at last birth and geographical area
	Packs/week		
	< 5	0.6 (0.4–1.1)	
	≥ 5	0.5 (0.3–0.8)	
	Pack–years		
	≤ 4	0.7 (0.4–1.2)	
	> 4	0.5 (0.3–0.8)	

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Ghadirian *et al.* (1998) Canada 1989–93	Ever-smoker Untipped cigarettes	0.7 (0.6–0.98) 0.4 (0.2–0.7)	Adjusted for age, marital status, parity, age at first full-term pregnancy, history of benign breast disease and ovarian cancer, income and body-mass index
Gammon *et al.* (1998) USA 1990–92	Former smoker Ever-smoker Current smoker	0.99 (0.8–1.2) 0.9 (0.8–1.1) 0.8 (0.7–1.01)	Women < 45 years of age. Adjusted for age, centre, usual alcohol consumption, parity, age at first birth, age at menarche, breastfeeding, abortion, miscarriage, menopausal status, ever being married, education, income, race, body-mass index at age 20 years, body-mass index as an adult, oral contraceptive use, non-contraceptive hormone use, calorie intake, history of breast biopsy, family history of breast cancer
Millikan *et al.* (1998) USA 1993–96	Former smoker	1.3 (0.9–1.8)	Adjusted for age, age at menarche, age at first full-term pregnancy, family history of breast cancer, benign breast biopsy and alcohol consumption
	Current smoker	1.0 (0.7–1.4)	
	Cigarettes/day		
	< 10	1.1 (0.8–1.6)	
	11–20	1.3 (0.9–1.9)	
	> 20	1.1 (0.7–1.7)	
	Duration (years)		
	≤ 10	1.0 (0.7–1.5)	
	11–20	0.8 (0.5–1.2)	
	> 20	1.6 (1.1–2.3)	
	Years since quitting		
	≥ 20	1.1 (0.7–1.9)	
	10–19	0.8 (0.5–1.4)	
	4–9	1.7 (1.0–3.0)	
	≤ 3	2.2 (1.2–4.0)	
Gammon *et al.* (1999) USA 1996–92	***TP53*-positive**		Cases with tissue studies, aged < 45 years. Adjusted for age, race, education, alcohol, body-mass index, age at first birth, parity, age at menarche, family history of breast cancer, prior breast biopsy, caloric intake and electric blanket use. Data available on intensity, duration, pack–years and age at start by *TP53* status for ever-smokers and current smokers
	Former smoker	1.7 (1.02–2.7)	
	Current smoker	1.3 (0.8–2.1)	
	***TP53*-negative**		
	Former smoker	1.2 (0.8–1.8)	
	Current smoker	0.7 (0.4–1.1)	
	Ratios of the odds ratios		
	Former smoker	1.4 (0.8–2.4)	
	Current smoker	2.0 (1.1–3.5)	

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Lash & Aschengrau (1999) USA 1983–86	Ever-smoker	2.0 (1.1–3.6)	Ever smoked compared with subjects not exposed to active or passive smoke. Current smokers defined as persons who had smoked within 5 years before diagnosis
	Current smoker	2.3 (0.8–6.8)	
	Cigarettes/day		
	≤ 20	2.1 (1.0–4.6)	
	> 20	1.6 (0.6–4.3)	
	Duration (years)		
	0–19	2.6 (1.2–5.5)	
	20–39	1.5 (0.7–3.2)	
	≥ 40	2.4 (1.1–5.5)	
	Age at starting smoking (years)		
	≥ 21	2.4 (1.0–5.7)	
	17–20	2.3 (1.0–5.5)	
	< 17	2.4 (0.8–7.2)	
	Years since quitting		
	> 15	2.2 (1.0–4.9)	
	5–15	3.9 (1.4–10)	
	< 5 or current	2.3 (0.8–6.8)	
Johnson *et al.* (2000) Canada 1994–97	**Premenopausal**		Referent groups were subjects not exposed to active or passive smoking.
	Former smoker	2.6 (1.3–5.3)	
	Ever-smoker	2.3 (1.2–4.5)	
	Current smoker	1.9 (0.9–3.8)	
	Postmenopausal		
	Former smoker	1.4 (0.9–2.1)	
	Ever-smoker	1.5 (1.0–2.3)	
	Current smoker	1.6 (1.0–2.5)	
Marcus *et al.* (2000) USA 1993–96	Former smoker	1.1 (0.8–1.3)	Women aged 20–74 years with focus on exposures during adolescence
	Current smoker	1.2 (0.9–1.5)	
	Cigarettes/day		
	< 20	1.0 (0.8–1.4)	
	≥ 20	1.1 (0.9–1.4)	
	Duration (years)		
	< 20	0.9 (0.7–1.2)	
	≥ 20	1.3 (1.1–1.8)	
	Age at starting smoking (years)		
	≥ 20	1.2 (0.8–1.5)	
	15–19	1.0 (0.8–1.3)	
	10–14	1.5 (0.9–2.5)	
Innes & Byers (2001) USA 1989–95	Smoking during pregnancy	3.1 (1.3–7.3)	Women aged 26–45 years. Adjusted for age, age at first birth, maternal education, maternal race and marital status

Table 2.1.9.2 (contd)

Reference Country and years of study	Smoking categories	Relative risk (95% CI)	Comments
Kropp & Chang-Claude (2002) Germany 1992–95 1999–2000	Former smoker	1.2 (0.8–1.7)	Women diagnosed by age 50 years.
	Ever-smoker	1.3 (0.9–1.9)	Never active/never passive smokers used as referent.
	Current smoker	1.5 (1.0–2.2)	
	Duration (years)		Adjusted for alcohol, total months of breastfeeding, education, family history of breast cancer, menopausal status and body-mass index
	1–9	0.99 (0.6–1.6)	
	10–19	1.4 (0.9–2.2)	
	≥ 20	1.5 (1.0–2.2)	
	Age at starting smoking (years)		*p* for trend = 0.047
	9–15	1.02 (0.6–1.7)	
	16–18	1.3 (0.8–1.9)	*p* for trend = 0.015
	≥ 19	1.5 (1.0–2.4)	
	Pack–years		
	≤ 10	1.2 (0.8–1.8)	
	11–20	1.8 (1.2–2.9)	
	≥ 21	1.1 (0.7–1.9)	
	Years since quitting		
	1–9	1.6 (0.98–2.8)	
	10–19	0.98 (0.6–1.6)	
	≥ 20	1.04 (0.6–1.9)	
	High exposure to active and passive smoking	1.8 (1.2–2.7)	

Table 2.1.9.3. Additional cohort studies on tobacco smoking and breast cancer: main characteristics of study design

Reference	Cohort sample	Cases/deaths identification	Comments
Bennicke *et al.* (1995) Denmark 1989–91	All women referred for mammography to the radiology department of a large public hospital, aged 15–92 years	Diagnosis of breast cancer from mammography and clinical examination	Former smokers were included in the ‘smoker’ category.
van den Brandt *et al.* (1995) Netherlands 1986–89	62 573 women aged 55–69 years (all menopausal); cases taken from entire cohort; controls taken from a subcohort of 1716 randomly sampled subjects	Incident cases	Case–control approach without matching; controls excluded cancers other than skin cancer.
Thomas *et al.* (1997) China 1989–91	267 040 women working in the Shanghai Textile Industry Bureau, recruited for a randomized trial of breast self-examination, born 1925–58	Cases identified primarily by trial workers during visits to the factory’s medical clinic	
Million Women Study Group (1999) UK 1996–99	121 000 women aged 50–64 years recruited nationwide when invited for routine breast screening; response rate, 71%	Cases identified by linkage with screening centres	Study designed primarily to investigate use of hormone replacement therapy and risk of breast cancer

Table 2.1.9.4. Cohort studies on tobacco smoking and breast cancer

Reference Country and years of study	Name of study No. of subjects	No. of cases	Smoking categories	Relative risk (95% CI)	Comments
Hiatt & Fireman (1986) (USA) 1964–80	Kaiser Permanente Medical Care Program Study 84 172 women	1363 cases		Incidence rate	Annual age-adjusted rate per 1000 person–years Relative risks are comparable for pre- and post-menopausal women.
			Current smoker	1.4	
			Former smoker	1.6	
			Nonsmoker	1.3	
				RR	
			Former smoker	1.2 (1.0–1.4)	
			Current smoker		
			Light	1.0 (0.8–1.1)	
			Moderate	1.2 (1.1–1.4)	
			Heavy	1.2 (0.9–1.6)	
Vatten & Kvinnsland (1990) (Norway) 1974–88	Norwegian Screening Study 24 329 women	242 cases		Incidence rate ratio	Adjusted for age at entry, age at diagnosis, occupation and body-mass index
			Cigarettes/day		
			1–9	1.2 (0.9–1.7)	
			≥ 10	0.9 (0.6–1.2)	
			Cases < 51 years		
			1–9 cigarettes/day	1.1 (0.7–1.7)	
			≥ 10 cigarettes/day	0.8 (0.5–1.2)	
			Cases ≥ 51 years		
			1–9 cigarettes/day	1.0 (0.6–1.7)	
			≥ 10 cigarettes/day	0.8 (0.5–1.3)	
Tverdal *et al.* (1993) (Norway) 1972–88	Norwegian Screening Study 24 535 women	70 deaths		Mortality rate	Annual mortality rate per 100 000 women Adjusted for age and area
			Never-smoker	19.9	
			Former smoker	18.8	
			Current smoker	28.0	
			1–9 cigarettes/day	29.4	
			≥ 10 cigarettes/day	24.8	

Table 2.1.9.4 (contd)

Reference Country and years of study	Name of study No. of subjects	No. of cases	Smoking categories	Relative risk (95% CI)	Comments
Calle *et al.* (1994) (USA) 1982–88	CPS II 604 412 women	880 deaths		Rate ratio	Adjusted for family history of breast cancer, body-mass index, education, alcohol consumption, breast cysts, age at first birth, age at menarche and age at menopause
			Former smoker	0.9 (0.7–1.03)	
			Ever-smoker	1.0 (0.9–1.19)	
			Current smoker	1.3 (1.1–1.5)	
			≥ 40 cigarettes/day	1.7 (1.2–2.6)	
			≥ 40 years	1.4 (1.1–1.8)	
			Age at starting smoking		
			< 16 years	1.6 (1.2–2.2)	
Bennicke *et al.* (1995) (Denmark) 1989–91	3240 women	230 cases	*Duration (years)*		Adjusted for age, parity, breastfeeding, family history of breast cancer and previous gynaecological surgery
			1–10	1.1 (0.6–2.4)	
			11–20	0.9 (0.5–1.7)	
			21–30	1.3 (0.8–2.1)	
			≥ 31	1.6 (1.1–2.3)	
Engeland *et al.* (1996) (Norway) 1966–93	Norwegian Cohort Study	41	Former smoker	1.1 (0.8–1.5)	
		138	Current smoker	1.0 (0.8–1.2)	
Nordlund *et al.* (1997) (Sweden) 1964–89	Swedish Census Study	996	Former smoker	1.2 (0.9–1.7)	
			Current smoker	0.95 (0.8–1.1)	
			Cigarettes/day		
			1–7	0.9 (0.7–1.1)	
			8–15	1.04 (0.8–1.4)	
			≥ 16	1.07 (0.7–1.7)	
			Age at starting smoking (years)		
			20–23	0.99 (0.6–1.5)	
			< 19	1.2 (0.8–1.8)	*p* for trend = 0.35

Table 2.1.9.4 (contd)

Reference Country and years of study	Name of study No. of subjects	No. of cases	Smoking categories	Relative risk (95% CI)	Comments
Egan *et al.* (2002) (USA) 1976–96	Nurse's Health Study 78 206 women	3140 cases	Current smoker Former smoker *Age at starting smoking (years)* 19–20 17–18 < 17	1.0 (0.9–1.2) 1.1 (1.0–1.2) 1.1 (1.0–1.2) 1.0 (0.9–1.1) 1.2 (1.0–1.4)	Smoking status ascertained at baseline and updated biennially from 1978–94. Adjusted for current age, age at menarche, age at first birth and parity, history of benign breast disease, family history of breast cancer in mother or sister, menopausal status and age at menopause, weight at age 18 years, adult weight change, adult height, g alcohol/week, total carotenoid intake and menopausal hormone use (current, former, never)

CI, confidence interval

Table 2.1.9.5. Relative risk of breast cancer in ever- versus never-smokers by study design and country

Study (country) Reference	No. of cases/ controls	% ever smoked cases/controls	Relative risk of breast cancer in ever-versus never-smokers (standard error)
I. Cohort studies			
Nurses Health Study (USA) Willett *et al.* (1987)	1224/5599	49/49	1.01 (0.07)
Iowa Women's Health (USA) Gapstur *et al.* (1992)	679/2725	25/26	0.93 (0.10)
Canadian NBSS (Canada) Friedenreich *et al.* (1993)	181/662	35/35	1.25 (0.23)
Netherlands Cohort (Netherlands) van den Brandt *et al.* (1995)	119/504	27/30	0.89 (0.23)
American Cancer Society (CPS II) (USA) Thun *et al.* (1997)	213/922	34/33	1.07 (0.19)
Million Women Study (UK) (1999)	324/1291	50/44	1.24 (0.15)
Other Hiatt & Bawol (1984); Mills *et al.* (1989); Land *et al.* (1994); Thomas *et al.* (1997)	1932/7655	4/5	0.78 (0.12)
All cohort studies	**4663/19 398**	**25/26**	**1.00 (0.04)**
II. Case–control studies, population controls			
Brinton (USA) Harvey *et al.* (1987)	649/872	29/26	1.12 (0.14)
Rohan (Australia) Rohan & McMichael (1988)	188/213	35/32	1.06 (0.31)
CASH (USA) Chu *et al.* (1989)	1817/1821	49/43	1.28 (0.08)
Bain/Siskind (Australia) Siskind *et al.* (1989)	248/514	32/29	1.31 (0.26)
Clarke (Canada) Rosenberg *et al.* (1990)	114/211	40/42	0.88 (0.31)
(Denmark) Ewertz (1991)	227/198	59/57	0.88 (0.27)
Paul & Skegg (New Zealand) Sneyd *et al.* (1991)	538/1058	43/41	1.09 (0.13)
Yang & Gallagher (Canada) Yang *et al.* (1992)	505/517	48/44	1.15 (0.17)
Long Island (USA) Weinstein *et al.* (1993)	153/208	37/34	0.99 (0.32)

Table 2.1.9.5 (contd)

Study (country) Reference	No. of cases/ controls	% ever smoked cases/controls	Relative risk of breast cancer in ever-versus never-smokers (standard error)
Rookus & van Leeuwen (Netherlands) (1994)	247/247	52/51	0.90 (0.21)
UK studies (UK) Smith *et al.* (1994)	655/662	47/45	1.08 (0.13)
Daling (USA) White *et al.* (1994)	211/286	42/42	0.87 (0.21)
Four-state study (USA) Longnecker *et al.* (1995a)	1507/2247	39/39	1.07 (0.09)
Ross & Paganini-Hill (USA) Longnecker *et al.* (1995b)	578/590	53/52	1.02 (0.13)
(Slovenia) Primic-Zakelj *et al.* (1995)	115/128	29/30	0.67 (0.38)
Stanford/Habel (USA) Rossing *et al.* (1996)	152/181	52/49	0.79 (0.26)
WISH (USA) Swanson *et al.* (1997)	353/241	59/68	0.63 (0.21)
Bernstein (USA) Enger *et al.* (1999)	336/317	50/48	1.18 (0.20)
Magnusson (Sweden) Magnusson *et al.* (1999)	1311/1312	32/33	0.91 (0.08)
McCredie & Hopper (Australia) McCredie *et al.* (1998); Hopper *et al.* (1999)	774/518	38/36	1.03 (0.15)
Chang-Claude (Germany) Chang-Claude *et al.* (2000)	168/251	46/52	0.94 (0.25)
Johnson (Canada) Johnson *et al*. (2000)	974/1110	42/40	1.14 (0.11)
Other Lee *et al.* (1987); Adami *et al.* (1988); Yuan *et al.* (1988); Ursin *et al.* (1992); Wang *et al.* (1992); Morabia *et al*. (1996); Viladiu *et al.* (1996); Gao *et al.* (2000)	2851/3567	11/13	0.99 (0.12)
All case–control studies, population controls	**14 671/17 269**	**36/35**	**1.07 (0.03)**
III. Case–control studies, hospital controls			
Le Gerber & Clavel (France) Le *et al.* (1986); Richardson *et al.* (1989); Clavel *et al.* (1991)	492/923	18/24	0.82 (0.16)

Table 2.1.9.5 (contd)

Study (country) Reference	No. of cases/ controls	% ever smoked cases/controls	Relative risk of breast cancer in ever-versus never-smokers (standard error)
Franceschi (Italy) La Vecchia *et al.* (1987); Ferraroni *et al.* (1998)	831/1025	31/31	1.01 (0.12)
La Vecchia (Italy) La Vecchia *et al.* (1989)	980/1034	28/30	0.82 (0.10)
Vessey (UK) Meara *et al.* (1989)	154/171	44/53	0.71 (0.30)
Katsouyanni (Greece) Katsouyanni *et al.* (1994)	219/462	21/24	1.28 (0.29)
Other Ferraroni *et al.* (1993); Levi *et al.* (1996)	245/550	20/26	0.72 (0.25)
All case–control studies, hospital controls	**2921/4165**	**27/29**	**0.89 (0.06)**
All studies	**22 255/40 832**	**33/30**	**1.03 (0.02)**

From Collaborative Group on Hormonal Factors in Breast Cancer Study (2002)

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2.1.10 *Cervical cancer*

A positive correlation between the incidence of cervical cancer and other cancers known to be related to cigarette smoking across populations prompted the hypothesis that smoking may affect the risk for cervical cancer (Winkelstein, 1977). Excess risk for cervical cancer among smokers has been observed in a number of case–control studies. However, the extent to which the relationship between smoking and cervical cancer reflected a causal association independent of infection with human papillomavirus (HPV) remained a cause for concern. It was believed that the association of smoking with cervical cancer may be causal, may reflect confounding or risk modification among women with HPV infection, or may even reflect causality via an effect of smoking on risk for HPV infection.

In the earlier IARC evaluation of tobacco smoking (IARC, 1986), the Working Group noted that the effect of smoking is confounded by sexual behaviour variables, but the data were not adequate to remove the confounding effect, and that a reasonable conclusion from the available studies of invasive cervical cancer is that the results, although they indicate a positive effect of smoking, are compatible with the residual effects of variables that play a fundamental role in the etiology of cervical cancer (IARC, 1986). At the time of the 1986 review, a specific causal agent had not been identified, but was proposed to be an infective agent related to sexual activity.

Infection with HPV is now recognized as the main etiological factor for invasive and pre-invasive cervical neoplasia worldwide (IARC, 1995). Persistent infection with certain high-risk types of HPV, i.e. HPV 16, 18, 31, 33, 45, 52 and 58, is considered to be a necessary cause of invasive cervical cancer (IARC, 1995). Using the most sensitive polymerase chain reaction-based assays, HPV DNA has been found in 99.7% of approximately 1000 cervical cancer specimens from 22 countries worldwide (Walboomers *et al.*, 1995) and odds ratios close to 100.0 for high-risk HPV types have been obtained in numerous case–control studies (IARC, 1995). Co-factors acting in conjunction with HPV, however, could be important for the development of cervical neoplasia or invasive cervical cancer. In order to investigate the possibility that smoking acts as a co-factor in conjunction with HPV in the production of cervical cancer, it is important to account accurately for the presence of HPV infection. Less than 10% of invasive cervical cancers have a histology of adenocarcinoma or adenosquamous-cell carcinoma, whereas squamous-cell types account for over 90%. This review, therefore, focuses on squamous-cell invasive cervical cancer; data for adenocarcinoma and adenosquamous-cell carcinoma are used for comparative purposes.

Ten cohort studies and 31 case–control studies have provided information about the association of cigarette smoking with the incidence of invasive squamous-cell cervical cancer and six cohort studies and 22 case–control studies evaluated the association of tobacco smoking with preinvasive neoplasms (cervical intraepithelial neoplasia (CIN) and cervical cancer *in situ*). In addition, seven case–control studies evaluated the association of adenocarcinoma and adenosquamous-cell carcinoma with tobacco smoking. The characteristics of and the main results from these studies are shown in Tables 2.1.10.1–2.1.10.12 (see Tables 2.1, 2.1.10.1 and 2.1.10.2 for details on study design). These tables are organized by type of disease and level of control for HPV status. HPV status was controlled for in data analysis or by restriction of analyses to HPV-positive cases and controls. Twenty-eight of the earliest case–control studies of invasive squamous-cell cervical cancer and 25 case–control studies and one cohort study on the association of CIN with smoking did not control for HPV status (Tables 2.1.10.3–2.1.10.6). Four case–control studies of invasive cervical cancer (Peng *et al*., 1991; Chichareon *et al*., 1998; Ngelangel *et al*., 1998; Lacey *et al*., 2001), and one cohort study (Moscicki *et al*., 2001) and four case–control studies (Muñoz et *al*., 1993; Ho *et al*., 1998; Yoshikawa *et al*., 1999; Kjellberg *et al*., 2000) of CIN controlled for HPV status by adjustment in the data analysis (Tables 2.1.10.7–2.1.10.9). More recent studies controlled for HPV status by restricting analyses to HPV-positive cases and controls. The results of eight case–control studies of invasive squamous-cell cervical cancer (Bosch *et al*., 1992; Eluf-Neto *et al*., 1994; Chaouki *et al*., 1998; Chichareon *et al*., 1998; Ngelangel *et al*., 1998; Rolon *et al*., 2000; Hildesheim *et al*., 2001; Santos et al., 2001) and two case–control studies of CIN (Olsen *et al*., 1998; Deacon *et al*., 2000) are shown in Tables 2.1.10.10 and 2.1.10.11. In addition, the results of six case–control studies that examined the association of adenocarcinoma and adenosquamous-cell carcinoma with tobacco (Brinton *et al*., 1986; Ursin *et al*., 1996; Chichareon *et al*., 1998; Ngelangel *et al*., 1998; Lacey *et al*., 2001; Madeleine *at al*., 2001) are shown in Table 2.1.10.12.

In these studies, the association between cervical cancer and smoking was not eliminated, even though most studies controlled for several well-established risk factors for cervical cancer, including early age at first sexual intercourse, history of multiple sexual partners, low socioeconomic status and, in the recent studies, infection with HPV. Most studies in which the risk values were not adjusted for HPV infection reported a relative risk of approximately 2.0 among smokers compared with nonsmokers. Women who had smoked for a long period or at high intensity generally had the highest risk. In several studies, the relationship was restricted to, or strongest among, recent or current smokers. Some studies reported that the highest risk occurred among women who had started smoking late in life, but other studies reported the opposite effect, namely a higher risk among women who had begun smoking at young ages (La Vecchia *et al*., 1986; Daling *et al*., 1996). In the studies that assessed the association of adenocarcinoma and adenosquamous-cell carcinoma of the cervix with smoking, there was generally no significant association noted for adenocarcinoma or adenosquamous-cell carcinoma of the cervix.

Recent studies have chosen to control for the confounding effect of HPV as indicated by either the presence of HPV DNA in cervical cells or of anti-HPV serum antibodies in multivariate analytical models, or have restricted their analyses to HPV-positive cases and controls.

Several of the studies reviewed, including the IARC multicentre pooled analysis of 10 studies of invasive cervical cancer (Plummer *et al*., 2003), examined tobacco smoking as a co-factor to HPV infection by restricting the analysis to HPV DNA-positive study participants, a decision justified by the necessity of HPV infection in the causation of invasive cervical cancer (Hildesheim *et al*., 2001). The results from these analyses showed no significant alteration in risk whether or not the study participants were HPV DNA-positive. Similarly, other studies that investigated the effect of smoking among HPV-seropositive cases and controls found that the effect of smoking remained, and there was evidence of a dose–response relationship. The association between smoking and invasive cervical cancer was not notably reduced by adjustment for a woman's reported number of lifetime sexual partners, age at first sexual intercourse or other potential confounding factors (Hildesheim *et al*., 2001). Thus, the effect of smoking is unlikely to represent a surrogate marker for a woman's sexual behaviour.

Cervical infection with HPV has not been found to be consistently associated with tobacco smoking in cross-sectional studies (Plummer *et al*., 2003). Therefore, it would appear that HPV is not a significant confounding factor for the association between cervical cancer and smoking.

The detection of HPV DNA has a different meaning for cases and control participants. In cases, HPV DNA-positivity indicates a persistent HPV infection, whereas some control participants may have a transient HPV infection or have been infected with HPV in the past and have cleared their infection. Given that the ascertainment of overall HPV prevalence and the relative distribution of HPV types may differ according to status as case or control, careful account of the type of HPV infection (such as high-risk versus low-risk types) must be taken.

Persistent cervical infections with HPV have been shown to increase the risk of progression of cervical dysplasia (Remmink *et al*., 1995). As there is currently no reliable marker of persistent HPV infection, case–control studies based on a cross-sectional measurement of HPV-DNA by polymerase chain reaction assays cannot distinguish between transient and persistent infections (Franco *et al*., 1999). To improve the likelihood that the effect being examined is that of smoking among persistent HPV carriers, analyses by some investigators were limited to women who were HPV-DNA-positive for high-risk HPV types that are more likely to represent persistent infections than non-oncogenic types (Franco *et al*., 2001). Increased rate ratios for smoking were observed in one study that conducted these analyses (Hildesheim *et al*., 2001).

Table 2.1.10.1. Case–control studies on tobacco smoking and cervical cancer: main characteristics of study design

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Tokuhata (1967) USA Not specified	266 cases and 1463 controls	Population-based study Cases and controls selected from county death registry among women ever married and having died after 1950 Controls: breast cancer, heart and other non-cancerous diseases City and county directories used to identify next-of-kin Response rates ≥ 95% for both cases and controls
Thomas (1972) USA 1965–69	324 cases, aged 15–50 years, and 302 controls	Hospital-based study Cases histologically confirmed Controls: 1:30 probability sample of the 15–50-year-old white female residents of the county having at least one smear on record from 1965–69
Williams & Horm (1977); Williams *et al.* (1977) USA, Not specified	266 cases and 3198 controls	Cases and controls from the Third National Cancer Survey (57% of those selected for interview). Controls included all cases of cancer of other sites except lung, larynx, oral cavity, oesophagus and bladder [no matching].
Harris *et al.* (1980) UK 1974–79	237 cases and 422 controls	Hospital-based study at two Oxford hospitals Controls attended gynaecological clinics during a similar period to the cases; a few additional controls had received an initial cervical smear at the Abingdon Health Centre; excluding controls who had had hysterectomy or with history of cancer or severe mental illness
Stellman *et al.* (1980) USA 1974–77	332 cases and 1725 controls, aged 20–89 years	Hospital-based study Cases histologically confirmed Controls hospitalized for non-neoplastic diseases Analysis restricted to ever-married women, excluding former smokers
Wigle *et al.* (1980) Canada 1971–73	676 cases (168 ICC and 508 CIS) and 3644 controls, aged 20–64 years	Hospital-based study Cases histologically confirmed Controls comprised women with primary cancers unrelated to smoking and with benign breast neoplasms.

Table 2.1.10.1 (contd)

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Buckley *et al.* (1981) UK 1974–79	237 cases and 422 controls, aged 32–70 years	Hospital-based study Cases histologically confirmed Controls were women attending gynaecological care units for cervical smears, excluding those who had had hysterectomy or abnormal smear.
Clarke *et al.* (1982) Canada 1973–76	178 cases, aged 20–69 years, and 865 controls matched on age	Population-based study among residents of York County, Toronto Cases histologically confirmed Controls selected from the same neighbourhood as the cases
Berggren & Sjöstedt (1983) Sweden 1974–78	609 cases and 6090 controls, aged 15–65 years	Population-based study Cases histologically confirmed Controls were residents of the same geographical area as the cases, born on the same day as the cases or soon thereafter, excluding women with previous history of cervical cancer or abnormal smear.
Lyon *et al.* (1983) USA 1975–77	217 cases and 243 controls	Population-based study among residents of the metropolitan area of Utah Cases histologically confirmed Controls selected by random-digit dialling to give an age- and geographically stratified sample of the same population
Marshall *et al.* (1983) USA 1957–65	513 cases and 490 controls matched on age	Hospital-based study Cases histologically confirmed Controls selected from a pool of patients with non-neoplastic diseases of sites other than the genitourinary and gastrointestinal tracts
Trevathan *et al.* (1983) USA 1980–81	374 (194 mild/moderate dysplasia, 81 severe dysplasia, 99 *in situ*) cases, aged 17–55 years, and 288 controls	Hospital-based study Cases histologically confirmed Controls with negative Pap smears and no prior cervical biopsy selected from women attending the Family Planning Clinic
Martin & Hill (1984) South Africa 1950–74	257 case–control pairs, matched on age, number of children and home area (age range, 22–89 years)	Hospital- and population-based study [% of histologically confirmed cases not indicated Controls free of cancer (no information on selection of controls)]

Table 2.1.10.1 (contd)

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Clarke *et al.* (1985) Canada 1979–81	250 cases aged 20–59 years, and 500 controls matched on age, neighbourhood and type of dwelling	Population-based study among residents of the Toronto area Cases histologically confirmed Controls with intact uterus and no history of cancer identified from municipal records
Mayberry (1985) USA Not specified	210 cases and 317 controls (data from previous study on HSV-2 and *Chlamydiae trachomatis* and cervical cancer)	Hospital-based study Cases histologically confirmed Controls free of cervical abnormalities who attended gynaecological and birth control clinics at the University of California Medical Center in San Francisco
Baron *et al.* (1986) USA 1957–75	1174 cases aged 40–89 years, and 2128 controls	Hospital-based study Controls in the same age range, admitted during the same time period, with no diagnosis of cancer during hospitalization and no smoking-associated respiratory or circulatory diseases
Brinton *et al.* (1986) USA 1982–84	480 cases (incl. 63 adenocarcinoma or adenosquamous carcinoma), aged 20–74 years, and 797 controls, matched on telephone exchange, race and age	Population-based study in five cities reporting to the Comprehensive Cancer Patient Data System – Birmingham (AL), Chicago, Denver, Miami and Philadelphia Controls obtained by random-digit dialling
La Vecchia *et al.* (1986) Italy 1981–84	155 ICC (aged 22–74 years) and 169 controls 89 CIN (aged 19–71 years) and 118 controls Cases and controls matched on age	Hospital-based study in six wards of three major university hospitals in Milan Cases histologically confirmed Controls for ICC admitted for acute conditions other than malignant, hormonal or gynaecological disorders; controls for CIN were women with normal cervical smear from the same screening clinics
Peters *et al.* (1986) USA 1980–81	200 cases and 200 controls, matched on race, date of birth and language of interview	Population-based study Cases histologically confirmed Controls identified by an algorithm defining a sequence of houses in the neighbourhood where the case lived at diagnosis

Table 2.1.10.1 (contd)

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Celentano *et al.* (1987) USA 1982–85	153 cases and 153 controls, matched on age, race, residence within neighbourhood, intact uterus	Population-based study among Maryland residents referred to the Division of Gynecologic Oncology at John's Hopkins Hospital, MD Cases histologically confirmed Controls without history of cervical cancer obtained by case nomination (97), canvassing neighbourhood (49) and from senior citizen centres (7)
Ebeling *et al.* (1987) Germany 1983–85	129 cases and 275 controls	Hospital-based study Cases histologically confirmed Controls identified at the Skin Disease Hospital and at the Orthopaedic University Hospital, which drew patients from the same area as the gynaecological hospitals; women with venereal diseases, prior CIN and prior hysterectomy excluded
Nischan *et al.* (1988) Germany 1983–85	225 cases, aged 64 years or younger, and 435 controls, matched on age	Hospital-based study in four hospitals in Leipzig Cases histologically confirmed Controls, excluding women with venereal diseases, prior CIN and prior hysterectomy, identified at the Skin Disease Hospital and at the Orthopaedic University Hospital
Brock *et al.* (1989) Australia 1980–83	116 cases, aged 18–65 years, and 193 controls, matched on age	Population-based study within the Sydney metropolitan area Cases histologically confirmed Controls selected from the files of the family doctor or from a university-affiliated general practitioner from the same residential area
Herrero *et al.* (1989) Colombia, Costa Rica, Mexico, Panama 1986–87	667 cases, aged less than 70 years, and 1430 controls	Hospital- and community-based study Cases histologically confirmed Hospital controls selected from primary referral hospitals (Costa Rica and Panama); from eight tertiary level government hospitals (Bogota); and from three Social Security hospitals (Mexico City); all hospitals located in the area of residence of the cases Community controls randomly selected from current census listings of the corresponding case's county of residence
Slattery *et al.* (1989) USA 1984–87	266 cases, aged 20–59 years, and 408 controls, matched on age and residence	Population-based study in the urban areas of Utah Cases histologically confirmed Controls selected using random-digit dialling; women who had had a hysterectomy before 1984 excluded

Table 2.1.10.1 (contd)

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Licciardone *et al.* (1989) USA 1984–86	331 cases and 993 controls matched on age	Cancer registry-based study Cases histologically confirmed Controls randomly selected from other patients reported to the Missouri Cancer Registry during the same time period after exclusion of cancers at smoking- or alcohol-related sites
Cuzick *et al.* (1990) UK 1984–88	497 cases (110 CIN I, 103 CIN II, 284 CIN III), aged 18–39 years, and 833 controls	Population-based study in the London area Cases histologically confirmed Controls: randomly selected patients of local general practitioners or family planning clinics in the catchment area from which cases were drawn
Jones *et al.* (1990) USA 1982–84	293 cases, aged 20–74 years, and 801 controls, matched on race and age	Population-based study in Birmingham, Chicago, Denver, Miami and Philadelphia Controls ascertained using random-digit dialling
Peng *et al.* (1991) China 1987–88	101 cases, and 146 controls selected to provide a similar distribution of age and occupation	Hospital-based study in Chengdu, Sichuan Cases histologically confirmed Controls: patients admitted to the gynaecological ward/clinic, excluding women with abnormal cervical cytology, prior hysterectomy, or vulvar cancer
Bosch *et al.* (1992, 1993); Muñoz *et al.* (1992, 1993) Spain, 1985–87 Colombia, 1985–88	525 cases, aged less than 70 years, and 512 controls, matched on age, place of recruitment and date of cytology	Population-based study in nine provinces in Spain and in one city in Colombia (Cali) Cases histologically confirmed Controls with normal cytology or with inflammation only (Pap smear grades I and II) randomly selected from the population that generated the cases; included only those women who had not had previous treatment for cervical cancer or a hysterectomy.
Coker *et al.* (1992) USA 1987–88	103 cases (40 CIN II and 63 CIN III), aged 18–45 years, and 268 controls	Hospital-based study in North Carolina Cases histologically confirmed Controls: University of North Carolina Hospital Family Practice Center patients receiving routine Pap smear and having normal cervical cytology
Parazzini *et al.* (1992) Italy 1981–90	366 cases (58 CIN I, 70 CIN II, 238 CIN III), aged 18–59 years, and 323 controls with comparable age distribution	Hospital-based study in Milan Cases histologically confirmed Controls: women with normal cervical smears interviewed at the same screening clinic where cases were identified

Table 2.1.10.1 (contd)

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Becker *et al.* (1994) USA 1989–92	201 cases, aged 18–40 years, and 307 controls	Hospital-based study in the Albuquerque metropolitan area Cases histologically confirmed Frequency-matched controls, with normal cervical cytology, selected from the same clinics to which cases were referred for colposcopic examination
Eluf-Neto *et al.* (1994) Brazil 1990–91	199 cases, aged 25–79 years, and 225 controls, matched on age	Hospital-based study in seven hospitals in São Paulo City Cases histologically confirmed Controls selected from the same hospitals, excluding women with known risk factors for cervical neoplasia, treated for gynaecological conditions, or having had hysterectomy or conization
de Vet *et al.* (1994) Netherlands Not specified	257 cases, aged 20–65 years, and 705 controls, matched on age	Multicentre randomized clinical trial Cases histologically confirmed Controls: random sample of the female population of three cities and one neighbouring village for each city; subjects with recent pregnancy, diabetes mellitus or severe bowel or liver dysfunction excluded
Lazcano-Ponce *et al.* (1995) Mexico 1990–92	397 ICC, 233 CIN III and 1005 controls	Population-based study Cases histologically confirmed Controls: random sample from houses in the Mexico City metropolitan area
Stone *et al.* (1995) Costa Rica 1982–85	564 cases (415 carcinoma *in situ*, 149 invasive cancer), aged 25–59 years, and 764 controls, matched on age	Population-based study Cases histologically confirmed, identified through the Costa Rican National Tumor Registry Controls selected from a national multistage probability household survey
Cuzick *et al.* (1996) UK 1985–91	121 cases, aged 40 years or younger, and 241 controls, matched on age	Population-based study Cases histologically confirmed Controls drawn from the same general practitioner as the cases
Daling *et al.* (1996) USA 1986–92	314 cases, aged 18–74 years, and 672 controls, matched on age	Population-based study Cases histologically confirmed Controls identified using random-digit dialling

Table 2.1.10.1 (contd)

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Hirose *et al.* (1996) Japan 1988–93	556 cases, aged 18 years or older, and 26 751 controls	Hospital-based study Cases histologically confirmed Controls: first-visit outpatients with no prior diagnosis of cancer
Kjaer *et al.* (1996) Denmark 1987–88	645 cases (586 carcinoma *in situ*, 59 invasive cancer), aged 20–49 years, and 614 controls, matched on age	Population-based study among women living in greater Copenhagen Cases histologically confirmed Controls identified by random sampling using the computerized Danish Central Population Register
Ursin *et al.* (1996) USA 1977–91	195 cases and 386 controls, matched on age, race and neighbourhood	Population-based study in Los Angeles County, CA Cases histologically confirmed Controls identified by visiting houses in the cases' neighbourhood according to a predetermined algorithm
Chaouki *et al.* (1998) Morocco 1991–93	214 cases, aged 18–80 years, and 203 controls, matched on age	Hospital-based study in Rabat Cases histologically confirmed Controls from the same cancer hospital and a nearby general hospital, excluding women with a history of hysterectomy or conization, and conditions related to risk factors for cervical neoplasm (other anogenital cancers, cancers of the breast, oral cavity, oesophagus, lung, bladder and liver, cardiovascular diseases, chronic bronchitis, emphysema and sexually transmitted diseases)
Chichareon *et al.* (1998) Thailand 1990–93	338 cases (including 39 with adenocarcinoma/adenosquamous carcinoma) and 261 controls	Hospital-based study in Hat-Yai Cases histologically confirmed Age-stratified controls without anogenital tract cancers, cancers of the breast, endometrium, ovary, colon, benign genital tumours, tobacco-related diseases or history of conization or hysterectomy, selected from the same hospital
Ho *et al.* (1998) USA 1992–94	258 women with HPV infection (163 CIN I, 51 CIN II and 44 CIN III)	Hospital-based study in New York Cases histologically confirmed Reference population constituted of women with CIN I. Eligibility criteria included having had cervical biopsy and/or endocervical curettage on the day of recruitment, not being pregnant, no history of cancer and having an intact cervix

Table 2.1.10.1 (contd)

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Kanetsky *et al.* (1998) USA 1993–95	32 cases (12 CIN I, 10 CIN II, 9 CIN III/CIS, 1 ungradable CIN), aged 18 years and above, and 113 controls	Hospital-based study at the Harlem Hospital Center Cases histologically confirmed Controls: HIV-negative, black, non-Hispanic women with normal cervical cytology recruited from the gynaecology and family planning clinics
Ngelangel *et al.* (1998) The Philippines 1991–93	356 cases (including 33 with adenocarcinoma/adenosquamous carcinoma) and 381 controls matched on age	Hospital-based study in Manila Cases histologically confirmed Controls without diseases associated with known risk factors for cervical neoplasia and no history of conization or hysterectomy, selected from the same hospital
Olsen *et al.* (1998) Norway 1991–92	90 cases (10 CIN II, 80 CIN III), aged 20–44 years, and 216 controls	Population-based study in Oslo Cases histologically confirmed Controls without cervical dysplasia enrolled from an age-stratified random sample of women obtained through the Norwegian Central Population Register
Parazzini *et al.* (1998) Italy 1981–93	261 cases, aged less than 45 years, and 257 controls	Hospital-based study Cases histologically confirmed Controls aged less than 45 years, admitted to the same network of hospitals for acute conditions unrelated to cervical cancer risk factors, and belonging to the same catchment areas as cases
Hsieh *et al.* (1999) China, Province of Taiwan Not specified	183 cases and 293 controls, matched on age, marital status and residential area	Population-based study in Taipei Cases histologically confirmed Controls randomly selected from local household registration offices
Yoshikawa *et al.* (1999) Japan 1995–96	167 cases (94 CIN I, 40 CIN II, 33 CIN III), aged 55 years or younger, and 167 controls, matched on age and hospital	Hospital-based study in nine hospitals Cases histologically confirmed Controls selected from subjects with normal cervical cytology
Kjellberg *et al.* (2000) Sweden 1993–95	122 cases, aged 25–59 years, and 346 controls	Population-based study in northern Sweden Cases histologically confirmed

Table 2.1.10.1 (contd)

Reference[a] Country and years of study	Number of cases and controls	Criteria for eligibility and comments
Rolon *et al.* (2000) Paraguay 1988–90	113 cases, aged 18–85 years, and 91 controls, matched on age	Hospital-based study in Asunción Cases histologically confirmed Controls without cervical cancer and with no history of conization or hysterectomy selected from outpatient clinics at the same hospitals; exclusion criteria included diseases associated with cervical cancer risk factors (anogenital tract cancers, tobacco-related diseases and cancer of the breast, endometrium, ovary or colon)
Lacey *et al.* (2001) USA 1992–96	263 cases (124 adenocarcinoma, 139 squamous-cell carcinoma), aged 18–69 years, and 307 controls, matched on age, race and geographical region	Multicentre population-based study Cases histologically confirmed Controls identified through random-digit dialling, excluding women with hysterectomy
Madeleine *et al.* (2001) USA 1990–96	150 cases, aged 18–70 years, and 651 controls, matched on age	Population-based study Cases histologically confirmed, identified through the SEER Cancer Surveillance System Controls identified using random-digit dialling among residents at reference date of the 13-county area in western Washington state; women with an intact uterus, who spoke English
Santos *et al.* (2001) Peru 1996–97	198 cases (173 squamous-cell carcinomas and 25 adenocarcinoma/adenosquamous carcinomas) and 196 controls, matched on age	Hospital-based study in two hospitals in Lima Cases histologically confirmed Controls selected from women without cervical cancer or history of conization or hysterectomy, attending the same hospitals; exclusion criteria included diseases associated with known risk factors for cervical cancer (cancers of the anogenital tract, tobacco-related cancers and cancer of the breast, endometrium, ovary or colon)

[a] Studies published after 1986, or before 1986 but not included in Volume 38 of the *IARC Monographs*
ICC, invasive cervical cancer; CIS, carcinoma *in situ*; CIN, cervical intraepithelial neoplasia

Table 2.1.10.2. Description of additional cohort studies on tobacco smoking and cervical cancer, cervical intraepithelial neoplasia (CIN) and carcinoma *in situ* (CIS) (with or without control for human papilloma virus (HPV) status)

Reference Country and years of study	Name of study	Cohort sample	Cases/deaths identification	Comments
Wright *et al.* (1978); Zondervan *et al.* (1996) UK 1968–77	Oxford Family Planning Association Study	17 032 women recruited in 17 large family planning clinics in England and Scotland, aged 25–39 years	Cases ascertained by follow-up in clinics	
Beral *et al.* (1988) UK 1968–87	Royal College of General Practitioners' Oral Contraception Study	47 000 women aged ≥ 15 years, half of whom were using oral contraceptives at recruitment	Cases ascertained by general practitioners	Study designed primarily to investigate oral contraceptive use and female genital cancer
Gram *et al.* (1992) Norway 1979–89	Tromsö Study	8143 women aged 20–49 years living in Tromsö with at least one negative test for CIN between 1977 and 1980	Cases ascertained by linkage to the Pathology Registry of the University Hospital	Participants were followed for development of CIN III or cervical cancer
Schiffman *et al.* (1993) USA 1989–90		21 146 women presenting for routine Pap smear screening	Cases diagnosed at the Kaiser Permanente clinic	Nested case–control study without matching; HPV-positive: 81% cases, 18% controls
Ylitalo *et al.* (1999) Sweden 1969–95		146 889 women born in Sweden and resident in Uppsala between 1969 and 1995, aged ≤ 50 years, and having had at least one smear test	Cases identified through National Cancer Registry	Nested case–control study; controls randomly selected among cohort, matched by date of entry into cohort (± 90 days), year of birth; with intact uterus and without history of prior in situ or invasive cervical carcinoma
Moscicki *et al.* (2001) USA 1990–2000		496 women examined at 2 family clinics with normal cytological findings at baseline and first follow-up excluding those testing HPV-negative at any time during follow-up	Cases ascertained at the clinics	Study designed primarily to investigate development of low-grade squamous intraepithelial lesions in HPV-infected women

Table 2.1.10.3. Case–control studies on tobacco smoking and invasive cervical cancer (ICC) (without control for human papillomavirus (HPV) status)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors	Comments
	Ever	Current	Former	By quantity/duration			
Tokuhata (1967) USA Not specified	1.2						Similar in white and black women
Williams & Horm (1977) USA Not specified				*Pack–years* ≥ 20 21–39 ≥ 40	**Invasive** 1.2 1.6 1.8	After adjustment for race, no. of children, socioeconomic indicators, a 'mild' positive association remained.	266 cases
Stellman *et al*. (1980) USA 1974–77				Risk ratios for > 10 cigarettes/day ranged from 1.4 to 1.6 before adjustments and from 1.2 to 1.3 after adjustment for age and socioeconomic status, the value depending on the amount smoked. Smokers of < 10 cigarettes/day have a relative risk of < 1.			Socioeconomic status has little confounding effect; the reduction of relative risks after adjustment is due mainly to age.
Wigle *et al*. (1980) Canada 1971–73		Invasive, 2.0 CIS, 3.8	Invasive, 1.0 CIS, 1.3	*Pack–years* < 10 11–20 21–30 ≥ 31	**Invasive** 1.2 1.7 2.1 2.7	No adjustment made for social or sexual variables	
Buckley *et al*. (1981) UK 1974–79		Combined risk (dysplasia, CIS, ICC) 7.0 7.8 3.2	 2.8 3.7 2.7			 No adjustment No. of sexual partners of husband Smoking of husband	Relative risk 35 among small series of multiple-partner women with husbands who smoked versus those with nonsmoking or formerly smoking husbands

Table 2.1.10.3 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors	Comments
	Ever	Current	Former	By quantity/duration			
Clarke *et al.* (1982) Canada 1973–76		2.3 (1.6–3.3)	1.7 (1.0–2.8)	< ½ pack/day > 1 pack/day	2.2 2.9	Age, education, age at first intercourse, sexual stability	
Marshall *et al.* (1983) USA 1957–65		1.6 (1.2–2.1)	0.8 (0.5–1.4)	< ½ pack/day ½–1 packs/day 1–2 packs/day > 2 packs/day	1.7 (1.1–2.6) 1.7 (1.2–2.3) 1.0 (0.8–1.2) 0.4 (0.2–1.2)		
Baron *et al.* (1986) USA 1957–75				1–14 packs/year ≥ 15 packs/year	1.4 (1.1–1.7) 1.8 (1.5–2.2)	Age, marital status, no. of pregnancies	
Brinton *et al.* (1986) USA 1982–84	1.5 (1.1–1.9)	1.5 (1.2–2.0)	1.3 (0.9–1.9)	*Years of smoking* < 10 10–19 20–29 30–39 ≥ 40 *Cigarettes/day* < 10 10–19 20–29 ≥ 40	 1.1 (0.7–1.7) 1.6 (1.1–2.4) 1.3 (0.9–2.0) 1.5 (1.0–2.4) 2.2 (1.2–4.2) 1.1 (0.6–1.7) 1.3 (0.9–2.0) 1.5 (1.1–2.1) 2.4 (1.4–4.1)	Age, race, no. of sexual partners, age at first intercourse, education	$p < 0.001$

Table 2.1.10.3 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors	Comments
	Ever	Current	Former	By quantity/duration			
La Vecchia *et al.* (1986) Italy 1981–84			0.8 (0.4–1.7)	*Current*		Age, marital status, education, social class, sexual partners, age at first intercourse, no. of sexual partners, parity, no. of abortions at menopause, no. of previous Pap smears, use of oral contraceptives and other use of female hormones and clinical history of other sexually transmitted diseases	
				< 15 cigarettes/day	1.7 (0.8–3.4)		
				≥ 15 cigarettes/day	1.8 (0.9–3.6)		
				Total duration of smoking (years)			
				< 10	1.3 (0.6–3.1)		
				10–19	1.0 (0.4–2.1)		
				20–29	1.4 (0.7–2.8)		
				30–39	1.5 (0.6–3.1)		
				≥ 40	7.8 (1.5–39.9)		$p = 0.05$
				Age at starting smoking (years)			
				> 24	1.4 (0.81–2.4)		
				18–24	1.2 (0.59–2.3)		
				< 18	1.9 (0.7–5.4)		
Peters *et al.* (1986) USA 1980–81				*Cigarettes/day*		Race, sex, date of birth and language of interview	
				0–5	1.0		
				6–19	1.5 (0.8–2.7)		
				≥ 20	3.7 (2.0–6.9)		
				Years of smoking			Women currently smoking > 5 cigarettes/day
				0–1 year	1.0		
				2–20 years	1.5 (0.8–2.8)		
				≥ 21 years	4.0 (2.0–7.8)		$p < 0.001$
Celentano *et al.* (1987) USA 1982–85				Years of smoking	1.0 (1.0–1.0)		

Table 2.1.10.3 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors	Comments
	Ever	Current	Former	By quantity/duration			
Eberling *et al.* (1987) Germany 1983–85	1.3 (0.8–2.3)					Age, no. of pregnancies, age at first pregnancy, number of sexual partners, age at first intercourse, history of discharge, months since last Pap smear	
Nischan *et al.* (1988) Germany 1983–85	1.2 (0.8–1.7)			Never	1.0	Age, no. of sexual partners, age at first intercourse, no. of pregnancies, years since last screening test	
				< 10 years	0.7		
				10–19 years	1.3		
				20–29 years	1.7		
				≥ 30 years	2.7 ($p < 0.05$)		
Herrero *et al.* (1989) Costa Rica, Colombia, Mexico, Panama 1986–87		1.0 (0.7–1.2)	1.0 (0.8–1.3)	*Cigarettes/day*		Age, no. of sexual partners, alcohol consumption	
				< 10	1.0 (0.8–1.2)		
				10–19	1.0 (0.6–1.7)		
				20–29	1.0 (0.6–1.5)		
				≥ 30	1.1 (0.5–2.5)		$p = 0.8$
				Age at starting smoking (years)			
				> 30	1.7 (1.1–2.6)		
				21–30	0.9 (0.7–1.4)		
				16–20	0.8 (0.6–1.1)		
				< 16 years	1.1 (0.7–1.6)		
				Duration of smoking (years)			
				< 10	1.0 (0.7–1.4)		
				10–19	1.0 (0.7–1.4)		
				20–29	1.1 (0.7–1.7)		
				30–39	0.6 (0.4–1.1)		
				≥ 40	1.5 (0.8–2.8)		$p = 0.8$

Table 2.1.10.3 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors	Comments
	Ever	Current	Former	By quantity/duration			
Herrero *et al.* (1989) (contd)					**HPV negative**		
				Ever-smoker	0.9 (0.7–1.3)		
				Cigarettes/day			
				< 10	1.0 (0.7–1.5)		
				≥ 10	0.8 (0.5–1.3)		
				Age at starting smoking (years)			
				> 30	1.4 (0.7–2.9)		
				≤ 30	0.9 (0.6–1.2)		
				Duration of smoking (years)			
				< 10	1.0 (0.6–1.7)		
				10–19	1.0 (0.6–1.6)		
				> 20	0.9 (0.6–1.5)		
					HPV positive		
				Ever-smoker	6.3 (4.3–9.2)		
				Cigarettes/day			
				< 10	5.5 (3.5–8.3)		
				≥ 10	8.4 (4.4–16.2)		
				Age at starting smoking (years)			
				> 30	13.1 (5.7–29.0)		
				≤ 30	5.1 (3.4–7.8)		
				Duration of smoking (years)			
				< 10	5.7 (3.0–10.6)		
				10–19	5.9 (3.1–11.1)		
				> 20	6.6 (3.6–12.1)		
Licciardone *et al.* (1989) USA 1984–86			1.7 (1.0–2.9)	< 1 pack/day	2.2 (1.4–3.6)	Age, alcohol consumption, stage at diagnosis	
				≥ 1 pack/day	3.9 (2.7–5.6)		

Table 2.1.10.3 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors	Comments
	Ever	Current	Former	By quantity/duration			
Bosch *et al.* (1992) Spain, 1985–87 Colombia, 1985–88	1.5 (1.0–2.2)					Age, centre, HPV status by PCR, no. of sexual partners, education, age at first birth, previous cytology screening	
Eluf-Neto *et al.* (1994) Brazil 1990–91	1.5 (1.0–2.3)					Age and socioeconomic status	
Lazcano-Ponce *et al.* (1995) Mexico 1990–92				Never smoker 1st tertile 2nd tertile 3rd tertile	1.0 1.4 (0.96–2.1) 1.2 (0.78–1.8) 1.3 (0.81–1.9)	Age, socioeconomic status, age at sexual intercourse, no. of sexual partners	Tertiles of tobacco consumption
Stone *et al.* (1995) Costa Rica 1982–85	1.3 (0.9–1.3)					Age	
Cuzick *et al.* (1996) UK 1985–91		1.2 (0.7–2.3)	1.3 (0.7–2.6)	*Pack–years* 0.1–5 6–10 11–20 > 20	 1.3 (0.6–2.6) 1.8 (0.8–4.1) 0.9 (0.4–1.9) 1.7 (0.6–4.7)	No. of sexual partners, age at first intercourse	p for trend = 0.54

Table 2.1.10.3 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors	Comments
	Ever	Current	Former	By quantity/duration			
Daling *et al.* (1996) USA 1986–92		2.5 (1.8–3.4)	1.5 (1.1–2.2)	*Duration of smoking (years)*		Age, no. of lifetime sexual partners	
				< 10	1.0		
				10–19	2.4 (1.1–5.3)		
				≥ 20	2.8 (1.1–6.9)		
		1.7 (1.1–2.6)	1.5 (1.0–2.5)			Age, no. of lifetime sexual partners, HSV-2 seropositivity, oral contraceptive use of 17 years or less, HPV 16 antibody status	
Hirose *et al.* (1996) Japan 1988–93		2.2 (1.8–2.7)		*Cigarettes/day*		Age of first visit	
				< 10	1.3 (0.8–2.1)		
				≥ 10	2.5 (2.0–3.1)		
Kjaer *et al.* (1996) Denmark 1987–88	0.8 (0.4–1.5)	1.0 (0.5–1.9)	0.5 (0.1–1.9)	*Duration of smoking (years)*		Age, no. of sexual partners, use of barrier method of contraception	Crude estimates also available, showing a weak association that disappears after adjustment
				≤ 4	0.9 (0.3–2.9)		
				5–14	1.0 (0.4–2.2)		
				≥ 15	0.9 (0.4–1.8)		
				Age at starting smoking (years)			
				≥ 19	0.7 (0.2–2.1)		
				16–18	0.7 (0.7–1.7)		
				≤ 15	1.1 (0.5–2.2)		
				Cigarettes/day			
				< 10	0.5 (0.2–1.5)		
				≥ 10	1.0 (0.5–1.9)		

Table 2.1.10.3 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors	Comments
	Ever	Current	Former	By quantity/duration			
Parazzini *et al.* (1998) Italy 1981–93		1.1 (0.8–1.7)	1.3 (0.6–2.8)	*Cigarettes/day* < 5 5–14 ≥ 15	 0.9 (0.4–2.3) 1.6 (0.8–2.9) 0.9 (0.5–1.5)	Age, education, calendar year, parity, no. of sexual partners, oral contraceptive use	Subjects aged < 45 years
Hsieh *et al.* (1999) China, Province of Taiwan Not specified	1.4 (0.4–5.3)					Age, educational level, monthly family income	

CI, confidence interval; CIS, carcinoma *in situ*; PCR, polymerase chain reaction; HSV, herpes simplex virus

Table 2.1.10.4. Cohort studies on tobacco smoking and invasive cervical cancer (ICC) (without control for human papillomavirus (HPV) status)

Reference Country and years of study	Name of study	No. of cases	Smoking categories	Relative risk (95% CI)	Adjustment factors/comments
Hirayama (1975) Japan 1965–73	Six-prefecture Study 142 857 women	288 deaths	Current smoker *Cigarettes/day* < 20 20–29	1.7 1.8 3.5	Standardized mortality ratio (SMR)
Garfinkel (1980) USA 1959–72	Cancer Prevention Study (CPS) I 590 562 women	308 deaths	Nonsmoker vs entire cohort	**SMR** 0.87	
Hirayama (1985) Japan 1965–81	Six-prefecture Cohort Study	Deaths (no. not specified)	*Cigarettes/day* 1–24 ≥ 25	**SMR** 1.6 1.9	 *p* for trend < 0.0001
Beral *et al.* (1988) UK 1968–87	47 000 women	65 ICC	*Cigarettes/day* 0 1–14 > 15	 5.4 1.1 0.9	Age, parity, smoking, social class, no. of previously normal cervical smears, history of sexually transmitted diseases
Tverdal *et al.* (1993) Norway 1972–88	Norwegian Screening Study 24 535 women	23 deaths	 Nonsmoker Former smoker Current smoker *Cigarettes/day* 1–9 > 10	**Mortality rate** 5.1 5.2 11.4 **RR** 1.0 2.4 (1.0–5.5)	Age, area; annual mortality rate/100 000 women
Engeland *et al.* (1996) Norway 1966–93	Norwegian Cohort Study 14 269 women	86 cases	Current smoker *Cigarettes/day* < 5 5–9 ≥ 10	2.5 (1.6–3.9) 1.9 (1.0–3.6) 3.3 (1.9–5.8) 2.4 (1.2–4.8)	No significant difference was observed for age at start of smoking, type of cigarette or urban/rural residence.

Table 2.1.10.4 (contd)

Reference Country and years of study	Name of study	No. of cases	Smoking categories	Relative risk (95% CI)	Adjustment factors/comments
Zondervan *et al.* (1996) UK 10 years	17 000 women		*Cigarettes/day*		
			< 1 (nonsmoker)	1.0	
			1–4	0.8 (0.3–2.5)	
			> 15	3.1 (1.3–7.3)	
Nordlund *et al.* (1997) Sweden 1964–89	Swedish Census Study	138 cases	Former smoker	1.01 (0.4–2.8)	
			Current smoker	2.5 (1.7–3.7)	
			Cigarettes/day		
			1–7	2.3 (1.5–3.7)	
			8–15	2.4 (1.4–4.2)	
			≥ 16	4.0 (2.0–8.1)	
			Age at starting smoking (years)		
			20–23	0.6 (0.2–1.6)	
			< 19	1.9 (1.0–3.8)	*p* for trend = 0.06
Tulinius *et al.* (1997) Iceland 1968–95	Reykjavík Study 155 800 women	40 cases	Former smoker	1.2 (0.4–3.9)	Age
			Current smoker (cigarettes/day)		
			1–14	2.6 (1.2–5.7)	
			15–24	2.5 (1.0–5.8)	
			≥ 25	1.7 (0.2–13)	
Liaw & Chen (1998) China, Province of Taiwan 1982–94	Taiwanese Study	6 deaths	Current smoker	5.3 (0.6–46.8)	

CI, confidence interval

Table 2.1.10.5. Case–control studies on tobacco smoking and cervical intraepithelial neoplasia (CIN) and carcinoma *in situ* (CIS) (without control for human papilloma virus (HPV) status)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/ duration	Relative risk (95% CI)	Adjustment factors	Comments
		Ever	Current	Former				
Thomas (1972) USA 1965–69	104 carcinoma, 105 dysplasia (as at biopsy)		Dysplasia, 1.2 Carcinoma, 0.8 Total, 1.1				13 variables, including age	Risk among users of oral contraceptives
Thomas (1973) USA 1965–69	209 CIS and dysplasia		CIS, 1.7 Dysplasia, 1.2					
			CIS, 1.5 Dysplasia, 1.1				Variety of social factors	‘Cases and controls did not differ significantly by the proportion that had ever smoked regularly, the proportion that smoked when interviewed, amount smoked, or age at which smoking started.' (statement by authors)
Harris *et al.* (1980) UK 1974–79	Dysplasia/CIS				*Cigarettes/day* 0 1–15 15–19 ≥ 20	 1.0 2.2 2.5 2.1	Age, no. of sexual partners, pregnancy outside marriage, years of oral contraceptive use	 *p* for trend = 0.003
Wigle *et al.* (1980) Canada 1971–73	168 invasive, 508 CIS		Invasive, 2.0 CIS, 3.8	Invasive, 1.0 CIS, 1.3	*Pack–years* < 10 11–20 21–30 ≥ 31	**CIS** 2.8 4.0 3.9 3.7	No adjustment made for social or sexual variables	

Table 2.1.10.5 (contd)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/ duration	Relative risk (95% CI)			Adjustment factors	Comments
		Ever	Current	Former						
Buckley *et al.* (1981) UK 1974–79	17 preinvasive,		7.0	2.8					Matched	
	14 invasive		7.8	3.7					No. of sexual partners of husband	
	reporting only 1 sexual partner		3.2	2.7	Before adjustment				Smoking of husbands of cases	Relative risk 35 among a small series of multiple-partner women with husbands who smoke versus those with nonsmoking or formerly smoking husbands
			2.2	2.0	After adjustment					
Berggren & Sjöstedt (1983) Sweden 1974–78	609 preinvasive		2.7 (crude)		*Age (years)*				Geographical area (urban/rural)	Relative risk changes sharply with age
					15–24	9.5 (4.0–22.4)				
					25–29	4.4 (2.9–6.8)				
					30–34	3.1 (2.1–4.5)				
					35–39	2.5 (1.7–3.6)				
					40–44	2.8 (1.7–4.7)				
					45–49	1.6 (0.9–2.8)				
					50–54	1.3 (0.6–3.2)				
					55–59	1.5 (0.5–4.2)				
					≥ 60	5.1 (1.1–23.4)				
Lyon *et al.* (1983) USA 1975–77	CIS		3.5 (2.3–5.2)						No. of lifetime partners, religion	
					Duration (years)				No. of lifetime partners, age	
					0	1.0				
					1–19	1.4				
					≥ 20	2.4				
Trevathan *et al.* (1983) USA 1980–81	Mild to moderate dysplasia	2.4 (1.6–3.7)	2.6 (1.7–4.1)	1.6 (0.8–3.6)	*Cigarettes smoked (pack–years)*	*In-situ*	*Severe dysplasia*	*Moderate dysplasia*	Age, no. of sexual partners, age at first intercourse, socioeconomic status, oral contraceptive use	χ^2 for trend: all *p* values significant; strong dose–response relationship
					< 1	2.3	2.5	0.7		
	Severe dysplasia	3.3 (1.9–5.8)	3.0 (1.6–5.6)	5.7 (2.4–13.5)	1–3.9	2.4	2.4	1.8		
					4–6.9	3.8	4.1	3.3		
	CIS	3.6 (2.1–6.2)	4.2 (2.7–7.5)	2.1 (0.8–5.6)	7–11.9	9.1	12.7	10.4		
					≥ 12	12.7	10.2	11.3		

Table 2.1.10.5 (contd)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/ duration	Relative risk (95% CI)	Adjustment factors	Comments
		Ever	Current	Former				
Trevathan *et al.* (1983) (contd)					*Age at starting smoking (years)*		Age, no. of sexual partners, age at first intercourse, socio-economic status, oral contraceptive use, pack–years of cigarette smoking	
					Never	1.0 1.0 1.0		
					≥ 20	0.5 0.3 0.3		
					17–19	2.0 7.2 1.7		
					15–16	2.6 2.0 2.1		
					< 15	4.8 5.8 3.1		
Martin & Hill (1984) South Africa 1950–74	257 cervical cancers	*Use of tobacco in any form*						
		1.5					Crude	*p* < 0.05
		1.3					Alcohol consumption	*p* > 0.05
Clarke *et al.* (1985) Canada 1979–81	Dysplasia		3.2 (*p* < 0.01)	1.3	*Cigarettes/day*		Sexual stability, age at first intercourse, grade of education, use of oral contraceptives	
					1–10	3.1		
					11–20	2.7		
					> 20	3.4		
Mayberry (1985) USA Not specified	CIN	1.7 (1.2–2.4)	1.9 (1.3–2.7)	1.3 (1.1–1.5)	*Intensity (pack–day)*	1.2 (0.7–2.0)	Age, marital status, education, social class, no. of sexual partners, age at first intercourse, no. of abortions, no. of previous Pap smears, oral contraceptive use, clinical history of other sexually transmitted diseases	Includes 35 women with severe dysplasia, 9 with CIS, and 10 with ICC
					< 1/2	1.8 (1.1–2.9)		
					1/2–1	2.2 (1.4–3.7)		
					1–2	1.5 (0.5–4.6)		
					> 2			
					Duration (years)			
					< 5	1.0 (0.5–1.9)		
					5–10	1.8 (1.2–2.8)		
					10–15	2.1 (1.2–3.7)		
					> 15	1.9 (1.0–3.8)		
					Age at starting smoking (years)			
					≥ 20	3.2 (1.6–6.6)		
					17–19	1.2 (0.8–2.0)		
					< 17	1.8 (1.2–2.8)		

Table 2.1.10.5 (contd)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/ duration	Relative risk (95% CI)	Adjustment factors	Comments
		Ever	Current	Former				
La Vecchia *et al.* (1986) Italy 1981–84	CIN			2.5 (0.9–6.7)	*Cigarettes/day*		Age, marital status, education, social class, age at first intercourse, no. of sexual partners, no. of abortions, age at menopause, no. of previous Pap smears, oral contraceptive use, clinical history of sexually transmitted disease	
					< 15	0.9 (0.5–1.6)		
					≥ 15	2.7 (1.3–5.2)		$p = 0.04$
					Age at starting smoking (years)			
					Never	1.0		
					> 24	1.2 (0.6–2.4)		
					18–24	1.6 (0.8–3.0)		
					< 18	3.3 (1.4–8.1)		
					Duration (years)			
					< 10	1.4 (0.7–2.9)		
					10–19	1.7 (0.9–3.1)		
					≥ 20	1.7 (0.8–3.7)		$p = 0.05$
Brock *et al.* (1989) Australia 1980–83	CIS		4.5 (2.2–9.1)	1.3 (0.6–3.0)	*Cigarettes/day*		Age at first intercourse, no. of sexual partners, use of oral contraceptives	
					< 10	2.3 (0.8–6.4)		
					10–19	2.0 (0.9–4.4)		
					20–29	3.8 (1.7–8.4)		
					≥ 30	5.1 (1.5–17.3)		
					Duration (years)			
					< 5	2.2 (0.7–7.0)		
					5–9	2.2 (0.8–6.1)		
					10–14	3.8 (1.6–9.6)		
					≥ 15	1.8 (0.7–4.6)		
Slattery *et al.* (1989) USA 1984–87	CIS (and ICC)		3.4 (2.1–5.6)	1.4 (0.8–2.5)	*Cigarettes/day*		Age, church attendance, education, no. of sexual partners	Included 35 cases of ICC
					None	1.0		
					1–15	2.2 (1.3–3.7)		$p = 0.001$
					> 15	2.2 (1.3–3.6)		
					Pack–years			
					≤ 5	1.5 (0.9–2.6)		
					> 5	2.8 (1.7–4.6)		
					Age at starting smoking (years)			
					> 16	2.4 (1.4–3.7)		
					≤ 16	2.6 (1.5–4.3)		

Table 2.1.10.5 (contd)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/ duration	Relative risk (95% CI)	Adjustment factors	Comments
		Ever	Current	Former				
Slattery *et al.* (1989) (contd)					*Duration (years)*			
					1–10	1.7 (1.0–2.8)		
					> 10	2.2 (1.2–3.9)		
Cuzick *et al.* (1990) UK 1984–88	CIN (CIN I, CIN II, CIN III)		1.5 ($p < 0.05$)	1.0	*Pack–years*		Age, social class and sexual reproductive factors	
					0	1.0		
					0.01–2	0.8		
					2.01–4	1.1		
					4.01–8	1.5		
					8.01–12	2.2		
					> 12	2.7 $p < 0.05$		
					Age at starting smoking (years)			
					Never	1.0		
					≥ 20	0.8		
					17–19	1.6		
					≤ 16	1.7 $p < 0.05$		
Jones *et al.* (1990) USA 1982–84	CIS	1.7 (1.2–2.4)	1.9 (1.3–2.7)	1.5 (1.0–2.4)	*Cigarettes/day*		Age, race, interval since last Pap smears, no. of abnormal smears, no. of lifetime partners, years of oral contraceptive use, years of diaphragm use, history of sexually transmitted diseases	
					< 10	1.6 (0.8–2.9)		
					10–19	1.4 (0.9–2.3)		
					20–29	1.7 (1.1–2.6)		
					≥ 30	2.3 (1.4–3.8)		$p < 0.001$
					Age at starting smoking (years)			
					≥ 30	0.5 (0.1–1.6)		
					21–29	1.9 (1.1–3.3)		
					17–20	1.6 (1.1–2.4)		
					≤ 16	2.2 (1.4–3.4)		
					Duration (years)			
					< 10	1.1 (0.7–1.9)		
					10–19	1.8 (1.2–2.9)		
					20–29	2.5 (1.6–4.1)		
					30–39	1.6 (0.8–3.2)		
					≥ 40	1.7 (0.6–4.7)		$p = 0.001$

Table 2.1.10.5 (contd)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/ duration	Relative risk (95% CI)	Adjustment factors	Comments
		Ever	Current	Former				
Coker *et al.* (1992) USA 1987–88	CIN II, CIN III	1.7 (0.9–3.3)	3.4 (1.7–7.0)		*Duration (years)* 1–4 5–9 ≥ 10 *Age at starting smoking (years)* > 18 16–17 < 16	 0.6 (0.2–1.7) 1.6 (0.6–4.0) 2.7 (1.1–6.9) 1.4 (0.6–3.2) 1.2 (0.5–3.2) 2.9 (1.1–8.0)	Age, race, education, no. of sexual partners, no. of Pap smears five years prior, genital warts	
Parazzini *et al.* (1992) Italy 1981–90	CIN I+II, CIN III		*CIN I+II* 2.2 (1.2–3.0) *CIN III* 2.5 (1.7–3.6)	*CIN I+II* 1.0 (0.4–2.5)	*CIN I+II* < 10 cigarettes/day ≥ 10 cigarettes/day *CIN III* < 10 cigarettes/day ≥ 10 cigarettes/day	 2.3 (1.3–3.9) 2.2 (1.5–3.9) 2.6 (1.5–4.7) 2.6 (1.7–4.1)	Age	χ^2 trend = 5.91 (*p* = 0.03) χ^2 trend = 22.12 (*p* = 0.001; former smokers excluded from trend calculation)
			CIN I+II 1.8 (1.1–2.9) *CIN III* 2.0 (1.3–3.1)	*CIN I+II* 1.1 (0.4–2.9) *CIN III* 1.7 (0.8–3.5)			Age at first birth, age at first intercourse, no. of partners, CIN grade in Milan (Italy), age, education, lifetime no. of Pap tests	
Becker *et al.* (1994) USA 1989–92	CIN II, CIN III	1.4 (1.0–2.1)	1.8 (1.2–2.8)	0.9 (0.5–1.5)	*Cigarettes/day* 1–9 10–19 ≥ 20 *Pack/years* < 2 2–5 ≥ 6 *Duration (years)* 0–1 1–4 5–9 ≥ 10	 1.2 (0.7–1.8) 1.4 (0.8–2.4) 2.4 (1.3–4.2) 1.0 (0.6–1.7) 1.6 (1.0–2.6) 2.0 (1.2–3.5) 1.0 1.3 (0.8–2.2) 1.2 (0.7–2.1) 1.7 (1.0–2.8)	Ethnicity, age, age at first intercourse, no. of lifetime partners	

Table 2.1.10.5 (contd)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/ duration	Relative risk (95% CI)	Adjustment factors	Comments
		Ever	Current	Former				
Becker *et al.* (1994) (contd)					*Use at menarche*			
					None	1.0		
					Before	2.2 (1.2–4.1)		
					After	1.3 (0.9–1.9)		
					1–9 cigarettes/day	1.9 (1.0–3.4)		
					for < 15 years	2.7 (1.2–6.4)		
					for ≥ 15 years	1.4 (0.5–3.4)		
					10–19 cigarettes/	1.6 (0.9–2.7)		
					day	2.1 (1.1–4.0)		
					for < 15 years	1.3 (0.7–2.6)		
					for ≥ 15 years			
					≥ 20 cigarettes/day	3.5 (2.1–5.9)		
					for < 15 years	7.0 (3.5–13.7)		
					for ≥ 15 years	2.2 (1.2–4.1)		
de Vet *et al.* (1994) The Netherlands not specified	Dysplasia			2.0 (1.1–3.4)			Age, education, no. of sexual partners, age at first intercourse, current frequency of intercourse, use of contraceptives, dietary intake of β-carotene, retinol, vitamin C and dietary fibre	
Stone *et al.* (1995) Costa Rica 1982–85	*In situ*		1.3 (1.0–1.7)				Age	

Table 2.1.10.5 (contd)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/ duration	Relative risk (95% CI)	Adjustment factors	Comments
		Ever	Current	Former				
Kjaer *et al.* (1996) Denmark 1987–88	CIS	2.3 (1.6–3.2)	2.4 (1.7–3.4)	1.6 (1.0–2.7)	*Cigarettes/day*		Age, no. of sexual partners, percentage of sexual active life without use of barrier contraceptives, years with intrauterine devices, no. of births, age at first episode of genital warts	
					≤ 4	1.2 (0.6–2.3)		
					5–14	2.0 (1.4–2.9)		
					15–19	2.4 (1.6–3.6)		
					≥ 20	2.8 (1.9–4.1)		
					Age at starting smoking (years)			
					≥ 19	2.3 (1.4–3.7)		
					16–18	2.4 (1.6–3.5)		
					14–15	2.2 (1.5–3.2)		
					≤ 13	2.2 (1.4–3.6)		
					Duration (years)			
					≤ 4	1.4 (0.8–2.4)		
					5–14	2.7 (1.9–4.0)		
					15–19	2.1 (1.4–3.2)		
					≥ 20	2.3 (1.3–3.9)		
Madeleine *et al.* (2001) USA 1990–96	*In situ*	0.9 (0.6–1.3)	0.8 (0.5–1.3)	1.0 (0.6–1.5)			Age, no. of sexual partners	

CI, confidence interval; ICC, invasive cervical cancer; CIN II and CIN III define disease progression

Table 2.1.10.6. Cohort studies on tobacco smoking and cervical intraepithelial neoplasia (CIN) and carcinoma *in situ* (CIS) (without control for HPV status)

Reference Country and years of study	Subjects	Number of cases	Smoking categories	Relative risks	Adjustment factors	Comments
Cederlöf *et al.* (1975) Sweden 1963–72	26 467 women	178; not explicitly stated but must contain mainly CIS cases	Former smoker Current smoker *Cigarettes/day* 1–7 8–15 ≥ 16	1.4 3.0 2.8 3.0 3.4	Age-adjusted Place of residence, income	Little confounding
Wright *et al.* (1978) UK 1968–74	17 032 women	65 cases: 33 CIS, 6 invasive, 26 dysplasia	*Cigarettes/day* 1–14 ≥ 15	 1.5 2.9	Significance unaltered by adjustment for contraceptive method	'In our view, it is unlikely that use of tobacco could have any direct effect on the cervix' (statement by authors)
Beral *et al.* (1988) UK 1968–87	47 000 women	207 CIS	*Cigarettes/day* 0 1–14 > 15	***In-situ*** 4.8 3.6 1.3	Adjusted for age, parity, smoking, social class, no. of previously normal cervical smears, history of sexually transmitted diseases	

Table 2.1.10.6 (contd)

Reference Country and years of study	Subjects	Number of cases	Smoking categories	Relative risks	Adjustment factors	Comments
Gram *et al.* (1992) Norway 1980–89	6812 women	185 cases (177 CIN, 8 ICC)	Former smoker	0.6 (0.4–1.1)	Adjusted for age, marital status, frequency of intoxication by alcohol	
			Current smoker	1.5 (1.0–2.2)		
			Cigarettes/day			
			1–14	1.4 (0.9–2.1)		
			≥ 15	1.8 (1.1–3.0) ($p = 0.02$)		
			Duration (years)			
			1–9	1.2 (0.7–1.9)		
			> 10	1.8 (1.2–2.8) ($p = 0.01$)		
			Age at starting smoking (years)			
			≥ 22	0.9 (0.4–1.9)		
			19–21	1.1 (0.6–2.0)		
			16–18	1.7 (1.1–2.7)		
			< 16	2.0 (1.1–3.5) ($p < 0.01$)		
Zondervan *et al.* (1996) UK 10 years	17 000 women	159 dysplasia 121 CIS	*Cigarettes/day*	**Dysplasia**		
			1–14	1.8 (1.2–2.7)		
			> 15	1.9 (1.2–2.9)		
				CIS		
			1–14	1.9 (1.2–3.0)		
			> 15	1.8 (1.0–2.9)		
Ylitalo *et al*. (1999) Sweden 1969–95	146 889 women	105 cases, 168 controls	Former smoker	1.5 (0.9–2.3)	Education, marital status, age at first intercourse, no. of sexual partners, age at menarche, parity, oral contraceptive use HPV DNA	Nested case–control study
			Current smoker	1.9 (1.3–2.9)		
			Cigarettes/day			
			1–4	1.4 (0.9–2.4)		
			5–9	2.1 (1.3–3.2)		
			10–14	2.1 (1.3–3.6)		
			≥ 15	1.3 (0.7–2.4)		

Table 2.1.10.6 (contd)

Reference Country and years of study	Subjects	Number of cases	Smoking categories	Relative risks	Adjustment factors	Comments
Ylitalo *et al*. (1999) (contd)			*Duration (years)*			
			1–9	1.7 (1.1–2.8)		
			10–19	1.8 (1.2–2.7)		
			≥ 20	1.8 (1.0–3.1)		
			Age at starting smoking (years)			
			12–15	2.1 (1.3–3.4)		
			16–17	1.4 (0.9–2.2)		
			18–19	2.0 (1.1–3.4)		
			≥ 20	1.7 (1.0–2.8)		
			Pack–years			
			< 1	1.3 (0.7–2.3)		
			2–3	2.2 (1.3–3.8)		
			4–5	2.1 (1.2–3.7)		
			6–7	2.6 (1.4–4.7)		
			8–11	1.5 (0.9–2.7)		
			≥ 12	1.5 (0.8–2.6)		
			Time since starting (years)			
			1–9	1.3 (0.6–2.7)		
			10–14	2.4 (1.4–4.4)		
			15–19	2.1 (1.3–3.5)		
			≥ 20	1.5 (0.9–2.4)		
			Years since quitting			
			≥ 10	1.9 (1.0–3.7)		
			1–9	1.5 (0.9–2.5)		
			0	1.9 (1.3–21.7)		

Table 2.1.10.7. Case–control studies on tobacco smoking and invasive cervical cancer (ICC) (adjusted for human papillomavirus (HPV) status)

Reference Country and years of study	Relative risk (95% CI)	Comments
	Ever	
Peng *et al.* (1991) China 1987–88	1.2 (0.5–2.8)	Age, income, residence, HPV 16/33 DNA positivity
Chichareon *et al.* (1998) Thailand 1990–93	1.6 (0.7–3.3)	HPV DNA, age, education, age at first intercourse, no. of live births, lifetime no. of sexual partners, any venereal disease, use of hormonal contraceptives, time since last Pap smear
Ngelangel *et al.* (1998) The Philippines 1991–93	11.2 (3.9–32.0)	HPV, age, no. of household amenities, age at first intercourse, no. of live births, no. of sexual partners, use of oral contraceptives, time since last Pap smear

CI, confidence interval

Table 2.1.10.8. Case–control studies on tobacco smoking and cervical intraepithelial neoplasia (CIN) and carcinoma *in situ* (CIS) (with adjustment for human papillomavirus (HPV))

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/duration			Adjustment factors
		Ever	Current	Former				
Muñoz *et al.* (1993)	CIN III				*Pack–years*	*Spain*	*Colombia*	Adjusted for age, centre,
Spain, 1985–87			1.3 (0.7–2.3)	0.9 (0.2–3.8)	0.1–4.9	0.5 (0.2–1.1)	1.6 (0.9–2.9)	HPV, no. of sexual partners,
Colombia, 1985–88			2.0 (1.3–5.0)	1.8 (0.9–3.5)	5–9.9	3.4 (1.5–8.0)	2.0 (0.8–5.1)	age at first intercourse,
					10–14.9	3.6 (1.1–11.4)	0.9 (0.8–2.3)	*Chlamydiae trachomatis*,
					≥ 15	2.2 (0.7–6.7)	1.8 (0.8–4.2)	husband's sexual partners
Ho *et al.* (1998) USA 1992–94	CIN I, II and III	CIN III compared with CIN I in HPV+ women			*Cigarettes/day*			Age, education, ethnicity, number of Pap smears in last 3 years, HPV status
			2.4 (1.1–5.2)	1.8 (0.6–5.2)	≤ 10		1.5 (0.6–3.7)	
					> 10		3.4 (1.2–9.2)	
					Pack–years			
					None		1.0	
					≤ 5		1.8 (0.7–4.3)	
					> 5		2.7 (1.2–6.2)	
Kanetsky *et al.* (1998) USA 1993–95	CIN I, II and III	1.7 (0.5–5.4)	1.8 (0.5–6.1)	1.3 (0.2–8.1)	*Age at starting smoking (years)*			Age, education, medical coverage, time since last Pap smear and HPV infection
					≥ 17		2.1 (0.6–7.8)	
					≤ 16		1.1 (0.2–5.4)	
					Duration (years)			
					≤ 14		1.3 (0.3–5.1)	
					≥ 15		2.4 (0.5–10.2)	
					Cigarettes/day			
					≤ 9		2.3 (0.6–9.6)	
					≥ 10		1.3 (0.3–5.1)	
					Pack–years			
					≤ 6		1.4 (0.4–5.6)	
					≥ 7		2.1 (0.5–8.8)	
Yoshikawa *et al.* (1999) Japan 1995–96	CIN I, II and III		0.8 (0.2–2.2)	0.3 (0.1–1.3)				HPV DNA

Table 2.1.10.8 (contd)

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status			By quantity/duration		Adjustment factors
		Ever	Current	Former			
Kjellberg *et al.* (2000) Sweden 1993–95	CIN II and III	3.0 (1.9–4.7)	3.1 (1.8–5.2)	2.8 (1.5–5.2)	1–4 cigarettes/day	1.9 (0.6–6.0)	HPV-capsid, age
					5–14 cigarettes/day	2.4 (1.3–4.6)	
					≥ 15 cigarettes/day	6.0 (2.7–13.3)	
					Joint effect of smoking and HPV seropositivity		
					Seronegative		
					Never-smoker	1.0	
					Ever-smoker	5.2 (1.8–15.2)	
					Seropositive		
					Never-smoker	4.6 (1.6–12.9)	
					Ever-smoker	7.2 (2.5–20.6)	
					HPV DNA-positive		HPV DNA
					1–4 cigarettes/day	0.5 (0.1–1.9)	
					5–14 cigarettes/day	3.2 (1.2–8.4)	
					≥ 15 cigarettes/day	5.9 (1.7–19.4)	
					HPV DNA-negative		
					Never-smoker	1	
					Ever-smoker	3.8 (1.3–11.2)	
					HPV DNA-positive		
					Never-smoker	93 (31–280)	
					Ever-smoker	186 (62–556)	

CI, confidence interval

Table 2.1.10.9. Cohort studies on tobacco smoking and cervical intraepithelial neoplasia (CIN) and carcinoma *in situ* (CIS) (with control for human papillomavirus (HPV) status)

Reference Country and years of study	Cohort characteristics	No. of cases	Smoking categories	Relative risk (95% CI)	Adjustment
Schiffman *et al.* (1993) USA 1989–90	21 146 women; nested case–control study	500 cases of CIN III, CIN II, CIN I, condylomatous atypia; 500 controls	Current smoker Former smoker	1.2 (0.8–1.8) 1.0 (0.6–1.6)	Age
Moscicki *et al.* (2001) USA 1990–2000	496 HPV DNA-positive women attending family planning clinics	109 incident cases of low-grade squamous intraepithelial lesions	Smoking daily	1.7 (1.2–2.6)	

Table 2.1.10.10. Study populations used in analysis of associations of tobacco smoking and invasive cervical cancer and carcinoma *in situ* in human papillomavirus (HPV)-positive study subjects

Reference Country and years of study	ASR (world)	HPV tested		HPV-positive				Ever-smokers (%)		Cigarettes per day controls
		Cases	Controls	Cases	(%)	Controls	(%)	Cases	Controls	
Invasive cervical cancer (ICC)										
Bosch *et al.* (1992); Muñoz *et al.* (1992) Colombia 1985–88	32.9	110	126	86	(78.2)	22	(17.5)	42.4	28.1	11
Bosch *et al.* (1992); Muñoz *et al.* (1992) Spain 1985–87	7.2	159	136	131	(82.4)	8	(5.9)	20.4	14.3	10
Eluf-Neto *et al.* (1994) Brazil 1990–91	31.3	187	196	181	(96.8)	34	(17.3)	47.2	36	10
Chaouki *et al.* (1998) Morocco 1991–93	18.8	188	176	182	(96.8)	38	(21.6)	2.8	4.4	7
Chichareon *et al.* (1998) Thailand 1990–93	20.7	378	261	363	(96.0)	41	(15.7)	17.1	13	5
Ngelangel *et al.* (1998) The Philippines 1991–93	22.7	364	381	349	(95.9)	35	(9.2)	20.4	7.2	8

Table 2.1.10.10 (contd)

Reference Country and years of study	ASR (world)	HPV tested		HPV-positive				Ever-smokers (%)		Cigarettes per day controls
		Cases	Controls	Cases	(%)	Controls	(%)	Cases	Controls	
Rolon *et al.* (2000) Paraguay 1988–90	41.1	112	90	109	(97.3)	17	(18.9)	32.2	19	3
Santos *et al.* (2001) Peru 1996–97	39.9	196	175	186	(94.9)	31	(17.7)	9.6	3.6	7
Hildesheim *et al.* (2001) Costa Rica Population-based nested case–control study	40 ICC, 128 HSIL		843 HPV$^+$			843 HPV$^+$				
Carcinoma *in situ*										
Bosch *et al.* (1993); Muñoz *et al.* (1993) Columbia 1985–87		135	181	96	(71.1)	19	(10.5)	37.2	23.7	10
Bosch *et al.* (1993); Muñoz *et al.* (1993) Spain 1985–88		157	193	115	(73.2)	9	(4.7)	54.5	38.4	9
TOTAL		1986	1915	1798		254				

ASR, age-standardized rate; HSIL, high-grade squamous intra-epithelial lesions

Table 2.1.10.11. Studies on tobacco smoking and cervical intraepithelial neoplasia (CIN) and carcinoma *in situ* (CIS) in human papillomavirus (HPV)-positive subjects

Reference Country and years of study	Type of disease	Relative risk (95% CI) by smoking status				By quantity/duration		Adjustment factors	Comments
		HPV status	Never-smoker	Ever-smoker	Former smoker				
Olsen *et al.* (1998) Norway 1991–92	CIN II and III (90 cases, 216 controls)	HPV-16-seronegative	1.0	4.4 (1.8–10.9)				Age	Case–control study; controlled for HPV status. Jointly unexposed (HPV-16-negative never-smokers used as the referent to determine risk of CIN II and III in HPV-positive smokers and nonsmokers)
		HPV-16-seropositive	2.9 (0.7–11.0)	15.3 (5.3–44.1)					
		HPV-16 DNA-negative	1.0	2.2 (0.8–5.6)					
		HPV-16 DNA-positive	15.7 (3.2–76.5)	65.9 (22.3–194.3)					
	(60 cases, 14 controls)	HPV-16 DNA-positive	1.0	4.6 (0.9–22.9)	4.2 (0.5–37.9)	*Duration (years)*			
						0	1.0		
						1–9	2.1 (0.3–12.3)		
						≥ 10	7.5 (1.2–45.8)		
						Cigarettes/day			
						1–10	3.3 (0.5–10.8)		
						≥ 10	5.9 (1.0–35.6)		
	(31 cases, 34 controls)	HPV-16 capsid-positive	1.0	5.1 (1.5–17.7)	4.3 (0.8–23.2)	*Duration (years)*			
						0	1.0		
						1–9	4.3 (0.9–20.3)		
						≥ 10	5.3 (1.4–20.0)		
						Cigarettes/day			
						1–10	4.6 (1.1–20.4)		
						≥ 10	6.5 (1.4–30.1)		
Deacon *et al.* (2000) UK	CIN III	CIN III	2.2 (1.4–3.4)	1.7 (0.76–3.8)		*Cigarettes/day*		Age, age at first inter-course, total no. of sexual partners, years since last regular relationship, history of spontaneous abortion	Nested case–control study within the Manchester cohort (199 HPV-positive cases, 181 HPV-positive and 203 HPV-negative controls)
						1–10	1.4 (0.7–2.5)		
						11–16	2.2 (1.2–3.9)		
						≥ 17	3.1 (1.8–5.3)		
						Duration (years)			
						Never	1.0		
						1–9	1.8 (0.89–3.6)		
						10–19	2.0 (1.2–3.3)		
						≥ 20	3.1 (1.6–6.2)		

Table 2.1.10.12. Case–control studies on tobacco smoking and invasive cervical cancer (ICC) (adeno- and adenosquamous carcinoma)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors
	Ever	Current	Former	By quantity/ duration		
Brinton *et al.* (1986) USA 1982–84	1.1 (0.7–1.9)	1.2 (0.7–2.1)	0.8 (0.4–2.0)	*Cigarettes/day*		
				< 10	1.5 (0.7–3.1)	
				10–19	0.9 (0.4–2.1)	
				20–29	0.9 (0.4–1.9)	
				> 30	2.0 (0.6–6.0)	
				Duration (years)		
				< 10	1.1 (0.4–2.8)	
				10–19	1.2 (0.5–2.5)	
				20–29	1.1 (0.6–2.1)	
				> 40	1.1 (0.3–3.7)	
Ursin *et al.* (1996) USA 1977–91		1.0 (0.5–1.9)	1.2 (0.7–1.9)	*Pack–years*		Education, income, weight gain from age 18 years to diagnosis, total no. of sexual partners, no. of sexual partners before age 20 years, duration of diaphragm use, history of stillbirths, known episodes of genital warts, use of oral contraceptives
				< 1300	1.7 (0.9–3.2)	
				1301–4000	1.0 (0.5–2.0)	
				4001–7500	0.6 (0.3–1.3)	
				> 7500	1.2 (0.6–2.3)	
		[1.7 (1.1–2.6)]	[1.5 (1.0–2.4)]			Life partners, HCV-2 seropositivity, oral contraceptive use at 17 years or less, HPV VLP antibody status
Chichareon *et al.* (1998) Thailand 1990–93	1.9 (0.4–8.9)					HPV DNA adjusted
	1.0 (0.2–6.8)					HPV DNA restricted
Ngelangel (1998) The Philippines 1991–93	0.9 (0.2–4.1)					Age, no. of household amenities, age at first intercourse, no. of live births, lifetime no. of sexual partners, use of hormonal contraceptives, time since last Pap smear Only 2 cases ever smoked.
	4.7 (0.2–129.0)					HPV DNA-adjusted
	13.6 (0.1–2599)					HPV DNA-restricted

Table 2.1.10.12 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors
	Ever	Current	Former	By quantity/ duration		
Lacey *et al.* (2001) USA 1992–96	**Adenocarcinomas**					Age, ethnicity, education, lifetime sexual partners and no. of Pap smears in the last 10 years, HPV
	0.8 (0.5–1.2)	0.6 (0.3–1.1)	1.0 (0.6–1.6)	< 1 pack/day	0.9 (0.5–1.5)	
				≥ 1 pack/day	0.7 (0.4–1.3)	
					p for trend, 0.28	
				< 5 pack–years	0.8 (0.4–1.6)	
				5–14 pack–years	0.9 (0.4–1.7)	
				≥ 15 pack–years	0.8 (0.41–1.6)	
					p for trend, 0.41	
				Duration (years)		
				≤ 10	0.7 (0.4–1.4)	
				11–20	0.9 (0.5–1.8)	
				≥ 20	0.8 (0.4–1.6)	
					p for trend, 0.5	
				Age at starting smoking (years)		
				≥ 21	0.7 (0.3–1.6)	
				18–20	1.0 (0.5–1.9)	
				16–17	0.8 (0.4–1.6)	
				11–15	0.6 (0.3–1.4)	
					p for trend, 0.51	
	Adenocarcinoma versus HPV+ controls only					
	0.7 (0.3–1.5)	0.5 (0.2–1.1)	1.0 (0.4–2.5)	< 5 pack–years	1.1 (0.4–2.8)	Age, ethnicity
				5–14 pack–years	0.8 (0.3–2.1)	
				≥ 15 pack–years	0.5 (0.2–1.6)	
				Duration (years)		
				≤ 10	0.9 (0.4–2.1)	
				11–20	1.3 (0.4–4.0)	
				≥ 20	0.4 (0.1–1.2)	
				< 1 pack/day	1.2 (0.5–2.9)	
				≥ 1 pack/day	0.4 (0.2–1.0)	

Table 2.1.10.12 (contd)

Reference Country and years of study	Relative risk (95% CI)					Adjustment factors
	Ever	Current	Former	By quantity/ duration		
	Squamous-cell carcinoma					
Lacey *et al.* (2001) (contd)	1.4 (0.8–2.3)	1.6 (0.9–2.9)	1.1 (0.6–2.1)	*Duration (years)*		Age, ethnicity, education, lifetime sexual partners, no. of Pap smear in the last 10 years, HPV
				≤ 10	1.0 (0.5–2.0)	
				11–20	1.9 (0.95–3.9)	
				≥ 20	1.5 (0.7–2.9)	
				Cigarettes/day		
				< 20	1.1 (0.6–1.9)	
				≥ 20	1.8 (1.0–3.3)	
				Age at starting smoking (years)		
				≥ 21	1.1 (0.4–2.6)	
				18–20	1.3 (0.6–2.7)	
				16–17	1.5 (0.7–2.9)	
				11–15	1.3 (0.6–2.6)	
				Pack–years		
				< 5	1.2 (0.6–2.4)	
				5–14	1.3 (0.7–2.6)	
				≥ 15	1.7 (0.9–3.2)	
Madeleine *et al.* (2001) USA (see data in Table 2.1.10.5)						

CI, confidence interval; HCV, hepatitis C virus; VLP, virus-like particles

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2.1.11 *Endometrial cancer*

A total of 27 case–control studies have examined the association between cigarette smoking and endometrial cancer. The principal design characteristics and results of these studies are summarized in Tables 2.1.11.1 and 2.1.11.2, respectively.

All but two case–control studies (Shu *et al*., 1991; Weir *et al*., 1994) reported an inverse association of cigarette smoking with endometrial cancer, and in the majority of these studies the decrease in risk was statistically significant (Weiss *et al*., 1980; Lesko *et al*., 1985; Baron *et al*., 1986; Franks *et al*., 1987; Levi *et al*., 1987; Stockwell & Lyman, 1987; Kato *et al*., 1989; Koumantaki *et al*., 1989; Elliott *et al*., 1990; Rubin *et al*., 1990; Brinton *et al*., 1993; Parazzini *et al*., 1995; McCann *et al*., 2000; Weiderpass & Baron, 2001). Quantitative measures of smoking in relation to endometrial cancer have been examined in 13 studies. Most studies showed a negative trend with increasing intensity (Lesko *et al*., 1985; Levi *et al*., 1987; Stockwell & Lyman, 1987; Parazzini *et al*., 1995; Weiderpass & Baron, 2001), duration (Brinton *et al*., 1993; Parazzini *et al*., 1995) or pack–years (Williams & Horm, 1977; Baron *et al*., 1986; Lawrence *et al*., 1987). Only one study found a significantly elevated risk for endometrial cancer related to smoking. This was in pre-menopausal women who smoked 10–20 cigarettes/day, and no dose–response relationship was observed (Weir *et al*., 1994). Also, one study found a significant positive trend between risk for endometrial cancer and amount smoked daily, but the effects of duration were not statistically significant (Shu *et al*., 1991).

In studies that investigated the risk associated with smoking cessation, the effect was greater among current smokers than among former smokers (Lesko *et al*., 1985; Levi *et al*., 1987; Lawrence *et al*., 1987, 1989; Rubin *et al*., 1990; Austin *et al*., 1993; Weiderpass & Baron, 2001) or was confined to current smokers (Tyler *et al*., 1985; Elliott *et al*., 1990; Brinton *et al*., 1993), and the association weakened with time since smoking cessation (Weir *et al*., 1994; Parazzini *et al*., 1995).

Three studies (Lesko *et al*., 1985; Brinton *et al*., 1993; Weir *et al*., 1994) examined results by menopausal status and showed that the reduced risk among smokers was restricted to women diagnosed with endometrial cancer after menopause.

Prospective cohort studies of smoking and endometrial cancer risk in which the problems of unbiased selection of study subjects and recall are minimized are scarce. The limited evidence that is available from prospective studies does not refute the existence of an inverse association between smoking and risk for endometrial cancer (Table 2.1.11.3).

Factors suggested as potential confounders in the evaluation of the association of endometrial cancer with exposure to cigarette smoke include estrogen replacement therapy, obesity, lack of physical activity and age at menopause. Several investigators have assessed whether the presence of selected risk factors could modify the relationship between smoking and risk for endometrial cancer. Some studies have noted a greater reduction in smoking-associated risk among obese women (Brinton *et al*., 1993; Parazzini *et al*., 1995). Others have reported a greater reduction in smoking–associated risk among women taking estrogen replacement therapy (Weiss *et al*., 1980), but not all studies support the existence of such an effect (Brinton *et al*., 1993).

The biological mechanisms that might underlie the reduced risk for endometrial cancer among smokers remain unclear. In the previous *IARC Monograph* on tobacco smoking (IARC, 1986), the Working Group noted that there was consistent evidence that menopause occurs 1–2 years earlier among cigarette smokers than in nonsmokers, indicating that smoking affects hormonal status, a factor known to be related to endometrial cancer. However, no conclusion was drawn regarding the observed reduction in endometrial cancer associated with tobacco exposure due to methodological problems with the interpretation of mortality studies.

Some researchers have suggested that exposure to tobacco may reduce estrogen production, a hypothesis that has received some support from findings that estriol excretion is reduced among postmenopausal smokers. Another theory is that smoking affects the metabolism, absorption or distribution of hormones. Recent studies have proposed a reduction in relative body weight and consequent decrease in levels of circulating estrogen and an earlier age at menopause as a possible mechanism (Terry *et al*., 2002b).

Table 2.1.11.1 Case–control studies on smoking and endometrial cancer: main characteristics of study design

Reference Country and years of study	Cases and controls	Criteria for eligibility
Williams & Horm (1977) USA Early 1960s	358 cases and 3188 controls	Hospital-based study Cases and controls from the Third National Cancer Survey Controls with tobacco-related cancers (lung, larynx, mouth, oesophagus and bladder) excluded
Weiss *et al.* (1980) USA 1975–76	322 cases and 289 controls	Population-based study in western Washington Cases aged 50–74 years; 85% response rate Controls randomly selected from general population; aged 50–74 years; controls who had a hysterectomy > 1 year before interview and non-Caucasians excluded
Kelsey *et al.* (1982) USA 1977–79	167 cases and 903 controls	Hospital-based study in Connecticut Cases confirmed histologically; aged 45–74 years; 67% response rate Controls in same age group admitted to surgical departments; large variety of diagnoses, none of which accounted for more than 4%; hysterectomy excluded; 72% response rate
Smith *et al.* (1984) USA 1980–82	70 cases and 612 controls	Population-based study Cases identified through Cancer Registry of Iowa; stage of cancer reviewed; aged 20–54 years Controls frequency-matched for age; controls with previous cancer of reproductive organs excluded 95% response rate for cases and controls
Lesko *et al.* (1985) USA 1976–83	510 cases and 727 controls	Hospital-based study in the north-east of USA, conducted using interviews Cases histologically confirmed; median age, 59 years; 95% response rate; history of previous or concurrent malignant disease and bilateral oophorectomy excluded Controls with specific, non-tobacco-related cancers: colorectal cancer (40%), melanoma (38%), lymphoreticular neoplasia or cancer of thyroid or adrenal glands (22%); history of previous or concurrent malignant disease and bilateral oophorectomy excluded; median age, 52 years
Tyler *et al.* (1985) USA 1980–82	437 cases and 3200 controls	Population-based cancer and steroid hormone study conducted using interviews Cases confirmed histologically; 72% of cases interviewed; aged 20–54 years Controls selected by random-digit dialling; aged 20–54 years; frequency-matched on age (5-year groups); 83% response rate

Table 2.1.11.1 (contd)

Reference Country and years of study	Cases and controls	Criteria for eligibility
Baron *et al.* (1986) USA 1957–65	476 cases and 2128 controls	Hospital-based study in Buffalo, NY Cases aged 40–89 years Controls with benign conditions of the uterus, breast, gastrointestinal tract and skin; cancers and diseases of the respiratory or circulatory systems excluded; aged 40–89 years
Franks *et al.* (1987) USA 1980–82	79 cases and 416 controls	Population-based study in 6 areas Cases confirmed histologically; postmenopausal women aged 40–55 years; perimenopausal women excluded Controls selected through random-digit dialling in same areas as cases; aged 40–55 years
Lawrence *et al.* (1987) USA 1979–81	200 cases and 200 controls	Population-based study in New York conducted using interviews Cases confirmed histologically as stage IA (83) or IB (117); aged 40–69 years; 65% of eligible cases participated. Controls randomly selected through driver's licence files; individually matched by county of residence and year of birth; 71% of first selected controls participated.
Levi *et al.* (1987) Italy 1983–85	357 cases and 1122 controls	Hospital-based study in Milan conducted using interviews Cases histologically confirmed; aged 31–74 years Controls with traumatic conditions (32%), non-traumatic orthopaedic disorders (25%), surgical conditions (15%) and eye, nose, throat and dental disorders (28%); aged 25–74 years; malignant, hormonal, gynaecological and tobacco-related diseases and hysterectomy excluded 98% of eligible cases and controls participated.
Stockwell & Lyman (1987) USA 1981	1374 cases and 3921 controls	Population-based study Study population identified through Florida Cancer Data System; 28% with unknown smoking status Controls with non-tobacco-related cancers: colon cancer (62%) or rectal cancer (23%), melanoma (11%), or endocrine neoplasms (4%) (tobacco-related cancer sites excluded) Controls older than cases
Kato *et al.* (1989) Japan 1980–86	239 cases and 8920 controls	Hospital-based study at Aichi Cancer Centre Cases aged ≥ 20 years Controls with cancer of stomach (31%), large intestine (19%), uterus other than corpus (17%), lung (7%) and other sites; alcohol-related cancer and cancer of ill-defined sites excluded

Table 2.1.11.1 (contd)

Reference Country and years of study	Cases and controls	Criteria for eligibility
Koumantaki *et al.* (1989) Greece 1984	83 cases and 164 controls	Hospital-based study among Greek Caucasians conducted using interviews Cases confirmed by biopsy; aged 40–79 years; 80% of eligible cases participated. Controls with traumatic fractures (58%), other traumatic conditions (6%), rheumatoid arthritis (46%) and other orthopaedic conditions (10%); hysterectomy excluded; aged 40–79 years; 95% participation rate
Lawrence *et al.* (1989) USA 1979–81	84 cases and 168 controls	Population-based study conducted using interviews Cases histologically confirmed stage 2–4; aged 40–69 years; 84% of eligible cases participated. Controls randomly selected through driver's license registry, individually matched (2:1) for county of residence and year of birth; 69% response rate
Elliott *et al.* (1990) USA 1985–87	46 cases and 140 controls	Population-based study in Baltimore conducted using interviews Cases confirmed histologically; mean age, 62.2 years Controls selected through random digit dialling after frequency-matching for prefix of telephone number (as proxy for area of residence); hysterectomy excluded; mean age, 54.3 years; 58% participation rate
Rubin *et al.* (1990) USA 1980–82	196 cases and 986 controls	Population-based study in 8 geographical areas conducted using interviews Cases from cancer and steroid hormone study, histologically confirmed; aged 40–54 years; 73% participation rate Controls selected by random digit dialling, frequency-matched on age (5-year groups); hysterectomy excluded; 84% participation rate
Shu *et al.* (1991) China 1988–90	268 cases and 268 controls	Population-based study in Shanghai conducted using interviews Cases histologically confirmed; aged 18–74 years; 91% of eligible cases participated. Controls randomly selected from Shanghai population registry, individually matched for age (± 2 years); hysterectomy excluded; 96% participation rate
Austin *et al.* (1993) USA 1984–88	168 cases and 334 controls	Hospital-based study in Alabama conducted using interviews Cases confirmed histologically; aged 40–82 years; 93% participation rate Controls from university optometry clinic, frequency-matched by age and race; hysterectomy excluded; 77% participation rate

Table 2.1.11.1 (contd)

Reference Country and years of study	Cases and controls	Criteria for eligibility
Brinton *et al.* (1993) USA 1987–90	405 cases and 297 controls	Population-based study in 5 areas conducted using interviews Cases confirmed histologically; aged 20–74 years; 87% of eligible cases participated. Controls < 65 years selected through random digit dialling and controls ≥ 65 years through Health Care Financing Administration files; individually matched on age (5-year group), race and area of residence; 66% of eligible controls participated
Weir *et al.* (1994) Canada 1977–78	88 cases and 551 controls	Population-based study conducted using interviews Cases confirmed histologically; aged 40–74 years Controls individually matched by age (± 5 years), neighbourhood and type of dwelling; hysterectomy and history of cancer excluded
Parazzini *et al.* (1995) Italy 1983–92	726 cases and 1452 controls	Hospital-based study in Milan conducted using interviews Cases confirmed histologically; aged 31–74 years Controls with traumatic conditions (34%), non traumatic orthopaedic conditions (26%), surgical conditions (15%) and other illnesses (25%) 98% participation rate for cases and controls
Hirose *et al.* (1996) Japan 1988–93	145 cases and 26 751 controls	Hospital-based study at Aichi Cancer Centre conducted using a questionnaire; 98% participation rate Cases confirmed histologically; aged ≥ 18 years Controls aged ≥ 20 years; cancer diagnosis excluded
Goodman *et al.* (1997) Hawaii, USA, 1985–93	332 cases and 511 controls	Population-based study conducted using interviews Cases confirmed histologically; aged 18–84 years; 66% of eligible cases participated. Controls randomly selected from population rosters, individually matched 2:1 or 3:1 for ethnicity and age (± 2.5 years); hysterectomy excluded; 73% participation rate
Jain *et al.* (2000) Canada 1994–98	552 cases and 562 controls	Population-based study in Toronto, Peel, Halton and York conducted using interviews Cases identified through Ontario Cancer Registry, histologically confirmed; aged 30–79 years Controls randomly selected from property assessment lists, frequency-matched by age (5-year group) and geographical area; hysterectomy excluded; low participation rate

Table 2.1.11.1 (contd)

Reference Country and years of study	Cases and controls	Criteria for eligibility
McCann *et al.* (2000) USA 1986–91	232 cases and 639 controls	Population-based study conducted using interviews Cases confirmed histologically; aged 40–85 years; 51% response rate Controls < 65 years randomly selected from driver's licence lists and for controls ≥ 65 years from Health Care Financing Administration lists, frequency-matched on age and county of residence; hysterectomy excluded; 51% of eligible controls participated.
Parslov *et al.* (2000) Denmark 1987–94	237 cases and 538 controls	Population-based study; questionnaire Cases histologically confirmed; aged 25–49 years; 93% participation rate Controls randomly selected from Danish Central Person Registry, individually matched by age and geographical region; 91% participation rate
Weiderpass & Baron (2001) Sweden 1994–95	789 cases and 3368 controls	Population-based study among postmenopausal Swedish women residents with intact uterus Cases confirmed histologically; aged 50–74 years; 75% participation rate Controls randomly selected from Swedish population registry; aged 50–74 years; 80% participation rate

Table 2.1.11.2. Case–control studies on smoking and endometrial cancer

Reference Country and years of study	Exposure estimates	Relative risk (95% CI)		Comments
Williams & Horm (1977) USA Early 1960s	*Pack–years* < 20 20–40 > 40	 0.89 0.79 0.74		Adjusted for age and sex
Weiss *et al*. (1980) USA 1975–76	*Non-contraceptive estrogen use (years)*	**Nonsmoker**	**Ever-smoker**	Adjusted for age, parity, weight, hypertension and estrogen use
	< 1	1.0	0.4 (0.2–0.7)†	†$p < 0.05$
	1–7	2.6 (1.2–5.6)	1.1 (0.5–2.5)	
	≥ 8	14.9 (6.7–33.2)	3.4 (1.6–7.4)	
Kelsey *et al*. (1982); Baron (1984) USA 1977–79	Ever-smoker	0.83		Adjusted for age, parity, weight, menopausal status, education, oral contraceptive/estrogen use
Smith *et al*. (1984) USA 1980–82	Sporadic smoker Continuous smoker	0.7 (0.4–1.4) 0.8 (0.4–1.5)		Crude odds ratio
Lesko *et al*. (1985) USA 1976–83	Former smoker Current smoker *Cigarettes/day* 1–14 15–24 ≥ 25	0.9 (0.6–1.2) 0.7 (0.5–1.0) 0.8 (0.5–1.3) 1.0 (0.6–1.5) 0.5 (0.3–0.8)		Adjusted for age, body-mass index, duration of conjugated estrogen use
	Smokers of ≥ 25/day† Premenopausal Postmenopausal	 0.9 (0.4–2.2) 0.5 (0.2–0.9)		†Compared with nonsmokers of the same category
Tyler *et al*. (1985) USA 1980–82	Ever-smoker Former smoker Current smoker	0.9 (0.7–1.1) 1.0 (0.7–1.4) 0.8 (0.7–1.1)		Adjusted for age, body weight, oral contraceptive use, alcohol consumption, menopausal status, hypertension and estrogen use

Table 2.1.11.2 (contd)

Reference Country and years of study	Exposure estimates	Relative risk (95% CI)		Comments
Baron *et al*. (1986)	*Pack–years*			Adjusted for age, marital status, parity and body-mass index
USA	1–14	0.8 (0.5–1.1)		(Quetelet index)
1957–65	≥ 15	0.6 (0.4–0.9)		
	p for trend	0.003		
Franks *et al*. (1987)	Ever-smoker	0.5 (0.3–0.8)		Crude odds ratio
USA				Adjustment for age, age at menopause, race, Quetelet index,
1980–82				hypertension, diabetes, infertility, parity, history of
				contraceptive use and geographical regions did not
				appreciably alter risk estimates.
Lawrence *et al*.	*Pack–years*	**Current**†	**Former**	[95% CI not reported]
(1987)	≤ 1	0.7	1.02	†*p* for trend < 0.025, one-sided
USA	> 1	0.5	0.6	
1979–81				
Levi *et al*. (1987)	Former smoker	0.9 (0.5–1.5)		Odds ratios adjusted for age, marital status, education,
Italy	Current smoker	0.5 (0.3–0.7)		social class, age at menarche, menopausal status, age at
1983–85	*Cigarettes/day*			menopause, parity, number of live births, family history of
	< 15	0.5 (0.3–0.8)		gynaecological cancer, body-mass index, use of oral
	≥ 15	0.4 (0.2–0.9)		contraceptive and estrogen replacement therapy
	p for trend	< 0.001		
Stockwell & Lyman	Former smoker	0.6 (0.5–0.8)		Adjusted for age, race and marital status
(1987)	Current smoker	0.5 (0.3–0.9)		
USA	*Cigarettes/day*			
1981	< 20	0.9 (0.7–1.2)		
	20–40	0.7 (0.5–0.9)		
	> 40	0.5 (0.3–0.9)		
Kato *et al*. (1989)	Ever-smoker	0.5 (0.3–0.8)		Adjusted for alcohol drinking, marital status, age, area of
Japan				residence, occupation and family history of breast cancer
1980–86				

Table 2.1.11.2 (contd)

Reference Country and years of study	Exposure estimates	Relative risk (95% CI)		Comments
Koumantaki *et al.* (1989) Greece 1984	Smoker	0.5 (0.3–0.9)		Relative risk for 20 years of smoking Adjusted for age, parity, age at menarche, age at menopause, height and weight
Lawrence *et al.* (1989) USA 1979–81	*Packs/day*	**Current**	**Former**	Matched analysis
	≤ 1	0.6	0.8	
	> 1	0.95	1.02	
	p for trend	> 0.3	> 0.3	
Elliott *et al.* (1990) USA 1985–87	Former smoker Current smoker	1.2 (0.5–3.0) 0.2 (0.1–0.7)		Adjusted for age, waist to hip circumference ratio and parity; controls significantly older than cases
Rubin *et al.* (1990) USA 1980–82	Former smoker Current smoker	0.8 (0.5–1.2) 0.7 (0.5–1.0)		Crude odds ratio
Shu *et al.* (1991) China 1988–90	Current smoker	1.7 (0.9–3.0)		Low prevalence of smoking (< 10%) Adjusted for age, number of pregnancies and weight
	Cigarettes/day			
	≤ *9*	1.3 (0.7–2.8)		
	≥ 10	2.3 (1.0–5.7)		
	p for trend	0.05		
	Age at starting smoking (years)			
	≥ 31	1.6 (0.7–3.5)		
	≤ 30	1.7 (0.8–3.8)		
	Duration (years)			
	≤ 19	1.7 (0.7–4.0)		
	≥ 20	1.6 (0.8–3.4)		
	p for trend	0.11		

Table 2.1.11.2 (contd)

Reference Country and years of study	Exposure estimates	Relative risk (95% CI)		Comments
Austin *et al*. (1993) USA 1984–88	Former smoker	0.8 (0.5–1.5)		Adjusted for age, race, education, body mass, use of replacement estrogens and number of pregnancies
	Current smoker	0.7 (0.4–1.2)		
Brinton *et al*. (1993) USA 1987–90	Ever-smoker	0.8 (0.5–1.1)		Adjusted for age, education, number of births, weight, use of oral contraceptives and use of hormone replacement therapy
	Former smoker	1.1 (0.7–1.6)		
	Current smoker	0.4 (0.2–0.7)		
	Cigarettes/day			
	< 20	0.8 (0.5–1.2)		
	20–29	0.7 (0.4–1.2)		
	≥ 30	0.7 (0.4–1.4)		
	p for trend	0.12		
	Age at starting smoking (years)			
	≥ 22	0.7 (0.4–1.2)		
	18–21	0.9 (0.6–1.5)		
	< 18	0.7 (0.4–1.1)		
	Duration (years)			
	< 20	1.0 (0.5–1.7)		
	20–39	0.8 (0.5–1.3)		
	≥ 40	0.5 (0.3–0.9)		
	p for trend	0.05		
		Premenopausal	Postmenopausal	
	Ever-smoker	1.8 (0.8–4.0)	0.6 (0.4–0.9)	
	Former smoker	3.0 (1.2–7.4)	0.8 (0.4–1.2)	
	Current smoker	0.5 (0.1–1.7)	0.4 (0.2–0.7)	
	Cigarettes/day			
	< 20	2.0 (0.7–5.5)	0.6 (0.3–0.9)	
	20–29	1.7 (0.6–5.2)	0.5 (0.3–0.9)	
	≥ 30	1.3 (0.2–7.1)	0.6 (0.3–1.3)	

Table 2.1.11.2 (contd)

Reference Country and years of study	Exposure estimates	Relative risk (95% CI)		Comments
Brinton *et al*. (1993) (contd)	*Age at starting smoking (years)*			
	≥ 22	2.7 (0.8–8.6)	0.4 (0.2–0.8)	
	18–21	1.3 (0.5–3.8)	0.8 (0.4–1.5)	
	< 18	1.7 (0.5–5.9)	0.5 (0.3–1.0)	
	Duration (years)			
	< 20	2.2 (0.9–5.5)	0.6 (0.3–1.3)	
	20–29	0.5 (0.1–2.4)	0.4 (0.2–0.9)	
	≥ 30	6.2 (0.9–42.3)	0.6 (0.4–1.0)	
	p for trend	0.15	0.02	
Weir *et al*.(1994) Canada 1977–78		Premenopausal (*n* = 14)	Postmenopausal (*n* = 74)	Adjusted for age, Quetelet index, estrogen use, age at menopause and education
	Ever-smoker	2.4 (0.7–8.9)	0.8 (0.5–1.4)	
	Current smoker	2.8 (0.7–11.3)	0.8 (0.5–1.5)	
	Cigarettes/day			
	< 10	0.6 (0.1–6.4)	0.8 (0.4–1.7)	
	10–20	6.4 (1.2–32.7)	1.0 (0.5–2.0)	
	≥ 21	2.1 (0.3–14.7)	0.6 (0.3–1.5)	
	Duration (years)			
	< 25	1.7 (0.3–9.7)	0.7 (0.3–1.6)	
	≥ 25	3.1 (0.7–13.1)	0.9 (0.5–1.6)	
	Years since quitting			
	≥ 10	–	0.9 (0.3–2.1)	
	< 10	1.8 (0.3–11.3)	0.8 (0.3–2.5)	

Table 2.1.11.2 (contd)

Reference Country and years of study	Exposure estimates	Relative risk (95% CI)	Comments
Parazzini *et al*. (1995) Italy 1983–92	Former smoker	0.6 (0.4–0.9)	Adjusted for age, education, parity, Quetelet index, menopausal status, diabetes, hypertension and use of oral contraceptives or estrogen replacement therapy [no trend calculated]
	Current smoker	0.8 (0.7–1.1)	
	Cigarettes/day		
	< 20	0.8 (0.6–1.1)	
	≥ 20	0.6 (0.4–0.9)	
	Duration (years)		
	< 20	1.0 (0.7–1.4)	
	≥ 20	0.5 (0.2–1.2)	
	Years since quitting		
	≥ 10	0.8 (0.5–1.4)	
	< 10	0.4 (0.2–0.8)	
Hirose *et al*. (1996) Japan 1988–93	Current smoker	0.7 (0.4–1.3)	Low smoking prevalence (13.3%) Adjusted for age and year of first visit
	Cigarettes/day		
	< 10	0.5 (0.1–2.1)	
	≥ 10	0.8 (0.4–1.5)	
Goodman *et al*. (1997) USA, Hawaii 1985–93	Ever-smoker	0.8 (0.6–1.2)	Adjusted for history of pregnancy, oral contraceptive use, unopposed-estrogen use, history of diabetes and body-mass index
Jain *et al*. (2000) Canada 1994–98	Ever-smoker	1.01 (0.8–1.3)	Low participation rate of controls Crude odds ratio

Table 2.1.11.2 (contd)

Reference Country and years of study	Exposure estimates	Relative risk (95% CI)		Comments
Parslov *et al*. (2000) Denmark 1987–94	 Ever-smoker	**Cases** 56.5	**Controls** 64.7	Values represent percentages Difference not significant after adjustment for other variables [data not shown]
Weiderpass & Baron (2001) Sweden 1994–95	Former smoker	0.9 (0.7–1.1)		Adjusted for age, use of hormone replacement therapy, body-mass index, parity, age at menopause, age at last birth, use of oral contraceptives, diabetes mellitus
	Current smoker	0.6 (0.5–0.8)		
	Cigarettes/day			
	1–10	0.9 (0.7–1.1)		
	11–20	0.7 (0.5–0.9)		
	> 20	0.7 (0.4–1.3)		
	Duration (years)			
	1–14	0.7 (0.2–2.6)		
	15–30	0.6 (0.3–1.1)		
	31–45	0.6 (0.3–0.9)		
	> 45	0.94 (0.91–1.0)		

Table 2.1.11.3. Cohort studies on smoking and endometrial cancer

Reference Country and years of study	Study subjects	Cases	Exposure estimates	Relative risk (95% CI)	Comments
Cederlöf *et al*. (1975); Baron (1984) Sweden 1963–72	Swedish Census Study 27 732 women	80 cases, 33 deaths	*Ever-smoker* Case Death	 0.7 1.9	Adjusted for age
Garfinkel (1980) USA 1959–72	Cancer Prevention Study (CPS) I 590 562 women	224	Regular smoker *vs.* entire cohort	~1[†]	Adjusted for age [†]Standardized mortality ratio for nonsmoker versus entire cohort is 96.
Engeland *et al*. (1996) Norway 1966–93	Norwegian Cohort Study 14 269 women 310 000 person–years	140	Former smoker Current smoker	1.2 (0.6–2.2) 1.1 (0.7–1.6)	Smoking habits recorded in 1964–65 Adjusted for attained age
Nordlund *et al.* (1997) Sweden 1964–89	Swedish Census Study 25 829 women	248	Former smoker Current smoker Cigarettes/day 1–7 8–15 ≥ 16 Age at starting smoking (years) 20–23 < 19	1.02 (0.5–2.0) 0.8 (0.6–1.2) 0.7 (0.4–1.1) 0.97 (0.6–1.6) 1.04 (0.4–2.5) 1.4 (0.6–3.0) 0.6 (0.2–1.5)	 p for trend = 0.35

Table 2.1.11.3 (contd)

Reference Country and years of study	Study subjects	Cases	Exposure estimates	Relative risk (95% CI)		Comments
Tulinius *et al*. (1997) Iceland 1968–95	Reykjavík Study 11 580 women	98	Former smoker	0.7 (0.4–1.3)		Adjusted for all variables significant at the 10% level in univariate analysis, i.e. body-mass index, body surface, body fat, lean body mass, weight, glycaemia, blood pressure (systolic and diastolic) and hypertension
			Cigarettes/day			
			1–14	0.5 (0.3–1.0)		
			15–24	0.5 (0.3–1.1)		
			≥ 25	0.9 (0.2–3.8)		
Terry *et al*. (1999) Sweden 1968–95	Swedish Twin Registry study 11 659 women	133	Former smoker	0.7 (0.3–2.0)		Low smoking prevalence (13%) Relative risks adjusted for age, physical activity, weight at enrolment and parity
			Cigarettes/day			
			1–10	1.2 (0.6–2.3)		
			≥ 11	0.5 (0.1–2.0)		
Terry *et al*. (2002a) Canada 1980–93	70 591 women	403	Former smoker	0.99 (0.8–1.3)		Adjusted for age, Quetelet index, education, physical activity, hormone replacement therapy, use of oral contraceptives, menopausal status, parity and alcohol consumption
			Current smoker	0.8 (0.6–1.1)		
			Cigarettes/day	**Current**	**Former**	
			1–20	1.1 (0.8–1.6)	1.04 (0.8–1.4)	
			> 20	0.6 (0.4–0.9)	0.9 (0.6–1.3)	
			p for trend	0.03	0.64	
			Duration (years)			
			1–20	0.9 (0.5–1.6)	0.9 (0.7–1.2)	
			> 20	0.8 (0.6–1.1)	1.1 (0.8–1.6)	
			p for trend	0.19	0.66	
			Pack–years			
			1–20	1.0 (0.7–1.5)	0.95 (0.7–1.3)	
			> 20	0.7 (0.5–1.1)	1.0 (0.7–1.5)	
			p for trend	0.10	0.97	
			Years since quitting			
			≥ 20		0.9 (0.7–1.2)	
			10–19		1.1 (0.6–1.8)	
			1–9		1.1 (0.7–1.8)	
			p for trend		0.54	

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2.1.12 *Prostate cancer*

In a review of prostate cancer and its relationship to smoking, Hickey *et al*. (2001) found that the relationship in cohort studies that examined only causes of death was stronger than that in studies in which the incidence of cancer was determined during the individuals' lives, which suggested to the reviewers that smoking might convert a relatively benign cancer into a more aggressive one. Alternatively, the small excesses observed in the mortality studies may have been caused by the diagnostic bias referred to as one of the problems with cohort studies in the General Remarks: namely, the effect of death in the course of a slowly progressive major disease, as prostate cancer may be, is attributed to the chronic disease when it actually occurred as a result of an acute disease related to smoking, such as bronchopneumonia or myocardial infarction. It is certain, from the many studies that have been reported, that any association with smoking is at most weak and the cohort studies in this review are consequently limited to those that reported cancer incidence rates. Their design is described in Tables 2.1 and 2.1.12.1. The results of 18 studies, including separately the two series reported by Hakulinen *et al*. (1997) are summarized in Table 2.1.12.2. One study included in the review of Hickey *et al*. (2001), namely that by Whittemore *et al*. (1984), has been omitted as 44% of the 243 cases were diagnosed only at death, thus causing it to share the potential bias of a mortality study.

Several of the incidence studies provide only rudimentary details about smoking behaviour as they were focused primarily on other factors. Of the 17 studies, two provided evidence of statistically significantly increased risks associated with smoking. Firstly, Adami *et al*. (1996) found some evidence of a dose–response relationship, with the risk increasing with the number of cigarettes smoked per day ($p = 0.04$), although the small number of heavy smokers (38) showed no excess incidence. Secondly, Cerhan *et al*. (1997) found a significantly increased risk of 2.7 (95% CI, 1.2–6.0) for the nine cigarette smokers in their series who smoked 20 or more cigarettes a day. Seven studies, however, found lower risks for current smokers than for nonsmokers, which was almost as many as the nine studies that found increased risks.

The results of 30 case–control studies have been reviewed by Levi and La Vecchia (2001). Two of the studies found some evidence of a positive relationship (Honda *et al*., 1988; based on 216 cases; Schuman *et al*., 1977; based on 48 cases) and a third found a significantly positive relationship with ever smoking, but no relationship with either dose or duration (van der Bulden *et al*., 1994; based on 345 cases). In contrast, the larger study by Villeneuve *et al*. (1999; based on 1623 cases) found a non-significant inverse relationship. The rest found no association worth noting.

Table 2.1.12.1. Description of additional cohort studies on smoking and prostate cancer

Reference Country and years of study	Name of study Cohort sample	Cases/deaths	Comments
Le Marchand *et al.* (1994) Hawai, USA 1975–89	Random sample among 20 316 men from the 5 main ethnic groups in Hawaii: Japanese, Caucasians, Filipino, Hawaiian/Part-Hawaiian, Chinese; aged ≥ 45 years	Cases identified by the Hawaiian Tumor Registry	Study investigating primarily animal fat intake and prostate cancer
Parker *et al.* (1999) USA 1986–95	1177 Iowa men aged 40–86 years	Cases ascertained by Iowa Cancer Registry	Cohort based on controls of a case–control study conducted in 1986–89; study investigating primarily farming activities and risk of prostate cancer
Cerhan *et al.*, 1997 USA 1982–93	Iowa 65+ Rural Health Study 1050 non-institutionalized residents of rural counties in Iowa, aged 65–101 years	Cases ascertained by State Health Registry of Iowa's cancer database	Study investigating primarily body mass and physical activity as risks for prostate cancer
Thompson *et al.* (1989) USA 1972–87	Adult residents of an upper-middle-class community in southern California, aged 50–84 years	1) Incident cases and 2) cases diagnosed before entering cohort or listed on death certificate without prior reporting	[Results based on total cases cannot be considered prospective.]

Table 2.1.12.2. Cohort studies on smoking and prostate cancer

Reference Country and years of study	Name of study No. of men	No. of cases	Exposure related to nonsmokers	Relative risk (95% CI)
Mills *et al*. (1989) USA 1976–82	Adventists' Health Study approximately 14 000 men	172	Former smoker Current smoker	1.2 (0.9–1.7) 0.5 (0.2–1.6)
Severson *et al*. (1989) USA 1965–86	American Men of Japanese Ancestry Study 8006 men	174	Former smoker Current smoker	0.9 (0.6–1.3) 0.9 (0.6–1.2)
Thompson *et al.* (1989) USA 1972–87	1776 men	54	Current smoker	1.3 (0.8–2.3)
Ross *et al*. (1990) USA 1981–88	Leisure World Study 5106 retirees	138	Former smoker Current smoker	0.8 (NS) 0.9 (NS)
Hiatt *et al*. (1994) (USA) 1979–85	Kaiser Permanente Medical Care Program Cohort II 43 432 men	222	Former smoker Current smoker < 20 cigarettes/day ≥ 20 cigarettes/day	1.1 (0.8–1.5) 1.0 (0.6–1.6) 1.9 (1.2–3.1)

Le Marchand
et al. (1994)
USA
1975–89
	8881 men	198	Cigarettes/day
			  Low quartile
			  Intermediate quartile (i)
			  Intermediate quartile (ii)
			  High quartile
				
				1.0
				0.9 (0.6–1.4)
				1.0 (0.7–1.6)
				1.0 (0.6–1.6)

Thune & Lund (1994) Norway 1972–91	Norwegian Screening Study 43 685 men	211	Per 10 cigarettes/day	1.1 (0.9–1.3)

Table 2.1.12.2 (contd)

Reference Country and years of study	Name of study No. of men	No. of cases	Exposure related to nonsmokers	Relative risk (95% CI)
Adami *et al.*	135 006 men	2368	Former smoker	1.1 (1.0–1.2)
(1996)	Swedish Construction Worker		Current smoker	1.1 (1.0–1.2)
Sweden	Cohort		Cigarettes/day	
1971–91			1–4	1.06 (0.93–1.20)
			5–14	1.10 (0.99–1.22)
			15–24	1.14 (0.99–1.31)
			≥ 25	1.00 (0.72–1.38)
				p for trend = 0.04
Engeland *et al.*	Norwegian Cohort Study	703	Former smoker	0.9 (0.7–1.1)
(1996)	11 863 men		Current smoker	1.1 (0.9–1.4)
Norway				
1966–93				
Grönberg *et al.*	Swedish Twin Registry Study	406	Former smoker	0.9 (0.7–1.2)
(1996)	9680 men		Current smoker	1.0 (0.7–1.4)
Sweden			Ever-smoker	
1959–89			Tobacco use (g/day)	
			1–9	1.1 (0.8–1.5)
			10–19	1.0 (0.7–1.4)
			≥ 20	0.7 (0.4–1.2)
Hakulinen *et al.*	Finnish Men's Cohort	209		SIR[a]
(1997)	4601 men		Never-smoker	1.1
Finland			Former smoker	0.9 [0.7–1.2]
1962–93			Current smoker	1.1 [0.9–1.4]
1972, 1977–93	11 373 men	109	Never-smoker	0.9
			Former smoker	1.1 [0.8–1.4]
			Current smoker	0.8 [0.6–1.1]

Table 2.1.12.2 (contd)

Reference Country and years of study	Name of study No. of men	No. of cases	Exposure related to nonsmokers	Relative risk (95% CI)
Cerhan *et al.* (1997) USA 1982–93	Iowa 65+ Rural Health Study 1050 men	71	Former smoker Current smoker (cigarettes/day) < 20 ≥ 20	1.2 (0.7–2.1) 1.8 (0.7–2.4) 2.7 (1.2–6.0)
Tulinius *et al.* (1997) Iceland 1968–95	Reykjavík Study 11 366 men	524	Compared with never-smokers differences for all smoking categories $p \geq 0.1$	
Veierød *et al.* (1997) Norway 1977–92	Norwegian Screening Study 25 708 men	69	Former smoker Current smoker (cigarettes/day) < 10 ≥ 10	0.6 (0.3–1.1) 0.5 (0.3–1.1) 0.6 (0.3–1.2)
Giovannucci *et al.* (1999) USA 1986–94	Health Professionals Follow-up Study 47 781 men	1369	Former smoker stopped ≥ 10 years Former smoker stopped < 10 years Current smoker	0.9 (0.9–1.0) 1.0 (0.9–1.2) 1.1 (0.9–1.3)
Heikkilä *et al.* (1999) Finland 1972–91	Mobile Clinic Health Study 16 481 men	166	Current smoker vs entire cohort	0.76
Parker *et al.* (1999) USA 1986–99	1177 men	81	Former smoker Current smoker (cigarettes/day) < 20 ≥ 20	1.3 (0.8–2.2) 1.7 (0.8–3.8) 1.9 (0.8–4.5)

NS, not significant
[a] Standardized incidence ratio calculated using the rates for Finland as the reference

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2.1.13 *Leukaemia*

The study of the effects of smoking on leukaemia presents a problem, because leukaemia is not one disease with a specific etiology, but a combination of several diseases that have a pathological characteristic in common (namely, an abnormal number of white cells in the blood) and which may have — and in some respects certainly do have — different causes. In principle, it would be desirable to consider separately at least four diseases: namely, the acute myeloid, chronic myeloid, acute lymphoid and chronic lymphoid leukaemias of adults. For therapeutic purposes, the myeloid leukaemias may be subdivided further, but the number of cases in most of the categories would be small and they have not generally been considered separately in etiological studies. Indeed even the acute and chronic forms have seldom been studied separately (although chronic lymphoid leukaemia is sometimes distinguished and may be classed with lymphomas) and the data available in relation to smoking permit only the examination of leukaemia as a whole and of the myeloid and lymphoid categories separately.

It is clear, from the many studies that have been reported, that any association of leukaemia with smoking is weak, so that the most valid evidence is likely to be obtained from cohort studies rather than from case–control studies. Two types of leukaemia (acute myeloid and acute lymphoid leukaemia) are usually rapidly fatal and there is little likelihood that cause of death would be attributed incorrectly to these leukaemias rather than to independent concurrent disease. It is also usually clear whether death during the course of chronic myeloid leukaemia is attributable to the disease itself. Only in the case of chronic lymphoid leukaemia is there any appreciable risk of death being attributed to the disease when it was actually due to an independent smoking-related condition. Table 2.1.13.1 therefore summarizes the results of both incidence and mortality studies. Many of these are studies of leukaemia only. In others, however, leukaemia was only one of many cancers examined and the results of these need to be interpreted with caution when the numbers are small, as they may have been singled out for report because they appeared to be of interest. Two such small mortality studies have been excluded, because cigarette smokers were compared with non-cigarette smokers (including men who smoked only pipes and/or cigars) rather than with lifelong nonsmokers (Tverdal *et al*., 1993; Weir & Dunn, 1970).

The results provide some weak evidence of an association of smoking with leukaemia. The incidence data are conflicting. The largest study, based on 400 cases, provided no evidence of an increased risk (Adami *et al*., 1998), but most of the others did, including two that reported statistically significant excesses for the heaviest cigarette smokers, but were based on very small numbers (Mills *et al*., 1990; Tulinius *et al*., 1997). The mortality data, in contrast, mostly showed small and statistically significant excesses of the order of 30–50% among current smokers, including the data from the US Veterans' study (McLaughlin *et al*., 1989) and the data in men from the two studies carried out by the American Cancer Society (Garfinkel & Boffeta, 1990). Three of the four studies of men, moreover, showed positive dose–response relationships. The only one of the six sets of data not to show any excess risk in cigarette smokers was that for women in the first of the American Cancer Society's studies, which described the observations made between 1959 and 1965 when few women had been smoking for very many years.

Eight studies gave separate data for myeloid leukaemias; six of these also gave data for lymphoid leukaemias, including three that did not provide any data for all leukaemias combined (Paffenbarger *et al*., 1978; Friedman, 1993; Doll *et al*., 1994). Separate data for myeloid and lymphoid leukaemia are summarized in Table 2.1.13.2, but descriptions of the studies are not included in this table, as most of them are described in Table 2.1.13.1 (McLaughlin *et al*., 1989; Garfinkel & Boffeta, 1990; Mills *et al*., 1990; Linet *et al*., 1991; Adami *et al*., 1998). Three, however, are not listed in Table 2.1.13.1 and are described below. Doll *et al.* (1994) followed 34 000 male physicians in the United Kingdom, who had been sent questionnaires about their smoking habits at the end of October 1951 and subsequently in 1957, 1966, 1972, 1978 and 1990, and determined the causes of death of those who died before November 1991. Paffenbarger *et al*. (1978) followed 50 000 former students (all males) at Harvard and Pennsylvania State Universities, who had been given questionnaires on entry in 1916–50 and 1931–40, respectively, and determined the causes of death of those who had died by 1975. In a case–control study nested in this cohort, each person who had died was matched with four controls from the same area, born in the same year, and alive at the time the affected person had died. Friedman (1993) followed 61 704 men and 81 287 women with known smoking habits, who had attended two Kaiser Permanente Medical Centers in the USA, for a regular health appraisal, from the time of first attendance in 1964–72 to the end of 1988, death, or cessation of requested follow-up and determined the incidence of leukaemia from their clinical records. The incidence of leukaemia among nonsmokers and former smokers did not take into account data for smokers of cigars or pipe, but the data for current smokers did so. The results of all the studies were adjusted for age and (where necessary) for sex and, in some instances, also for additional characteristics, i.e. for calendar year of observation by Doll *et al*. (1994) and for area of residence by Nordlund *et al*. (1997).

There is strong evidence for an association of cigarette smoking with myeloid leukaemia. Six out of eight sets of data for men, or for men and women treated as a single group, showed excess relative risks for current cigarette smokers. All of the excess risks were more than 60% and all were associated with dose–response relationships. The exceptions were the data set of Adami *et al*. (1998) in Sweden and a small data set for white insurance policy-holders in the USA reported by Linet *et al*. (1991). Of the two data sets for women, one (the first obtained by the American Cancer Society) showed no association with smoking whereas the other (the second obtained by the American Cancer Society) suggested a weak association that was not statistically significant (Garfinkel & Boffetta, 1990).

The data for lymphoid leukaemia are very different. Only two of eight studies provide any evidence of an increased risk associated with smoking (Paffenbarger *et al*., 1978; Linet *et al*., 1991) and in neither case was the excess risk statistically significant.

Although the strongest evidence comes from cohort studies, some data are also available from case–control studies, details of which are not included in this review. It is worth noting, however, that when Brownson *et al*. (1993) undertook an overview of the published studies of cigarette smoking and adult leukaemia, they found that a pooled analysis of eight case–control series (including the study by Paffenbarger *et al*. (1978) as a case–control study) gave relative risks of 1.1 (95% CI, 1.0–1.2) for all leukaemias, 0.9 (95% CI, 0.8–1.1) for chronic lymphoid leukaemia, 1.2 (95% CI, 0.9–1.5) for chronic myelocytic leukaemia and 1.3 (95% CI, 1.1–1.5) for acute non-lymphoid leukaemia (equivalent to acute myeloid leukaemia in most studies).

Five subsequent studies provided inconsistent, but generally similar results when smokers were compared with nonsmokers. Mele *et al.* (1994) reported on 118 cases of acute myeloid leukaemia and 28 cases of acute lymphoid leukaemia in three Italian cities from 1987 to 1990. The relative risks obtained were 1.6 (95% CI 0.9–2.8) for acute myeloid leukaemia in current smokers [smokers with a history of consumption of more than 10 pack–years are at greater risk] and 0.6 (95% CI, 0.2–2.0) for acute lymphoid leukaemia in current smokers. Wakabayashi *et al*. (1994) reported on 75 cases of acute non-lymphoid leukaemia seen at the Hyogo College of Medicine in Japan from 1981 to 1990; a relative risk of 1.76 (95% CI, 0.96–3.23) was found for smokers. Kane *et al*. (1999) reported on 695 cases of acute myeloid leukaemia and 99 cases of acute lymphoid leukaemia seen in five areas of England from 1991 to 1996; the odds ratios for current smokers were 1.4 (95% CI, 1.1–1.8) for acute myeloid leukaemia and 1.3 (95% CI, 0.7–2.3) for acute lymphoid leukaemia. Bjork *et al* (2001) reported on 372 cases of acute myeloid leukaemia seen in southern Sweden; the relative risks obtained were greater than 1.0 when smoking had continued for more than 20 years for both light smokers (1–10 cigarettes per day: odds ratio, 1.1; 95% CI, 0.65–1.9) and moderate or heavy smokers (>10 cigarettes per day: odds ratio, 1.6; 95% CI, 1.0–2.4) but were less than 1.0 when smoking had continued for 20 years or less. However, Stagnaro *et al*. (2001) reported on 646 cases of leukaemia in 12 areas of Italy and found odds ratios of less than 1.0 for current smokers both for all leukaemia (0.88; 95% CI, 0.69–1.1) and acute myeloid leukaemia (0.93; 95% CI, 0.81–1.4) and an increased odds ratio for current smokers only for acute lymphoid leukaemia (1.2; 95% CI, 0.54–2.5).

For the most part, case–control studies and cohort studies show a difference in risk between myeloid and lymphoid leukaemias.

Characteristics of tobacco-related cases

In general, it has not been possible to link individual malignant neoplasms with specific causes. In the case of leukaemia, some evidence may be obtained from knowledge of the chemicals in tobacco smoke and their relationship to specific cytogenetic changes. For example, benzene, a well-known leukaemogen is known to be present in significant concentrations in tobacco smoke.

According to Korte *et al*. (2000), linear extrapolation from the known effects of high doses suggests that benzene may be responsible for 8–48% of smoking-induced cancer and a somewhat higher proportion (12–58%) of smoking-induced acute myeloid leukaemia. Specific increases in the frequency of partial loss of chromosomes 5 and 7 and translocations involving chromosomes 8 and 21 have been found in the lymphocytes of healthy Chinese workers occupationally exposed to benzene (Smith *et al*., 1998; Zhang *et al*., 1998) and similar chromosomal abnormalities have been noted in smokers in 5–10% of cases of adult acute myeloid leukaemia (Walker *et al*., 1994; Grimwade *et al*., 1998).

There have as yet been few detailed studies on the cytogenetics of acute myeloid leukaemia subdivided by the individuals' smoking habits, but some of them offer support for the concept of a specific effect of benzene in the smoker. Lebailly *et al*. (2002) divided 472 cases of acute myeloid leukaemia into six cytogenetic groups and found higher odds ratios among smokers than in nonsmokers in 32 cases with 8:21 translocations (ever-smokers, 4.77; 95% CI, 1.77–12.85; current smokers, 7.07; 95% CI, 2.64–18.95) and diminished odds ratios in 54 cases with 15:17 translocations (ever-smokers, 0.57; 95% CI, 0.32–1.00; current smokers, 0.41; 95% CI, 0.23–0.96), bearing out the earlier findings reported by Sandler *et al*. (1993) and Davico *et al*. (1998) from studies with smaller numbers. Among 155 cases of acute myeloid leukaemia with recognizable chromosomal aberrations, Sandler *et al*. (1993) found 19 8:21 translocations, giving an odds ratio for ever-smokers of 1.7 (95% CI, 0.60–5.13) and 26 with 15:17 translocations, giving an odds ratio of 0.42 (95% CI, 0.17–1.01), whereas among 26 cases of acute non-lymphoid leukaemia with recognizable chromosomal aberrations, Davico *et al*. (1998) found nine with aberrations of chromosome 8 (six 8+, two 8– and one 8:21 translocation), giving odds ratios of 4.1 (95% CI, 0.5–35.5) relative to patients with normal karyotypes for smokers of ≤ 10 cigarettes/day and 14.2 (95% CI, 1.4–142.3) for heavier smokers.

Only Bjork *et al*. (2001) failed to obtain similar results. Among 73 cases of acute myeloid leukaemia with recognizable chromosomal aberrations, 12 had 8+ aberrations, giving an odds ratio for ever versus never-smokers of 0.91 (95% CI, 0.25–3.30). Smoking, however, was light in this study, with a medium number of pack–years of 21 for all aberrations and 14 for 8+ aberrations.

Table 2.1.13.1. Cohort studies on tobacco smoking and leukaemias (all types)

Reference Country and years of study	Population studied	No. of cases	Smoking categories	Relative risk (95% CI)	Comments
Incidence studies					
Mills *et al.* (1990) USA 1976–82	Adventists' Health Study 34 198 men and women	45 men and women	Former smoker	2.0 (1.0–4.0)	
			Current smoker	2.1 (0.5–9.2)	
			Cigarettes/day		
			1–14	1.0 (0.3–3.0)	
			15–24	2.4 (0.9–6.4)	
			≥ 25	3.0 (1.3–7.2)	*p* for trend = 0.09
Engeland *et al.* (1996) Norway 1966–93	Norwegian Cohort Study 11 863 men, 14 269 women	64 men	Former smoker	0.9 (0.5–1.9)	
			Current smoker	0.6 (0.9–1.2)	
		51 women	Former smoker	0.3 (0.0–2.2)	
			Current smoker	1.3 (0.7–2.5)	
Nordlund *et al.* (1997) Sweden 1963–89	Swedish Census Study 26 032 women	110 women	Former smoker	1.0 (0.3–3.3)	Adjusted for age and place of residence
			Current smoker	1.2 (0.7–2.1)	
			Cigarettes/day		
			1–7	1.5 (0.8–2.9)	
			8–15	0.9 (0.3–2.7)	
			> 15	0.7 (0.1–5.0)	
Tulinius *et al.* (1997) Iceland 1968–1995	Reykjavík Study 11 366 men, 11 580 women	33 men and 26 women	No category of smoking	($p < 0.10$)	
			Former smoker	2.1 (0.7–6.4)	
			Cigarettes/day		
			1–14	1.1 (0.3–3.8)	
			15–24	4.0 (1.5–10.3)	

Table 2.1.13.1 (contd)

Reference Country and years of study	Population studied	No. of cases	Smoking categories	Relative risk (95% CI)	Comments
Adami *et al.* (1998) Sweden 1971–91	Swedish Construction Workers Study 333 288 men	400 men	Former smoker	0.9 (0.6–1.1)	
			Current smoker	1.0 (0.8–1.2)	
			Cigarettes/day		
			1–14	1.1 (0.9–1.4)	
			≥ 15	≥ 1.0 (0.7–1.3)	
			Duration (years)		
			1–10	0.9 (0.5–1.5)	
			11–20	0.8 (0.5–1.2)	
			21–30	1.2 (0.9–1.7)	
			≥ 31	0.9 (0.7–1.2)	
Mortality studies					
McLaughlin *et al.* (1989), USA 1954–80	US Veterans' Study 293 916 men	1588 men			
		142	Nonsmoker	1.0	
		848	Ever smoker	1.3 ($p < 0.01$)	
		299	Former smoker	1.3 ($p < 0.01$)	
		549	Current smoker	1.3 ($p < 0.01$)	
			Cigarettes/day		
		82	< 10	1.1	
		286	10–20	1.3 ($p < 0.01$)	
		181	≥ 21	1.3 ($p < 0.01$)	p for trend < 0.001
Garfinkel & Boffetta (1990) USA 1959–65	Cancer Prevention Study I 437 197 men, 588 148 women	477 men and 339 women		*Men* *Women*	
			Former smoker	1.4* 0.9	*$p < 0.05$
			Current smoker	1.5* 0.8	
			Cigarettes/day		
			1–19	1.3* 0.8	*$p < 0.05$
			≥ 20	1.6* 0.8	

Table 2.1.13.1 (contd)

Reference Country and years of study	Population studied	No. of cases	Smoking categories	Relative risk (95% CI)	Comments
Garfinkel & Boffetta (1990) 1982–86	Cancer Prevention Study II 489 696 men, 622 488 women	327 men and 235 women	Former smoker	1.4* 1.3*	*$p < 0.05$
			Current smoker	1.5* 1.0	
			Cigarettes/day		
			1–19	1.6* 1.1	*$p < 0.05$
			≥ 20	1.4* 0.9	
Linet *et al.* (1991) USA 1966–86	17 633 men Lutheran Brotherhood Insurance Study	72 men	Any tobacco use	1.1 (0.6–1.9)	
			Cigarettes and other tobacco	1.3 (0.7–2.3)	
			Only cigarettes	1.2 (0.6–2.6)	
			Ever-smoker		
			Cigarettes/day		
			≤ 10	0.9 (0.4–1.7)	
			11–20	1.3 (0.7–2.6)	
			> 20	1.8 (0.8–3.7)	p for trend < 0.05

Table 2.1.13.2. Cohort studies on tobacco smoking and myeloid and lymphoid leukaemias

Reference Country and years of study	Myeloid leukaemia				Lymphoid leukaemia			
	Sex	No. of cases	Status/quantity	Relative risk (95% CI)	Sex	No. of cases	Smoking categories	Relative risk (95% CI)
Incidence studies								
Mills *et al*. (1990) Adventists' Health Study	Men and women	12	Nonsmoker	1.0	No data			
		10	Former smoker	2.2 (0.9–5.5)				
		1	Current smoker	2.0 (0.3–16.7)				
			Cigarettes/day					
		4	1–14	1.9 (0.6–6.3)				
		2	15–24	1.5 (0.3–7.0)				
		5	≥ 25	3.6 (1.1–11.1)				
Friedman (1993)[a] Kaiser Permanente Medical Care Program Cohort I	Men	7	Nonsmoker	1.0	Men	71 (total)	Nonsmoker	1.0
		13	Former smoker	2.3 (0.9–5.7)			Former smoker	1.0 (0.5–1.8)
		26	Current smoker	2.8 (1.2–6.4)			Current smoker	0.8 (0.5–1.4)
			Cigarettes/day					
		7	< 20	Reference				
		14	20–40	1.4 (0.6–3.1)				
		5	> 40	1.6 (0.5–5.1)				
	Women	27	Nonsmoker	1.0	Women	46 (total)	Nonsmoker	1.0
		8	Former smoker	1.3 (0.6–2.8)			Fomer smoker	0.6 (0.2–1.7)
		14	Current smoker	0.9 (0.4–1.7)			Current smoker	0.6 (0.3–1.3)
Adami *et al*. (1998) Swedish Construction Workers Cohort	Men	58	Never-smoker	1.0	No data			
		30	Former smoker	0.7 (0.5–1.2)				
		83	Current smoker	1.0 (0.7–1.4)				
			Cigarettes/day					
		84	0	1.0				
		61	1–14	1.3 (0.9–1.7)				
		26	≥ 15	0.8 (0.5–1.3)				

Table 2.1.13.2 (contd)

Reference Country and years of study	Myeloid leukaemia					Lymphoid leukaemia				
	Sex	No. of cases	Status/quantity	Relative risk (95% CI)		Sex	No. of cases	Smoking categories	Relative risk (95% CI)	
Mortality studies										
Paffenbarger *et al*. (1978) Harvard Alumni Study	Men	41 (total)	Current smoker	2.4[b]		Men	27 (total)	Current smoker	1.3	
			≥ 10 cigarettes/day	3.6[b]				≥ 10 cigarettes/day	2.7	
McLaughlin *et al*. (1989) US Veterans' Study	Men	71	Nonsmoker	1.0			106	Nonsmoker	1.0	
		62	Former smoker	1.3			84	Former smoker	1.2	
		142	Current smoker	1.6[b]			129	Current smoker	1.0	
			Cigarettes/day[d]					*Cigarettes/day*		
		23	< 10	1.5			15	< 10	0.7	
		64	10–20	1.5[b]			71	10–20	1.1	
		55	> 20	2.0[b]			43	> 20	1.1	
Garfinkel & Boffetta (1990) Cancer Prevention Study I		Total		**Men**	**Women**		Total		**Men**	**Women**
	Men	150	Former smoker	2.2[b]	0.4	Men	130	Former smoker	1.3	0.6
	Women	99	Current smoker	2.5[b]	0.7	Women	86	Current smoker	0.9	0.9
			Cigarettes/day					*Cigarettes/day*		
			1–19	2.3[b]	0.6			1–19	0.8	0.9
			≥ 20	2.9[b]	0.7			≥ 20	1.0	0.8
Cancer Prevention Study II		Total					Total			
	Men	147	Former smoker	1.2	1.3	Men	93	Former smoker	1.4	1.9
	Women	124	Current smoker	1.7[b]	1.2	Women	59	Current smoker	0.8	0.9
			Cigarettes/day					*Cigarettes/day*		
			1–19	1.7	1.5			1–19	0.9	0.7
			≥ 20	1.8	1.0			≥ 20	0.7	1.1

Table 2.1.13.2 (contd)

Reference Country and years of study	Myeloid leukaemia				Lymphoid leukaemia			
	Sex	No. of cases	Status/quantity	Relative risk (95% CI)	Sex	No. of cases	Smoking categories	Relative risk (95% CI)
Linet *et al*. (1991) Lutheran Brotherhood Insurance Study	Men	8	Nonsmoker	1.0	Men	5	Nonsmoker	1.0
		22	Any tobacco use	0.8 (0.3–1.7)		24	Any tobacco use	1.4 (0.5–3.5)
		17	Cigarettes and other tobacco	1.0 (0.4–2.2)		15	Cigarettes and other tobacco	1.5 (0.6–4.2)
		2	Cigarettes only	0.3 (0.1–1.6)		8	Cigarettes only	2.7 (0.9–8.3)
			Cigarettes/day				*Cigarettes/day*	
		5	≤ 10	0.5 (0.2–1.6)		9	≤ 10	1.5 (0.5–4.6)
		8	11–20	0.8 (0.3–2.1)		9	11–20	1.7 (0.6–5.2)
		6	> 20	1.3 (0.5–3.8)		4	> 20	1.9 (0.5–7.2)
Doll *et al*. (1994) British Doctors' Study	Men	66			Men	98		
			Former smoker	[2.0]			Former smoker	[0.6]
			Current smoker	[1.8]			Current smoker	[0.9]
			Cigarettes/day[e]				*Cigarettes/day*	
			1–14	[0.8]			1–14	[1.1]
			15–24	[2.3]			15–24	[0.6]
			≥ 25	[2.5]			≥ 25	[0.9]

[a] Myeloid refers to acute non-lymphoid leukaemia and lymphoid to chronic lymphoid leukaemia.
[b] $p < 0.05$
[c] $p < 0.01$
[d] p for trend < 0.001
[e] p for trend < 0.05

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2.1.14 *Other organs*

The cancers reviewed in this section generally have low incidence and mortality rates and are not considered to be strongly associated with cigarette smoking. This raises the possibility of preferential reporting of positive associations in cohort studies.

(*a*) *Cancer of the salivary gland*

A population-based case–control study on salivary gland cancer (based on 25 cases) from Puerto Rico (Hayes *et al*., 1999) reported relative risks of 9.0 for men and 4.2 for women. Increasing number of cigarettes smoked per day showed a statistically significant trend for men ($p = 0.02$) and a statistically non-significant trend for women ($p = 0.07$). Two other case–control studies (Spitz *et al*., 1990; Swanson & Burns, 1997), however, found no increase in risk for cancer of the salivary gland among cigarette smokers, or only for the highest category of smoking intensity (≥ 80 pack–years).

(*b*) *Cancer of the small intestine*

Results are available from three case–control studies on the association between smoking and cancer of the small intestine; two found a two- to fourfold increase in risk among smokers (Chen *et al*., 1994; Wu *et al*., 1997), and the third indicated a 90% increase in risk (Kaerlev *et al*., 2002). In contrast, two other case–control studies, one conducted in the USA and the other in Italy, found no evidence for an effect of smoking on cancer of the small intestine (Chow *et al*., 1993; Negri *et al*., 1999).

(*c*) *Cancers of the gallbladder and extra-hepatic bile ducts*

Cancers of the gallbladder and extra-hepatic bile ducts were considered in the previous *IARC Monograph* on tobacco smoking (IARC, 1986), but many more studies have been published since then. The results of the relevant cohort and case–control studies are summarized in Table 2.1.14.1.

In the US Veterans' Study, Chow *et al.* (1995) found marginally elevated relative risks in former smokers and significantly elevated risks in current smokers. Subjects who reported smoking more than 20 cigarettes per day also had significantly elevated relative risks. Starting smoking at a younger age (< 20 years) increased relative risks relative to subjects who had started smoking at a later age (> 20 years). Elevated, but non-significant risks were found in relation to duration of smoking.

Chow *et al*. (1994) studied 34 men and 30 women from Los Angeles county, CA, USA, with bile duct cancers, and 15 men and 26 women with cancer of the ampulla of Vater. These cases were compared with 97 men and 158 women chosen by random-digit dialling or from the Health Care Financing Administration files if over 65 years of age. All cases were histologically verified. Elevated, but non-significant risks were found in former smokers in all groups except for women with cancer of the ampulla of Vater.

Moerman *et al*. (1994) compared 114 cases of bile duct cancer with 487 population controls. After adjustment for age, sex and respondent status, former smokers were at a lower risk (0.7; 95% CI, 0.4–1.2) than current smokers (1.3; 95% CI, 0.8–2.2) and a non-significant trend in relative risks was observed in relation to the duration of smoking: 1.5 for current smokers at interview and 1.4, 1.1 and 1.2 in those who smoked for 2, 5 and 10 years, respectively, before the interview.

Yen *et al.* (1987) recruited 67 patients with bile duct cancer from 11 hospitals in Massachussets, USA, and 273 controls admitted with cancers unrelated to tobacco or alcohol consumption. After adjustment for age and sex, a negative association was found in relation to former smoking (odds ratio, 0.5), and in relation to current smoking (odds ratio, 0.4; $p < 0.05$).

Zatonski *et al.* (1992) compared 73 cases of gallbladder cancer with 186 controls in Opole, Poland. No significant association was found in relation to lifetime number of cigarettes smoked (odds ratio, 0.6 for < 197 100 cigarettes in lifetime; 1.1 for more).

Scott *et al.* (1999) compared the medical records of 68 cases of gallbadder cancer, all histologically verified, from six hospitals in Massachussets, USA, with 272 controls with gallstones or who underwent cholecystectomy. No significant associations between gallbladder cancer and any smoking category (ever, current, former, years smoked or years since quitting) were found. A statistically non-significant fivefold increase in risk was found in relation to smoking after adjustment for age, sex, the presence/absence of gallstones and history of gallstones.

[The Working Group noted that medical records are not necessarily a reliable source of information on tobacco smoking.]

Chalasani *et al.* (2000) compared 26 cases of cholangiocarcinoma to 87 controls from eight hospitals in the USA. After adjustment for age and duration of primary sclerosing cholangitis, no significant association was found in relation to former or current smoking.

Confounding

In considering cancer of the gallbladder and extra-hepatic bile ducts, particular attention has to be paid to potential confounders, namely body-mass index and gallbladder disease.

Chow *et al.* (1994) noted an increased risk for extrahepatic bile duct cancer in relation to body-mass index in both men (odds ratio, 4.0; 95% CI, 1.1–14.2) and women (odds ratio, 2.7; 95% CI, 0.8–9.4) in the highest body-mass index quartile. In addition, a history of gallbladder disease, gallstones and gallbladder inflammation was found to be an important risk factor for the development of gallbladder cancer. Gallbladder disease was also found to be an important risk factor in the study by Scott *et al.* (1999) (odds ratio, 17.2; 95% CI, 1.5–190), by Zatonski *et al.* (1992) and in a recent SEARCH case–control study on 196 cases and 1515 controls (odds ratio, 4.4 for gallbladder disease) (Zatonski *et al.*, 1997). The only study reviewed that was stratified by smoking and gallbladder disease and body-mass index was that of Zatonski *et al.* (1992) that did not find an association with tobacco smoking.

(*d*) *Soft-tissue sarcoma*

One cohort study found an association between cigarette smoking and mortality from soft-tissue sarcoma after 26 years of follow-up, but no dose–response relationship was found with the number of cigarettes smoked per day, duration of smoking or number of pack–years (US Veterans' Study: Zahm *et al*., 1992). No effect of cigarette smoking was detected in an Italian hospital-based case–control study (Franceschi & Serraino, 1992).

(*e*) *Skin cancer*

(i) *Melanoma*

A number of case–control studies have found no difference in the prevalence of tobacco smoking between patients with malignant melanoma and controls (Østerlind *et al*., 1988; Siemiatycki *et al*., 1995; Westerdahl *et al*., 1996; Lear *et al*., 1998; de Hertog *et al*., 2001). An inverse association was found in one study (Green *et al*., 1999).

(ii) *Non-melanoma skin cancer*

Tobacco smoking has been linked to the incidence of squamous-cell carcinoma in a prospective follow-up study of patients with prior skin cancer (Karagas *et al*., 1992) and in the Nurses' Health Study (Grodstein *et al*., 1995), as well as in several case–control studies (Aubry & MacGibbon, 1985; Lear *et al*., 1998; de Hertog *et al*., 2001). In contrast, neither cohort studies (Nurses' Health Study: Hunter *et al*., 1990; Skin Cancer Prevention Study: Karagas *et al*., 1992; Health Professionals' Follow-up Study: van Dam *et al*., 1999) nor case–control studies (Sahl *et al*., 1995; Lear *et al*., 1998; de Hertog *et al*., 2001) found an effect of smoking on the incidence of basal-cell carcinoma.

(*f*) *Ovarian cancer*

Two studies have shown an association of smoking with ovarian cancer (British Doctors' Study: Doll *et al*., 1980; Green *et al*., 2001), but most studies were null (Smith *et al*., 1984; Stockwell & Lyman, 1987; Whittemore *et al*., 1988; Polychronopoulou *et al*., 1993; Norwegian Cohort Study: Engeland *et al*., 1996; Kuper *et al*., 2000). Recent interest in separating histological types of ovarian cancer has prompted researchers to report associations separately. Two studies have reported that smokers were at excess risk for mucinous epithelial ovarian cancer (Marchbanks *et al*., 2000; Green *et al*., 2001), but not for other histological types (Marchbanks *et al*., 2000), but a third study did not support these findings (Kuper *et al*., 2000).

(*g*) *Testicular cancer*

No association has been found between cigarette smoking and risk for testicular cancer (Henderson *et al*., 1979; Coldman *et al*., 1982; UK Testicular Cancer Study Group, 1994; Siemiatycki *et al*., 1995). One study found an increased risk, but positive dose–response relationships for duration and intensity of smoking were seen only in patients from one of three hospitals (Brown *et al*., 1987).

(*h*) *Cancer of the central nervous system*

The incidence of gliomas has been associated with smoking in men (Hurley *et al.*, 1996; Lee *et al.*, 1997), but not in women (Hurley *et al.*, 1996; Blowers *et al.*, 1997; Lee *et al.*, 1997) or in both sexes combined (Ryan *et al.*, 1992). One study reported increased risks for meningiomas associated with smoking (Ryan *et al.*, 1992). Another study found an association of brain tumours with smoking untipped cigarettes, but not with smoking filter-tipped cigarettes (Burch *et al.*, 1987). Other studies have shown a lack of association of tobacco use with tumours of the central nervous system (Hochberg *et al.*, 1990; US Veterans' Study: McLaughlin *et al.*, 1995).

(*i*) *Thyroid cancer*

Three studies have reported an inverse association of smoking with risk for thyroid cancer (Galanti *et al.*, 1996; Kreiger & Parkes, 2000; Rossing *et al.*, 2000). Two studies have reported no association (Ron *et al.*, 1987; Kaiser Permanente Medical Care Program Study: Iribarren *et al.*, 2001) and two a positive association with smoking (Sokic *et al.*, 1994; Memon *et al.*, 2002).

(*j*) *Cancer of the adrenal gland*

There are few data on risk factors for adrenal carcinoma. The US Veterans' Study reported a fivefold increase in risk among current cigarette smokers during 26 years of follow-up, with risk being particularly high among those who smoked most intensely (Chow *et al.*, 1996). Other forms of tobacco use were associated with a statistically non-significant increase in risk. A case–control study in the USA found a twofold increase in risk for adrenal cancer among heavy smokers in men, but not in women (Hsing *et al.*, 1996).

(*k*) *Lymphoma*

(i) *Non-Hodgkin lymphoma*

Six cohort studies have examined the association between non-Hodgkin lymphoma and smoking. In five of these, no increased risk among smokers was evident (British Doctors' Study: Doll *et al.*, 1994; US Veterans' Study: McLaughlin *et al.*, 1995; Swedish Construction Workers' Cohort: Adami *et al.*, 1998; Kaiser Permanente Medical Care Program Study: Herrinton & Friedman, 1998; Iowa Women's Health Study: Parker *et al.*, 2000). However, in one prospective study, men who had ever smoked cigarettes had a twofold increase in risk for non-Hodgkin lymphoma, and the risk was still higher among the heaviest smokers (Lutheran Brotherhood Insurance Study: Linet *et al.*, 1992). In general, data from case–control studies also fail to support a large effect of smoking on the incidence of non-Hodgkin lymphoma (reviewed by Peach & Barnett, 2001; Stagnaro *et al.*, 2001).

Only three studies have examined histological subtypes of non-Hodgkin lymphoma. In the Iowa Women's Health Study (37 336 women followed for 11 years), smoking was associated with increased risk for follicular non-Hodgkin lymphoma (Parker *et al*., 2000). Similarly, two other studies reported a weak positive association between smoking and risk for follicular lymphoma, but no effect for other histological types (Herrinton & Friedman, 1998; Stagnaro *et al*., 2001).

(ii) *Hodgkin lymphoma*

Three studies provided no support for the hypothesis that smoking increases risk for Hodgkin disease (Abramson *et al*., 1978; Bernard *et al*., 1987; Stagnaro *et al*., 2001) and four studies found weak associations (Harvard Alumni Study: Paffenbarger *et al*., 1977; US Veterans' Study: McLaughlin *et al*., 1995; Siemiatycki *et al*., 1995; Swedish Construction Workers Cohort: Adami *et al*., 1998).

(*l*) *Multiple myeloma*

Nine studies suggested no association between smoking and risk of multiple myeloma. Support for this conclusion comes from a number of cohort studies (US Veterans' Study: Heineman *et al*., 1992; Lutheran Brotherhood Insurance Study: Linet *et al*., 1992; Kaiser Permanente Medical Care Program Study: Friedman, 1993; British Doctors' Study: Doll *et al*., 1994; US Veterans' Study: McLaughlin *et al*., 1995; Swedish Construction Workers' Cohort: Adami *et al*., 1998) and case–control studies (Linet *et al*., 1987; Brown *et al*., 1992; Stagnaro *et al*., 2001). Only the relatively small Adventists' Health Study reported an increased incidence of multiple myeloma among former and current smokers and statistically significant trends by number of cigarettes and duration of smoking (Mills *et al*., 1990).

Table 2.1.14.1. Studies on tobacco smoking and cancers of the biliary tract and gallbladder

Reference Country and years of study	Subjects (cases and controls)	Smoking category	Relative risk (95% CI) (relative to never-smokers)				Comments
Cohort study							
Chow *et al.* (1995) USA 1954–80	US Veterans' Study 250 000 men; 303 biliary tract cancers	Former smoker	1.2 (0.8–1.8)				Adjusted for age and calendar time period; age at starting smoking and number of years of smoking also adjusted for cigarettes/day
		Current smoker	1.5 (1.1–2.0)				
		Cigarettes/day					
		< 10	1.6 (1.0–2.6)				
		10–20	1.2 (0.8–1.8)				
		≥ 21	1.8 (1.2–2.7)				
		Age at starting smoking (years)					
		< 20	1.8 (1.1–3.1)				
		20–24	1.6 (0.9–2.9)				
		> 24	1.4 (0.8–2.7)				
		Duration (years)					
		< 30	1.6 (0.8–3.3)				
		30–39	1.7 (0.9–2.9)				
		≥ 40	1.7 (1.0–2.9)				
Case–control studies							
Yen *et al.* (1987) USA 1975–79	67 extrahepatic bile duct cancers, 273 controls with other cancers	Former smoker	0.5 (0.3–1.0)				Adjusted for age and sex
		Current smoker	0.4 (0.2–0.9)				
		Packs/day					
		1	0.3 (1.0–0.9)				
		> 1	0.5 (0.2–1.2)				
Chow *et al.* (1994) USA 1985–89	105 extrahepatic bile duct (EBD) and ampulla of Vater (AV) cancers, 255 population-based controls		EBD		AV		Adjusted for age and ethnic origin
			Men	Women	Men	Women	
		Ever-smoker	1.7 (0.6–4.8)	1.6 (0.7–3.5)	4.7 (0.6–37.9)	0.7 (0.3–1.8)	
		Pack–years					
		1–50	1.1 (0.3–3.3)	1.0 (0.4–2.6)	4.9 (0.6–41.5)	0.4 (0.1–1.2)	
		> 50	2.2 (0.7–6.9)	3.1 (0.8–11.8)	4.3 (0.5–39.1)	2.9 (0.9–10.0)	

Table 2.1.14.1 (contd)

Reference Country and years of study	Subjects (cases and controls)	Smoking category	Relative risk (95% CI) (relative to never-smokers)	Comments
Scott *et al*. (1999) USA 1983–94	68 gallbladder cancers, 272 controls with gallstones	Ever-smoker	1.4 (p = 0.3)	Age-adjusted
		Current smoker	0.9 (p = 0.8)	
		Former smoker	1.9 (p = 0.2)	
		Years of smoking	1.0 (p = 0.4)	
		Years since quitting	1.0 (p = 0.4)	
Zatonski *et al*. (1992) Poland 1985–88	73 gallbladder cancers, 186 controls	*Lifetime no. of cigarettes smoked*		Adjusted for age, sex and education
		< 197 100	0.6 (0.2–1.7)	
		≥ 197 100	1.1 (0.4–3.1)	
			p for trend = 0.9	
Moerman *et al*. (1994) Netherlands 1984–87	114 biliary tract cancers, 487 population controls	Former smoker	0.7 (0.4–1.2)	Adjusted for age, sex and respondent type
		Current smoker	1.3 (0.8–2.2)	
		Cigarette smoker		
		At interview	1.5 (0.9–2.4)	
		2 years before	1.4 (0.9–2.2)	
		5 years before	1.3 (0.8–2.1)	
		10 years before	1.2 (0.8–2.0)	
Chalasani *et al*. (2000) USA 1991–98	26 cholangio-carcinomas with primary sclerosing cholangitis (PSC), 87 cancer-free controls with PSC	Ever-smoker	0.7 0.1–3.6)	Adjusted for duration of PSC and area

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2.2 Pipe, cigar, bidi and other tobacco smoking

2.2.1 *Pipe and cigar smoking*

(*a*) *Introduction*

Although cigar and pipe smoking are less common than cigarette smoking throughout much of the world, these products are used extensively in certain countries and subcultures. Furthermore, the resurgence in the use of premium cigars in the USA between 1993 and 1997 illustrates how aggressive marketing of a specific tobacco product can rapidly increase its usage, even in cultures where it appears to be no longer fashionable.

The data on cancer risk in relation to cigar and pipe smoking are more limited than those available from studies of cigarette smoking. Fewer people have exclusively smoked cigars and/or pipes than have exclusively smoked cigarettes. The published studies are generally based on men, even though women in certain countries smoke cigars and/or pipes. Most studies of smoking cessation have greater statistical power to examine cigarette smoking than smoking of cigars or pipes. The smaller number of exclusive cigar and/or pipe smokers limits the opportunity to examine cancer risk in relation to the amount and duration of smoking, or to assess interactions with alcohol consumption. Persons who smoke cigarettes in combination with cigars and/or pipes typically have a risk for tobacco-attributable cancers that is intermediate between those who smoke cigarettes only and those who exclusively smoke cigars or pipes. The analyses presented here pertain only to exclusive cigar and/or pipe smokers, excluding smokers who also smoked cigarettes. While the main characteristics of the case–control studies are presented together with the results of the studies, the reader is referred to the beginning of Section 2 for a description of the cohort studies presented.

The tables are subdivided between (a) studies on smokers of pipes only and cigars only and (b) studies on smokers of both pipes and cigars, and studies that combined pipe and/or cigar smokers in one category.

(*b*) *Cancer of the lip, oral cavity and pharynx*

(i) *Cancer of the lip*

Clinical reports as early as 1795 linked pipe smoking with carcinoma of the lip (ICD-9: 140) and tongue (ICD-9: 141) (Sömmering, 1795; Clemmesen, 1965) as noted by Doll (1998). These reports were not taken very seriously, however, and these carcinomas were generally attributed to the heat of the clay pipe stem rather than to any intrinsic carcinogenicity of tobacco (Doll, 1998). Several case series and case reports published since the 1920s have noted the association of lip cancer with various combinations of pipe smoking, sunlight, ionizing radiation, and/or alcohol consumption (Broders, 1920; Ahlbom, 1937; Ebenius, 1943; Bernier & Clark, 1951; Hämäläinen, 1955; Wynder *et al.*, 1957).

Two large case–control studies of lip cancer provide information on the relationship of lip cancer with pipe and cigar smoking. Keller (1970) studied 314 male cases, representing a 20% sample of patients discharged from all Veterans Administration hospitals in the USA from 1958 until 1962. Two control groups were identified by sampling — one of patients with cancers of the mucous membrane of the mouth and pharynx, the other of patients discharged during the same period with no oral or pharyngeal cancer. Smoking of pipes, cigars and cigarettes was significantly associated with lip cancer. [The Working Group noted that the data did not include the amount smoked or duration of smoking and that only frequencies of exposure were compared.]

Spitzer *et al*. (1975) studied all male cases of squamous-cell carcinoma of the lip occurring in Newfoundland, Canada, over an 11-year period (1961–71; 366 cases). Three control groups were selected: 132 patients with oral cavity cancer, 81 patients with squamous-cell carcinoma of the skin of the head and neck and 210 randomly selected population controls. In comparison with the population controls, the relative risk for lip cancer associated with pipe smoking, adjusted for age, was 1.5 ($p < 0.05$). [The Working Group noted that the study focused on risk for lip cancer related to the occupation of fishing and gave no other information on tobacco use.]

Subsequent case–control and prospective studies of oropharyngeal cancer have not been sufficiently large to examine lip cancer separately in relation to exclusive use of pipes and/or cigars.

(ii) *Oral and pharyngeal cancer*

Cohort studies

Table 2.2.1 presents the results from seven cohort studies that looked at cancers of the oral cavity and pharynx (ICD-9: 140–149) among men who smoked exclusively cigars and/or pipes (Hammond & Horn, 1958; Kahn, 1966; Doll & Peto, 1976; Carstensen *et al*., 1987; Shanks & Burns, 1998; Iribarren *et al*., 1999; Shapiro *et al*., 2000).

The largest study was based on 12 years of follow-up of the Cancer Prevention Study I (CPS-I) cohort (Shanks & Burns, 1998). Twenty-five deaths from cancers of the oral cavity and pharynx were identified between 1959 and 1972 among the 15 191 men who reported current and exclusive smoking of cigars at the time of enrolment in the study. The age-standardized relative risk for death from cancer of the oral cavity and pharynx was 7.9 (95% CI, 5.1–11.7) among all cigar smokers, relative to lifelong nonsmokers and increased with the number of cigars smoked per day to 15.9 (95% CI, 8.7–26.8) in men who smoked five or more cigars per day. The corresponding estimate for men who reported current smoking of cigarettes exclusively was 8.2 (95% CI, 7.2–9.4). Mortality results were not reported for the 9623 men who smoked exclusively pipes at the time of enrolment in the study, or for former smokers of either cigars or pipes.

Iribarren *et al*. (1999) reported a higher incidence of cancer of the oral cavity and pharynx among 1546 men who reported current smoking of cigars only and no past cigarette smoking at the time of enrolment in the Kaiser Permanente Medical Care Program between 1964 and 1973 than in nonsmokers. Follow-up from 1971 until 1996 identified eight subjects with oral and pharyngeal cancer among the cigar smokers. The relative risk among cigar smokers compared with that of 16 228 men who had never smoked cigarettes and did not smoke a pipe at enrolment was 2.6 (95% CI, 1.2–5.8). Among cigar smokers, risk was higher among men who smoked five or more cigars per day (relative risk, 7.2; 95% CI, 2.4–21.2) than in those who smoked less than five cigars per day (relative risk, 1.3; 95% CI, 0.4–4.4). [The Working Group noted that the inclusion of former pipe smokers in the referent group in this analysis potentially underestimates the association between cigar smoking and cancer of the oral cavity and pharynx.]

Shapiro *et al*. (2000) examined death rates from cancers of the oral cavity and pharynx among 7888 current and 7868 former cigar smokers in the Cancer Prevention Study II (CPS-II), followed from 1982 to 1994. The relative risk was highest among men who reported smoking three or more cigars per day (relative risk, 7.6; 95% CI, 2.9–19.6) and those who had smoked cigars for ≥ 25 years (relative risk, 4.6; 95% CI, 1.6–13), relative to lifelong nonsmokers.

Case–control studies

The case–control studies published since 1986 have consistently shown an increased risk for cancer of the oral cavity and pharynx among men who exclusively smoke cigars or pipes (Table 2.2.2).

Zheng *et al*. (1990) identified 404 patients diagnosed with histologically confirmed oral cancer (ICD 141, 143–145) at participating hospitals in Beijing in 1988–89. An equal number of controls matched on age, sex and hospital were randomly selected from non-cancer patients attending hospital for minor surgery and other conditions judged to be of less than 1-year duration. Among pipe smokers, the odds ratio adjusted for alcohol consumption, years of education, sex and age was 5.7 (95% CI, 2.4–13.3) in men and 4.9 (95% CI, 1.5–16.0) in women. The corresponding estimates associated with cigarette smoking only were 1.6 (95% CI, 1.0–2.6) in men and 2.0 (95% CI, 0.9–4.4) in women.

La Vecchia *et al*. (1998) reported an association between exclusive cigar smoking and cancers of the upper aerodigestive tract from a hospital-based case–control study in Italy and Switzerland. The cases in this study included cancers of the oesophagus as well as tumours of the oral cavity and pharynx and overlap with those in an earlier study by Franceschi *et al*. (1990).

Four other case–control studies have combined cigar and pipe smokers to examine the relationship of tobacco and alcohol consumption with cancers of the oral cavity and pharynx (Blot *et al*., 1988; Franceschi *et al*., 1990, 1992; Fernandez Garrote *et al*., 2001). The largest of these studies is that by Blot *et al*. (1988), based on 762 cases of oropharyngeal cancer diagnosed in four population-based tumour registries in the USA and 837 controls. Trained interviewers collected the information on tobacco and alcohol consumption. The relative risk estimate for men who smoked 40 or more cigars per week was 16.7 (95% CI, 3.7–76.7) when compared with the risk in never-smokers. The corresponding estimate in men who smoked 40 or more pipes per week was 3.1 (95% CI, 1.1–8.7).

Franceschi *et al*. (1990, 1992) reported a strong association between ever smoking cigars or pipes and diagnosis of cancers of the oral cavity (all subsites combined) in a hospital-based case–control study in Italy (relative risk, 20.7; 95% CI, 5.6–76.3). The association was stronger for cancer of the mouth (relative risk, 21.9; 95% CI, 3.8–125.6) than for cancer of the tongue (relative risk, 3.4; 95% CI, 0.3–39.1).

Fernandez Garrote *et al.* (2001) examined the relationship between cigar or pipe smoking and incident cancer of the oral cavity and pharynx in a hospital-based study in Cuba. The relative risk estimate among men who smoked four or more cigars or pipes per day was 20.5 (95% CI, 4.7–89.7).

Table 2.2.3 presents the results of two studies that have stratified the analysis of cancer of the oral cavity and pharynx in relation to cigar and/or pipe smoking by levels of alcohol consumption (Blot *et al.*, 1988; Iribarren *et al.*, 1999). Men who smoked cigars and/or pipes and consumed three or more alcoholic drinks per day (Iribarren *et al.*, 1999) or 30 or more alcoholic drinks per week (Blot *et al.*, 1988) had a substantially higher risk than men who drank alcohol but abstained from smoking, or smoked pipe and/or cigar but drank alcohol only occasionally.

(*c*) *Lung cancer*

In most published cohort studies (Table 2.2.4) and case–control studies (Table 2.2.5), men who exclusively smoke cigars and/or pipes have a consistently higher risk for cancer of the trachea, lung and bronchus (ICD-162) than men who have never smoked any tobacco product.

Lung cancer risk increased with the number of cigars smoked per day in both the CPS-I (Shanks & Burns, 1998) and CPS-II (Shapiro *et al.*, 2000) cohorts and in the Kaiser Permanente Medical Care Program cohort (Iribarren *et al.*, 1999)

Lung cancer risk increased with the amount and/or duration of smoking in two large European multi-centre, hospital-based case–control studies (Lubin *et al.*, 1984; Boffetta *et al.*, 1999) and in a case–control study in China (Lubin *et al.*, 1992).

In the case–control by Boffetta *et al.* (1999), lung cancer risk decreased with time since cessation of cigar or pipe smoking.

The relationship between depth of inhalation and lung cancer risk from cigar and/or pipe smoking has been examined in several studies (Lubin *et al.*, 1984; Benhamou *et al.*, 1986; Shanks & Burns, 1998; Boffetta *et al.*, 1999; Shapiro *et al.*, 2000). Lung cancer risk was generally highest in cigar smokers who report that they inhale the smoke, but cigar smokers who report no inhalation still have a lung cancer risk two to five times higher than that for lifelong nonsmokers (Boffetta *et al.*, 1999; Shapiro *et al.*, 2000). Men who had switched from cigarette smoking to pipes or cigars reported deeper inhalation of the smoke and had higher risks for lung cancer than men who had always smoked pipes or cigars (Wald & Watt, 1997).

There is some evidence that the risk for lung cancer from cigar smoking may have increased over time. The relative risk estimates in cohort studies from the 1950s and 1960s generally ranged from 1.5 to 2.0 for men who were current smokers of either pipes or cigars at the time of the study (Kahn, 1966). However, all of the cohort studies (Doll & Peto, 1976; Carstensen *et al.*, 1987; Lange *et al.*, 1992; Tverdal *et al.*, 1993; Ben-Shlomo *et al.*, 1994; Shanks & Burns, 1998; Iribarren *et al.*, 1999; Shapiro *et al.*, 2000) and case–control studies (Lubin & Blot, 1984; Benhamou *et al*., 1986; Damber & Larsson, 1986; Boffetta *et al*., 1999) published after 1975 have reported relative risk estimates of > 2.0, many with point estimates above 4.0.

(*d*) *Laryngeal cancer*

(i) *Cohort studies*

Cigar and pipe smoking were found to be strongly associated with increased risk for cancer of the larynx (ICD-9: 161) among men in three cohort studies (Table 2.2.6) (Kahn, 1966; Shanks & Burns, 1998; Shapiro *et al*., 2000).

Kahn (1966) identified six deaths from laryngeal cancer among male US veterans who smoked exclusively cigars at the time of enrolment in the US Veterans' Study and were followed from 1954 until 1962. The age-adjusted relative risk estimate associated with current cigar smoking was 10.3 (95% CI, 2.6–41.3).

Death from laryngeal cancer was associated with cigar smoking in analyses based on a 12-year follow-up of men in the CPS-I cohort (Shanks & Burns, 1998). The age-adjusted relative risk associated with current cigar smoking was 10.0 (95% CI, 4.0–20.6), based on seven deaths from laryngeal cancer among cigar smokers. The relative risk estimate was increased to 26.0 (95% CI, 8.4–60.7) among men who smoked five or more cigars per day and to 53.3 (95% CI, 0.7–296) among those who reported moderate to deep inhalation. The increased risk for laryngeal cancer associated with current cigar smoking during the 12-year follow-up was similar to the increased risk associated with current cigarette smoking during the first four years of follow-up [relative risk, 10.0; 95% CI, 3.5–28.5] (US Department of Health and Human Services, 1989).

Seven deaths from laryngeal cancer were recorded in CPS-II during follow-up from 1982 until 1994 among men who exclusively smoked cigars (Shapiro *et al*., 2000). Current cigar smoking was associated with an increased death rate from laryngeal cancer compared with never-smokers (relative risk, 10.3; 95% CI, 2.6–41.0). The corresponding age-adjusted estimate associated with current cigarette smoking was 10.5 (95% CI, 3.6–30.4) among men in CPS-II during the first 4 years of follow-up (1982–86) (US Department of Health and Human Services, 1989). In dose–response analyses based on a small number of cases, the relative risk associated with cigar smoking was higher in current smokers than in former smokers, in those who smoked more cigars per day, who reported smoking for 25 or more years and who reported inhaling the cigar smoke.

(ii) *Case–control study*

In a hospital-based case–control study in northern Italy, Franceschi *et al*. (1990) identified 162 incident cases of men with laryngeal cancer and 1272 controls between June 1986 and June 1989 (Table 2.2.7). Only one case exclusively smoked cigars or pipes, whereas 94% of cases and 76% of controls smoked cigarettes.

Several of the studies that examined the relation of cigar and/or pipe smoking to laryngeal cancer are not considered here, either because they included persons who also smoked cigarettes (Falk *et al*., 1989; Muscat & Wynder, 1992) or because cigarette smokers were included in the referent group (Freudenheim *et al*., 1992).

(*e*) *Oesophageal cancer*

(i) *Cohort studies*

Exclusive smoking of cigars and/or pipes has been associated with increased risk for cancer of the oesophagus (ICD-9: 150) in several cohort studies (Table 2.2.8) (Kahn, 1966; Carstensen *et al*., 1987; Shanks & Burns, 1998; Shapiro *et al*., 2000).

In the US Veterans' Study, 14 deaths from oesophageal cancer occurred between 1954 and 1962 among men who, at enrolment, reported currently or formerly smoking cigars exclusively (Kahn, 1966). Risk was higher among current cigar smokers (relative risk, 5.3; 95% CI, 2.4–12.1, based on 12 deaths), than in former cigar smokers (relative risk, 2.4; 95% CI, 0.5–10.9, based on two deaths). Few male veterans had smoked pipes exclusively. The association between current pipe smoking and oesophageal cancer was based on only three deaths (relative risk, 2.0; 95% CI, 0.6–7.1).

Pipe and cigar smoking were associated with similar increases in death rate from oesophageal cancer in a cohort of 25 129 Swedish men (Carstensen *et al*., 1987). The Swedish Census Study cohort is unusual in that 27% of the men smoked a pipe, whereas only 5% smoked exclusively cigars and 32% cigarettes. The relative risk estimate associated with current pipe smoking was 3.6 (95% CI, 1.1–11.8, based on six deaths), whereas the association with current cigar smoking was 6.5 (95% CI, 1.3–33.5, based on two deaths).

The largest study of the association of oesophageal cancer with cigar smoking was based on CPS-I, in which 30 deaths from oesophageal cancer were identified among 15 191 men who reported exclusive cigar smoking at the time of enrolment (Shanks & Burns, 1998). The overall relative risk associated with current cigar smoking was 3.6 (95% CI, 2.2–5.6) relative to lifelong nonsmokers. Risk increased with the number of cigars smoked per day and with the self-reported depth of inhalation.

Shapiro *et al*. (2000) identified 17 deaths from oesophageal cancer among 15 756 men participating in CPS-II who reported current or former cigar smoking at the time of enrolment and were followed from 1982 through 1994. The relative risk estimate was slightly higher in current cigar smokers (relative risk, 1.8; 95% CI, 0.9–3.7) than in former cigar smokers (relative risk, 1.3; 95% CI, 0.6–2.8). Dose–response analyses based on nine deaths among current cigar smokers showed an increase in the risk of oesophageal cancer with the duration of smoking, but not with the number of cigars smoked per day or with depth of inhalation.

(ii) *Case–control studies*

The case–control studies on smoking and oesophageal cancer are summarized in Table 2.2.9 (Franceschi *et al*., 1990; Kabat *et al*., 1993; La Vecchia *et al*., 1998).

Kabat *et al*. (1993) examined the relationship of pipe and/or cigar smoking to specific histological types of oesophageal cancer in a hospital-based case–control study of 431 male cases and 4544 hospital controls in the USA. Eleven cases of squamous carcinoma of the oesophagus and nine cases of adenocarcinoma of the distal oesophagus or gastric cardia had smoked pipes and/or cigars only. The risk among pipe and/or cigar smokers was not significantly higher than that of lifelong nonsmokers for squamous carcinoma (relative risk, 1.8; 95% CI, 0.8–4.1) or adenocarcinoma (relative risk, 1.1; 95% CI, 0.5–2.3).

None of the studies of pipe and/or cigar smoking in relation to oesophageal cancer have been sufficiently large to assess the possible interactions between smoking and alcohol consumption.

(*f*) *Stomach cancer*

Pipe and/or cigar smoking were consistently associated with a small increase in incidence of stomach cancer (ICD-9: 151) in most cohort studies (Table 2.2.8) and case–control studies (Table 2.2.9), but the number of cases who smoked cigars and/or pipes exclusively was small and the 95% confidence intervals in these studies often included the null.

Chao *et al*. (2002) examined the relationship between tobacco smoking and death from stomach cancer among men who currently or formerly smoked cigars or pipes at the time of enrolment in CPS-II. Increased mortality from stomach cancer was associated with current cigar smoking (relative risk, 2.3; 95% CI, 1.5–3.5; 25 deaths) and pipe smoking (relative risk, 1.3; 95% CI, 0.8–2.2; 16 deaths). Relative risk estimates were highest in men who reported smoking five or more cigars per day (relative risk, 4.2; 95% CI, 2.3–7.6) and those who inhaled the smoke (relative risk, 3.9; 95% CI, 1.9–8.0).

(*g*) *Colorectal cancer*

Current pipe and/or cigar smoking were associated with an increased risk for cancer of the colon and/or rectum (ICD-9: 153–4) in several cohort studies (Table 2.2.10).

The largest analysis is based on follow-up of the US Veterans' Study from 1954 until 1980. Heineman *et al*. (1995) reported a higher death rate from both colon cancer (relative risk, 1.3; 95% CI, 1.1–1.4) and rectal cancer (relative risk, 1.4; 95% CI, 1.2–1.8) among men who exclusively smoked pipes and/or cigars compared with never-smokers. The relative risk for colon cancer increased significantly with the number of cigars smoked per day (p for trend = 0.004) and the relative risk for rectal cancer increased with the number of pipes smoked per day (p for trend = 0.007).

Current smoking of pipes and/or cigars was associated with an increased risk for colon or colorectal cancer in the British Doctors' Study (relative risk, 1.7; 95% CI not stated) (Doll & Peto, 1976), the Lutheran Brotherhood Insurance Study (relative risk, 1.6; 95% CI, 0.8–3.2) (Hsing *et al*., 1998) and the Finnish Mobile Clinic Health Examination Study (relative risk, 1.5; 95% CI, 0.8–2.6) (Knekt *et al*., 1998). Current cigar and/or pipe smoking was also significantly associated with increased mortality from colorectal cancer among men in the CPS-II who had smoked for 20 or more years (relative risk, 1.3; 95% CI, 1.1–1.6) (Chao *et al*., 2000).

The Working Group was aware of no published case–control studies of exclusive pipe and/or cigar smoking in relation to cancers of the colon and rectum.

(*h*) *Cancer of the liver and intrahepatic bile ducts*

Carstensen *et al.* (1987) reported an association between current cigar smoking and increased death rates from cancer of the liver and biliary passages (ICD-9: 155–156) among 25 129 Swedish men followed from 1963 to 1979 (relative risk, 7.2; 95% CI, 2.2–23.4, based on four deaths) (Table 2.2.11).

Hsing *et al.* (1990a) reported an increased risk for primary liver cancer among current pipe and/or cigar smokers participating in the US Veterans' Study (relative risk, 3.1; 95% CI, 2.0–4.8).

(*i*) *Cancer of the gallbladder and extrahepatic bile ducts*

Cancer of the extrahepatic bile ducts (ICD-O: 156.1) was also associated with cigar and/or pipe smoking in a population-based case–control study of 105 histologically confirmed cases and 255 controls in Los Angeles County, USA (Table 2.2.12) (Chow *et al*., 1994). Two cases of cancer of the extrahepatic bile duct occurred among men who had ever smoked cigars or pipes exclusively (relative risk, 1.6; 95% CI, 0.3–9.9), compared with lifelong nonsmokers. Two additional cases involved the ampulla of Vater (relative risk, 7.6; 95% CI, 0.6–100.4).

(*j*) *Cancer of the pancreas*

Pipe and/or cigar smoking were associated with an increased risk for pancreatic cancer (ICD-9: 157) in most of the cohort studies (Table 2.2.13) and case–control studies (Table 2.2.14).

(i) *Cohort studies*

The largest study encompassed a 12-year follow-up of men in CPS-I (Table 2.2.13) (Shanks & Burns, 1998). The age-adjusted relative risk for death from pancreatic cancer among current exclusive cigar smokers, compared with lifelong nonsmokers, was 1.6 (95% CI, 1.2–2.1), based on 56 deaths. The risk for pancreatic cancer increased with the number of cigars smoked per day and with the depth of inhalation of the cigar smoke.

Higher risks for pancreatic cancer in current cigar smokers than in nonsmokers were also reported among men in the US Veterans' Study (relative risk, 1.5; 95% CI, 0.99–2.3, 27 deaths) (Kahn, 1966), in the Kaiser Permanente Medical Care Program Study (relative risk, 1.2; 95% CI, 0.5–2.9, 6 cases) (Iribarren *et al*., 1999) and in CPS-II (relative risk, 1.3; 95% CI, 0.9–1.9, 28 deaths) (Shapiro *et al*., 2000).

Current pipe smoking was significantly associated with increased risk for pancreatic cancer in the Swedish Census Study (relative risk, 2.8; 95% CI, 1.5–5.2) (Carstensen *et al*., 1987).

(ii) *Case–control study*

In the hospital-based case–control study reported by Muscat *et al*. (1997), men who ever smoked cigars exclusively had an increased risk for pancreatic cancer (relative risk, 3.1; 95% CI, 1.4–6.9) (Table 2.2.14). For ever smoking a pipe, the odds ratio for pancreatic cancer incidence was 1.8 (95% CI, 0.9–5.3).

(*k*) *Cancer of the bladder and kidney*

Epidemiological studies of cigar and/or pipe smoking in relation to cancers of the urinary bladder (ICD-9: 188) and kidney (ICD-9: 189) are summarized in Table 2.2.15 (cohort studies) and Table 2.2.16 (case–control studies). Men who exclusively smoked pipes had a significantly increased risk for bladder cancer in the Swedish Census Study (relative risk, 4.0; 95% CI, 1.9–8.6), the largest prospective study to evaluate pipe smoking (Carstensen et al., 1987). Men who smoked more than three cigars daily had an increased risk for bladder cancer relative to that of lifelong nonsmokers in CPS-I (Shanks & Burns, 1998) and CPS-II (Shapiro et al., 2000).

Taken separately, none of the cohort or case–control studies included a sufficient number of cases who smoked pipes or cigars exclusively to evaluate dose–response relationships precisely. The largest study of bladder cancer was the pooled analysis of European case–control studies by Pitard *et al.* (2001). The risk for bladder cancer increased significantly with number of years of smoking for both pipes (p for trend = 0.006) and cigars (p for trend < 0.001).

The four studies on kidney cancer (Kahn, 1966; Jensen *et al.*, 1988; McLaughlin *et al.*, 1995; Iribarren *et al.*, 1999) had limited statistical power to assess associations between pipe or cigar smoking and cancers of the renal pelvis or parenchyma.

(*l*) *Prostate cancer*

Men who exclusively smoked pipes or cigars had higher death rates from prostate cancer (ICD-9: 185) than lifelong nonsmokers during the first 8.5 years of follow-up of the US Veterans' Study (Kahn, 1966). Compared with lifelong nonsmokers, the relative risk estimate was 1.5 (95% CI, 0.98–2.4) for men who currently smoked pipes, and 1.5 (95% CI, 1.03–2.2) for current cigar smokers. Little association was seen between prostate cancer mortality and pipe and/or cigar smoking in the 26-year follow-up of the same cohort (Hsing *et al*., 1991). [The Working Group noted that the information on smoking was not updated during either follow-up, so that misclassification of exposure could have attenuated the findings in the longer follow-up.]

Hsing *et al*. (1990b) also studied the much smaller Lutheran Brotherhood Insurance Study cohort (Table 2.2.17). Mortality from prostate cancer was higher among men who ever smoked pipes or cigars than in lifelong nonsmokers (relative risk, 1.6; 95% CI, 0.7–3.5), although the association was based on only nine deaths. No increase in risk for prostate cancer was seen among men who currently smoked pipes in the Norwegian Screening Study (Tverdal *et al*., 1993) or among men who ever smoked pipes or cigars in a population based case–control study in Montreal, Canada (Table 2.2.18; Sharpe & Siemiatycki, 2001).

(*m*) *Cancer of the haematopoietic system*

The cohort studies (Table 2.2.19) and case–control studies (Table 2.2.20) that have related cigar and/or pipe smoking to haematopoietic cancers are generally too small to be informative.

(*n*) *Cancer of other organs*

The Norwegian Screening Study examined the relationship between pipe and/or cigar smoking and the risk for brain cancer (Tverdal *et al.*, 1993). The number of cases was too small to be informative (Table 2.2.21).

2.2.2 *Bidi and other tobacco smoking*

(*a*) *Introduction*

This section covers smoking in forms practiced mainly in South Asia and in Africa. Most of the available studies have been conducted in India on the association of cancer with bidi smoking as well as, depending on the region studied, smoking of chillum (clay pipe), cheroot and chutta, including reverse chutta smoking. Other studies have reported on *khii yoo* smoking in Northern Thailand, kiraiku smoking in Kenya and reverse cigarette smoking.

Bidi smoking is the most common form of tobacco smoking in India. The bidi is an indigenous smoking stick 4–8 cm long, usually containing 0.15–0.25 g coarse tobacco flakes rolled in a rectangular piece of dried *temburni* leaf (*Diospyros melanoxylon*). The number of bidis produced and consumed in India is 7–8 times higher than the number of cigarettes, thus most studies on health risks to smokers in India have concentrated on bidi smoking. Moreover, cigarette smoking is common generally only in higher socioeconomic groups. Besides bidis and cigarettes, other smoking habits include various indigenous forms of pipe and cheroot smoking. Cheroots are small cigars made of heavy-bodied cured tobacco rolled in a dried tobacco leaf and tied with a thread. Chuttas are coarsely prepared cheroots. The length of chuttas varies from 5 to 12 cm. Chutta smoking is widespread in coastal areas of Andhra Pradesh, Tamil Nadu and Orissa. The hookah, or hooka, is a pipe that allows the tobacco smoke to pass through water before the smoker inhales it (water pipe). The chillum is a straight, conical clay pipe used for tobacco smoking.

When assessing the carcinogenic effects of smoking, it is necessary to consider several potentially confounding common habits such as chewing of betel quid with tobacco, chewing tobacco with or without lime, and drinking alcoholic beverages. Betel-quid chewing is the chewing of a quid made up of fresh betel leaves (*Piper betle*), areca nut (*Areca catechu*), slaked lime (calcium hydroxide) and almost always, tobacco. Various condiments are often added in small quantities. Other forms of smokeless tobacco include a powder or paste used to clean the teeth and snuff.

(*b*) *Cancer of the oral cavity and pharynx*

Results of case–control studies on bidi and other tobacco smoking and cancer of the oral cavity and pharynx are presented in Table 2.2.22.

(i) *Cancer of the oral cavity*

Three hospital-based case–control studies on cancers of subsites of the oral cavity (gingiva, tongue and floor of the mouth, buccal and labial mucosa) were conducted at the Regional Cancer Centre in Trivandrum, Kerala, a state in southern India, during 1983–84. Control patients, matched for age (within 5 years), sex and religion, were selected among outpatients who came for treatment to the Medical College in Trivandrum, with respiratory, intestinal and genitourinary infections or who came for a cancer check-up for sites other than the head and neck. Both cases and controls were interviewed by trained social workers to elicit sociodemographic information, history of habits and clinical details. All cancer cases were confirmed by biopsy. Chewing of betel quid with or without tobacco, bidi smoking, cigarette smoking, alcohol use and nasal snuff inhalation were the main habits practiced by the study population. These studies analysed only men for smoking and alcohol habits because few women practiced these habits.

The case–control study on carcinoma of the gingiva consisted of 187 cases and 895 matched controls (Sankaranarayanan *et al*., 1989a). After using forward stepwise logistic regression on the four main habits of chewing of betel quid with tobacco, bidi smoking, alcohol drinking and snuff inhalation, the relative risk for smoking bidis for 20 years or less was 2.6 (95% CI, 0.7–9.9) and that for smoking bidis for more than 20 years was 2.1 (95% CI, 1.2–27.9).

The study on cancer of the tongue (n = 188) and floor of the mouth (n = 40) included 158 men and 70 women (Sankaranarayan *et al*., 1989b). Two controls were selected for each case and matched for age (within 5 years), sex and religion. Forward stepwise logistic regression was used to estimate relative risk for chewing of betel quid with tobacco, bidi smoking, bidi–cigarette smoking and cigarette smoking. A relative risk of 7.5 (95% CI. 2.6–21.7) was noted for men who smoked 20 or more bidis per day.

The study of cancer of the buccal and labial mucosa included 413 cases and 895 controls (Sankaranarayan *et al*., 1990a). When forward stepwise logistic regression was used to create a multivariate model of risk for cancer of the buccal and labial mucosa adjusted for other habits, bidi smoking had a relative risk of 2.9 (95% CI, 1.3–6.6) for a duration of the habit up to 20 years and 1.7 (95% CI, 1.1–2.6) for a habit that continued for 21 years or more.

A hospital-based case–control study was carried out during 1980–84 at the Tata Memorial Hospital, a cancer hospital in Mumbai (Bombay), India, on 713 men who were histopathologically diagnosed with oral cancer and 635 controls free from cancer, benign lesions or infectious diseases (Rao *et al*., 1994). The average age of the case group was

50.4 years and that of the control group was 45.4 years. Those who smoked bidis had a relative risk of 1.6 (95% CI, 1.3–2.0) for oral cancer. Men who smoked hookah and chillum had a relative risk of 5.0 (95% CI, 1.4–22.0). The trends in relative risks by intensity and duration of bidi smoking were both statistically significant ($p < 0.001$). [The Working Group noted that the study had several deficiencies, particularly in the selection of controls that resulted in cigarette smoking apparently being protective for oral cancer. The data analysis seemed to be confined to univariate analysis.]

A hospital-based case–control study was undertaken on 647 male patients with tongue cancer at the Tata Memorial Hospital, in Mumbai, India, between 1980 and 1984 (Rao & Desai, 1998). During the same period, 635 men, the majority of whom had come to the hospital for a check-up and were found to be free of cancer, benign lesions and infection, were selected as unmatched controls. Habits included betel quid, areca nut, tobacco and lime, bidi, cigarettes and other forms of tobacco smoking. Bidi smoking was by far the most common smoking habit. Unconditional logistic regression was used to estimate relative risk after stratification by age and place of residence. Bidi smoking was a significant risk factor for cancer of the base of the tongue (relative risk, 5.9; 95% CI, 4.2–8.2). Bidi smoking did not pose a statistically significant relative risk for cancer of the anterior tongue at any level of smoking intensity, but the relative risks for cancer of the base of the tongue were statistically significant at all levels of smoking intensity and a statistically significant trend was observed. Duration of smoking was not a significant predictor of risk for cancer of the anterior tongue, but it was for cancer of base of the tongue, with a significant trend that peaked at 21–30 years (relative risk, 7.7; 95% CI, 4.8–13.0). A model created with unconditional logistic regression that included bidi smoking, alcohol drinking, illiteracy, non-vegetarian diet and tobacco chewing showed that the greatest risk for cancer of the base of the tongue came from smoking bidis (relative risk, 4.7; 95% CI, 3.5–6.3). Cancer of the anterior tongue was not associated with bidi smoking in this model.

A population-based case–control study of upper aerodigestive tract cancers was conducted in Bhopal, central India (Dikshit & Kanhere, 2000). Men who had cancers that had been recorded during 1986–92 by the Bhopal Population-Based Cancer Registry were potential cases. Those with tongue cancer (not otherwise specified) or registered from death certificate only were excluded. Only those subjects who gave complete information on tobacco use were included, giving 163 lung cancer patients, 247 oropharyngeal cancer patients and 148 oral cavity cancer patients (all squamous-cell carcinomas) as study cases. A total of 260 controls were randomly selected after age stratification of a sample of about 2500 men recruited during 1989–92 in a tobacco habit survey of a random sample of Bhopal voters. After adjustment for age and tobacco quid chewing, the relative risk for smokers (bidis and/or cigarettes) was 1.5 (95% CI, 0.9–2.4). Smoking for more than 30 years led to a significant relative risk for oral cavity cancer of 4.3 (95% CI, 2.0–9.1). The estimated relative risk for the highest of three levels of cumulative years of smoking was 6.0 (95% CI, 2.6–13.7).

A hospital-based case–control study of cancer of the oral cavity was conducted in three areas of southern India (Bangalore, Madras and Trivandrum) between 1996 and

1999 (Balaram *et al.*, 2002). A total of 591 incident cases were enrolled (309 men, 282 women). Control subjects were selected from the same hospitals (centres) as cases and were frequency-matched by centre, age and sex. In Madras and Bangalore, the controls were relatives and friends of other cancer patients. In Trivandrum, controls were selected from general medical outpatients or attendees of the cancer clinics who had been found free of malignancy. The control group included 292 men and 290 women. Odds ratios for men who smoked bidis were: for < 20 bidis per day, 2.0 (95% CI, 1.1–3.8); and for ≥ 20 per day, 2.5 (95% CI, 1.4–4.4).

(ii) *Pharyngeal cancer*

A hospital-based case–control study of oropharyngeal cancer was carried out in Nagpur, Maharashtra in Central India (Wasnik *et al.*, 1998). The cases were 123 patients newly diagnosed with oropharyngeal cancer, confirmed by histopathology. Each case was matched with two hospital controls on age and sex. For each case, one control was selected from non-cancer patients and the other from patients with cancer at sites other than head and neck. Unconditional logistic regression analysis was used with the major risk factors identified from an initial model. Odds ratios for tobacco smoking, predominantly in the form of bidi and/or chillum, were 2.3 (95% CI, 1.2–3.7) after adjusment for tobacco chewing and outdoor occupation. [The Working Group noted some problems with the data analysis.]

A case–control study was undertaken on 1698 men with pharyngeal and laryngeal cancers seen at the Tata Memorial Hospital, Mumbai from 1980 to 1984 (Rao *et al.*, 1999). There were 678 patients with cancer of oropharynx, 593 patients with cancer of the hypopharynx, and 427 patients with cancer of the larynx. A total of 635 controls were selected from male outpatients at the same hospital who had been found to be free from cancer, benign tumours and infectious disease. The estimated relative risk for bidi smoking was 5.6 (95% CI, 4.1–7.6) for cancer of the oropharynx and 2.0 (95% CI, 2.0–3.5) for cancer of the hypopharynx. A dose–response relationship was observed for intensity and duration of bidi smoking for both sites. When unconditional logistic regression was performed with adjustment for alcohol, illiteracy, diet and tobacco chewing, bidi smoking was the most important factor for both sites.

In the study by Dikshit and Kanhere (2000) (described in Section 2.2.2(*b*)(i)), a high relative risk for oropharyngeal cancer among subjects who smoked only bidis (odds ratio, 7.9; 95% CI, 5.1–12.4) and a positive relationship with intensity of bidi smoking were observed.

(iii) *Oral leukoplakia*

Case reports

A case of reverse cigarette smoking was reported from the Hospital 'De Tjongerschans', Heerenveen, the Netherlands, where a dentist had referred a 59 year-old woman who had smoked for 40 years with the glowing end inside the mouth, having learnt the habit from her mother who originated from Aruba in the Netherlands Antilles.

Oral examination revealed a thick, leathery palatal mucosa with burnt, charred areas. The buccal mucosa at both sides showed diffuse leukoplakic lesions. Biopsy of the palatal leukoplakia showed hyperkeratosis with slight to moderate epithelial dysplasia. After 4 years of follow-up, no malignant changes were noted (Hogewind *et al.*, 1987).

A 69-year old immigrant from the Philippines was referred to the Department of Stomatology at the School of Dentistry, University of Manitoba in Winnipeg, Canada, with an unusual lesion of the hard palate. She reported having practiced reverse smoking for 10 years, having begun the habit in the Philippines. A white lesion covered her entire hard palate and near the mid-line there was an area of charred tissue. Minor salivary glands stood out as red spots, as in nicotine stomatitis. A biopsy of the hard palate revealed moderate hyperkeratinization without dysplasia. A 50-year-old woman who had emigrated from the Caribbean had a clinical history similar to that of the woman described above. She was diagnosed with hyperkeratinization without dysplasia (Stoykewych *et al.*, 1992).

Cross-sectional and case–control studies (Table 2.2.23)

A cross section of villagers aged 21 years and above, in four villages in three districts of Andhra Pradesh where it was known that reverse chutta smoking was practised, was surveyed for palatal lesions (Van der Eb *et al.*, 1993). A random sample of 758 persons was drawn from the electoral rolls and 480 of them (250 women, 230 men) were examined and interviewed by health professionals with special training. Many could not be examined due to bad weather, others due to emigration or death, but refusals were uncommon. Reverse chutta smokers constituted 33.3% of the sample, about two-thirds of which were women; conventional chutta smokers amounted to 12.5% (mainly men); bidi smokers, 4.2% (all men); cigarette smokers, 2.9%; tobacco chewers, 2.1 %; and those with mixed habits, 4.2%. Non-tobacco users constituted 33.5% of the sample, about two-thirds of which were women, and 7.3% were former smokers. Palatal lesions were found with all smoking habits, but were far more common and most severe in reverse smokers. The age and sex-standardized percentages of palatal lesions were as follows: 0.9% of the men and 3.9% of the women who were nonsmokers; 55% of the bidi smokers; 54.7% of the men and 63.3% of the women who were conventional chutta smokers; and 93.0 % of the men and 92.2 % of the women who practised reverse chutta smoking. Palatal lesions found in higher proportions in reverse smokers included preleukoplakia, leukoplakia and palatal keratosis. All but one of the atrophic areas were found in current and ex-reverse chutta smokers and all the nine carcinomas found were in current reverse chutta smokers.

A population-based case–control study of leukoplakia was carried out in Kenya by house-to-house survey using a cluster-sampling technique (Macigo *et al.*, 1996). Individuals with leukoplakia found through oral examination (n = 85) were enrolled as cases. Controls (n = 141) were matched for sex, age and the cluster of origin. Tobacco was smoked in the form of cigarettes and *kiraiku* rolls, a type of local, handmade, smoking sticks, using cured, dried and crushed tobacco, rolled in any one of the following: dried banana leaves and stem peelings, dried corn husks, newspaper or other paper. The relative risk for oral leukoplakia in current cigarette smokers was 8.4 (95% CI, 4.1–17.4) and that for current *kiraiku* smokers was 10.0 (95% CI, 2.9–43.4). In former *kiraiku* smokers, the relative risk was 4.9 (95% CI, 2.3–10.4). Duration of smoking before cessation showed a trend towards greater risk with increasing duration. A gradual downward trend was seen for the number of years since quitting *kiraiku* smoking; however, the relative risk for an interval of more than 10 years since quitting was still significantly increased. [The Working Group noted that the study did not adequately control for possible confounding with cigarette smoking.]

Intervention studies

A large controlled prospective intervention trial for primary prevention of oral cancer was conducted in India in the districts of Ernakulam (Kerala), Bhavnagar (Gujarat) and Srikakulam (Andhra Pradesh). The intervention cohort consisted of over 12 000 tobacco users of 15 years of age and older in each of the three districts. Members of this cohort were interviewed about their tobacco use and examined for the presence of oral lesions. They took part in an educational programme on tobacco use through annual follow-ups during 1977–88. The control cohort consisted of over 17 000 persons, all tobacco users aged 15 and over in randomly selected villages in the same three districts, who were examined and followed up in a similar manner to that for the intervention cohort, but with minimal educational intervention during 1966–77 (Gupta *et al.*, 1986a). Eight annual follow-up surveys were conducted after the first 2 years, covering a 10-year period (1977–88). The analysis was restricted to tobacco users with an appropriate length of follow-up period. The results are discussed district by district, and are summarized in Table 2.2.24.

Bhavnagar District

The size of the intervention cohort in Bhavnagar was 12 221 and that of the control cohort was 3704, all subjects were men as very few women used tobacco in that area. Both bidis and clay pipes were commonly smoked by men in the Bhavnagar District. A small proportion of men practised chewing habits.

After five years of follow-up, the proportion of individuals re-examined at least once in the intervention cohort was 96.5% and in the control cohort, 83.5%. The proportions of individuals who quit their tobacco habits in the control and intervention cohorts were 9% and 13%, respectively. There was little difference in the incidence rate of leukoplakia between the two cohorts (Gupta *et al.*, 1986b).

Srikakulam District

The size of the intervention cohort in Srikakulam District was 12 038 and that of the control cohort was 7542. Smoking was the major tobacco habit, practised mostly in the form of reverse chutta smoking. Men also smoked chuttas in the conventional manner, and bidis. Women practised only reverse chutta smoking. The proportions of individuals who quit their tobacco habits in the control and intervention cohorts were 3.5% and 17%, respectively.

Incidence rates of oral precancerous lesions (mainly palatal lesions associated with reverse smoking) were substantially lower in the intervention cohort than in the control cohort for all tobacco habit groups. The 5-year age-adjusted incidence rates per 1000 for palatal changes for women who were reverse smokers were 513.9 in the control area and 292.0 in the intervention area and, among men, 427.7 and 163.3, respectively. The rate ratio for the protective effect of intervention on reverse smokers was 0.38 in men and 0.57 in women (Gupta *et al.*, 1986b).

Ernakulam District

At baseline in the intervention cohort, the prevalence of leukoplakia was 2.9% in the intervention cohort and 2.7% in the control cohort (Mehta *et al.*, 1982).

After eight years of follow-up, the expected number of cases of leukoplakia in the intervention cohort was calculated using age- and sex- specific incidence rates from the control cohort. The observed number of leukoplakia was only 41% of the expected number in men and only 28 % of the expected number in women (Gupta *et al.*, 1990).

After 10 years of follow-up, 14.3% of tobacco users in the intervention cohort had discontinued their tobacco habit as compared with 4.5% in the control cohort. Among individuals who reported stopping bidi smoking, only one bidi-associated leukoplakia and one central papillary atrophy of the tongue were found, compared to the expected 5.8 leukoplakia, 6.0 central papillary atrophy and 27.1 other bidi-associated oral mucosal lesions (leukoedema, preleukoplakia and smokers' palate), based on the incidence rates among all other individuals. The differences in observed and expected rates were statistically significant ($p < 0.05$) (Gupta *et al.*, 1992).

The relative risks for malignant transformation for the nodular form of leukoplakia were reported to be 3243.2, for ulcerated leukoplakia 43.8 and for homogeneous leukoplakia 25.6 when compared with individuals with a tobacco habit, but no oral precancerous lesions (Gupta *et al.*, 1989).

[The Working Group noted the 10-year calendar time difference between the intervention and control cohorts.]

The educational intervention that was undertaken in these studies was helpful in reducing the use of tobacco in all areas and in increasing cessation rates in two of the three areas. Spontaneous regression rates of oral precancerous lesions were higher among individuals who reported stopping or reducing their tobacco use than in those who did not. The incidence rates of oral precancer were lower in the intervention cohorts in two of the areas (leukoplakia in Ernakulam and palatal changes in Srikakulam) than in the respective control cohorts.

(*c*) *Lung cancer*

In northern Thailand, hand-rolled cigars called *khii yoo* are commonly smoked. In a hospital-based case–control study conducted in Chiang Mai, Thailand, the odds ratios for lung cancer for *khii yoo* smoking were 1.2 in men and 1.5 in women ($p > 0.05$) (Simarak *et al.*, 1977).

In the case–control study by Dikshit & Kanhere (2000), described in Section 2.2.2(*b*)(i), the age-adjusted relative risk for lung cancer among smokers of bidis only was 11.6 (95% CI, 6.4–21.3) (Table 2.2.25).

A hospital-based case-control study of lung cancer was conducted in Chandigarh, northern India. A total of 235 men with cytologically or histologically confirmed lung cancer was recruited between January 1995 and June 1997. Four hundred and thirty-five male controls were selected from visitors and attendants of the patients. Results were presented both separately and combined for bidi, cigarette and hookah smoking. For the purpose of analysing smokers of different types of tobacco products, cigarette equivalents were calculated by applying a weight of 1 (= 1g of tobacco) to cigarettes, 0.5 to bidis, and 4 hookahs. The odds ratio for bidi smoking was 5.8 (95% CI, 3.4–9.7), and for hookah smoking, 1.9 (95% CI, 0.9–4.4). Risks by intensity of smoking bidis increased at successively higher intensities. The highest odds ratio for 9 pack–years was for bidi (3.9; 95% CI, 2.1–7.1), followed by hookah (1.9; 95% CI, 0.9–4.4) and cigarette (1.9; 95% CI, 0.9–4.4). There was a clear decreasing trend for years since quitting (Gupta *et al.*, 2001).

(*d*) *Laryngeal cancer*

The case–control studies on bidi smoking and laryngeal and oesophageal cancer are summarized in Table 2.2.26.

In a hospital-based case–control investigation in Trivandrum, India, information on 190 men with squamous-cell carcinoma of the larynx confirmed by biopsy and 546 male controls was collected during 1983–84 (Sankaranarayanan *et al.*, 1990b). Unconditional logistic regression, sometimes with a forward stepwise approach, was used to produce estimates of relative risk adjusted for age and religion. Occasional users were excluded from the analyses of frequency, duration and age at starting smoking. All levels of intensity of bidi smoking were associated with significant relative risk estimates, ranging from 1.8 (95% CI, 1.1–2.9) to 5.1 (95% CI, 2.7–9.6), with a highly significant trend ($p < 0.001$). When duration of bidi smoking was tested in a forward stepwise logistic regression model adjusted for cigarette smoking, alcohol consumption and the combination of bidi with cigarette smoking, the relative risk for bidi smoking for more than 21 years was 7.1 (95% CI, 4.0–12.5), with a highly significant trend ($p < 0.001$). Daily intensity of bidi and cigarette smoking also exhibited a highly significant trend in this model ($p < 0.001$).

The case–control study described in the section on cancer of the pharynx (Rao *et al.*, 1999) also included 427 patients with cancer of larynx. A total of 635 controls were selected from male outpatients at the same hospital who had been found to be free from cancer, benign tumours and infectious disease. Cases and controls were stratified into four 5-year age groups and by place of residence. The estimated relative risk for bidi smoking was 2.3 (95% CI, 1.7–3.2). A dose–response relationship was observed for number of bidis smoked daily. When unconditional logistic regression was performed using five factors, bidi smoking was the most important risk factor.

(*e*) *Oesophageal cancer*

A hospital-based case–control study of oesophageal cancer was carried out during 1983–84 at the Regional Cancer Centre, Trivandrum in Kerala, India (Sankaranarayanan *et al.*, 1991). Among 267 cases recruited to the study, 67% were histopathologically confirmed and the remainder were radiologically diagnosed. From outpatients attending the centre and surrounding medical complex during this period, 895 controls with non-malignant or pre-malignant conditions were selected. Relative risks were adjusted for age and religion through unconditional logistic regression. Significant effects were noted in men for all levels of intensity of bidi smoking and for a duration of more than 20 years of bidi smoking (Table 2.2.26). The trends for intensity and for duration of smoking of bidis and of bidis and cigarettes were all significant. In a forward stepwise logistic regression model, duration of bidi smoking and daily frequency of bidi/cigarette smoking emerged as statistically significant factors.

A hospital-based case–control study investigated the risk for oesophageal cancer by subsite and histomorphology at the Kidwai Memorial Institute of Oncology, Bangalore, in Karnataka, India (Nandakumar *et al.*, 1996). Of 549 patients (284 men, 265 women) diagnosed with oesophageal cancer between 1982 and 1985, data were collected on 343 (177 men, 166 women) using a structured questionnaire. Of these, 236 cases had a microscopically confirmed diagnosis of squamous-cell carcinoma. For each case, two controls were randomly selected from a database of 1875 patients who were proven not to have cancer or benign tumours. They were matched on sex, 5-year age group, area of residence and calendar time of their hospital visit. Among the men, 12 cases and 15 controls predominantly smoked bidis but also smoked cigarettes, and were combined with the bidi smokers. Similarly, four men who predominantly smoked cigarettes but also smoked bidis were considered to be cigarette smokers. Women were not included in the analyses because few of them practised those habits. After adjusting for tobacco chewing, chewing of betel quid without tobacco, alcohol drinking and cigarette smoking, bidi smoking had an odds ratio of 4.0 (95% CI, 2.3–6.8) for cancer of the oesophagus. Bidi smoking resulted in a significantly elevated risk for all three segments of the oesophagus, but the highest was for the upper third (odds ratio, 7.1; 95% CI, 1.1–46.8), followed by the middle third (odds ratio, 6.0; 95% CI, 2.5–14.5) and the lower third (odds ratio, 3.9; 95% CI, 1.4–10.7).

In a case–control study conducted from February 1994 to March 1997 at the All India Institute of Medicine (AIIMS), New Delhi, 150 patients with histopathologically confirmed oesophageal cancer were enrolled as cases (Nayar *et al.*, 2000). An equal number of controls were selected from individuals accompanying patients to the same hospital, after matching for age (± 5 years), sex and socioeconomic status. Both cases and controls had to meet the criterion that they had not suffered from any major illness in the past that had caused them to change their dietary consumption pattern. Data were stratified on socioeconomic status into five groups. Using unconditional stepwise logistic regression, bidi smoking showed an odds ratio of 2.0 (95% CI, 1.2–3.3). This was adjusted for other risk factors in the model, such as chewing of betel leaf with tobacco and low consumption of vegetables other than leafy vegetables.

(*f*) *Stomach cancer*

A hospital-based case–control study of stomach cancer was conducted at the Cancer Institute (WIA), Madras, located in south India, as part of a multi-centre study (Gajalakshmi & Shanta, 1996; see Table 2.2.27). Patients with stomach cancer confirmed by histology, endoscopy, barium meal or surgery were included in the study. The control pool was formed by cancer patients diagnosed at the Cancer Institute, excluding those with cancer of the oral cavity, pharynx, larynx, lung, urinary bladder, pancreas and gastro-intestinal tract. Each case was matched with a cancer patient from the control pool on age, sex, religion and mother tongue. Details collected on smoking habits included type of tobacco smoked, age at starting smoking, amount smoked per day, and age at cessation (more than 6 months prior to diagnosis of cancer). The odds ratio for stomach cancer for current smoking of any type of tobacco was 2.7 (95% CI, 1.8–4.1); for current bidi smoking the odds ratio was 3.2 (95% CI, 1.8–5.7); that for chutta smoking was 2.4 (95% CI, 1.2–4.9); that for having more than one smoking habit was 8.2 (95% CI, 1.7–38.9). The trend for increasing lifetime exposure to bidi smoking was highly significant ($p < 0.001$). A significant trend for increasing lifetime chutta smoking was also seen. In a multivariate model including tobacco habits, alcohol drinking and various dietary factors, as well as income, education and area of residence, the odds ratios for current smokers, former smokers and ever-smokers were not substantially different from those in the above models.

Table 2.2.1. Cohort studies on exclusive pipe and/or cigar smoking and cancer of the oral cavity and pharynx

Reference Study and years of study	Site ICD codes	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe only or cigar only				
Hammond & Horn (1958) American Cancer Society (9-State) Study 1952–55	Oral cavity, pharynx, larynx, oesophagus	Never-smoker (4) Ever pipe only (7) Ever cigar only (10)	1.0 3.5 [1.02–12.0] 5.0 [1.6–15.9]	Age
Kahn (1966) US Veterans' Study 1954–62	Oral cavity 140–144 (ICD-7)	Never-smoker (11) Former pipe only (1) Current pipe only (4) Former cigar only (2) Current cigar only (9)	1.0 2.5 [0.3–19.1] 3.1 [0.99–9.8] 3.0 [0.7–13.5] 4.1 [1.7–9.9]	Age
	Pharynx 145–148 (ICD-7)	Never-smoker (4) Former pipe only (0) Current pipe only (1) Former cigar only (1) Current cigar only (0)	1.0 – 2.0 [0.2–17.7] 3.7 [0.4–32.8] –	Age
Carstensen *et al*. (1987) Swedish Census Study 1963–79	Oral cavity, pharynx, larynx 140–146, 148, 161 (ICD-8)	Never-smoker (4) Current pipe only (3) Current cigar only (1)	1.0 1.4 [0.3–6.3] 0.6 [0.1–5.4]	Age, residence
Shanks & Burns (1998) Cancer Prevention Study I 1959–72	Oral cavity, pharynx, excluding salivary glands	Never-smoker (18) Current cigar only (25) 1–2 cigars/day 3–4 cigars/day > 5 cigars/day No inhalation Slight inhalation Moderate and deep inhalation	1.0 7.9 (5.1–11.7) 2.1 (0.4–6.2) 8.5 (3.7–16.8) 15.9 (8.7–26.8) 7.0 (4.1–11.0) 7.8 (1.6–22.9) 27.9 (5.6–81.5)	Age
	Pharynx	Never-smoker (10) Current cigar only (12) 1–2 cigars/day 3–4 cigars/day > 5 cigars/day	1.0 6.7 (3.5–11.8) 3.8 (0.8–11.1) 7.5 (2.0–19.3) 9.9 (3.2–23.2)	

Table 2.2.1 (contd)

Reference Study and years of study	Site ICD codes	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/ comments
Shanks & Burns (1998) (contd)		No inhalation	6.9 (3.3–12.6)	
		Slight inhalation	5.0 (0.1–27.7)	
		Moderate and deep inhalation	15.5 (3.6–12.1)	
Iribarren *et al*. (1999) Kaiser Permanente Medical Care Program Study 1971–96	Oral cavity, pharynx	Never-smoker (39)	1.0	Age, race, body-mass index, diabetes, alcohol, occupational exposures
		Current cigar only (8)	2.6 (1.2–5.8)	
		< 5 cigars/day (3)	1.3 (0.4–4.4)	
		> 5 cigars/day (4)	7.2 (2.4–21.2)	
	Oral cavity, pharynx, larynx, oesophagus	Never-smoker (57)	1.0	
		Current cigar only (10)	2.0 (1.0–4.1)	
		< 5 cigars/day (4)	1.1 (0.4–3.1)	
		> 5 cigars/day (5)	5.2 (2.0–13.5)	
Shapiro *et al*. (2000) Cancer Prevention Study II 1982–94	Oral cavity, pharynx	Never-smoker (20)	1.0	Age, alcohol, use of smokeless tobacco
		Former cigar only (4)	2.4 (0.8–7.3)	
		Current cigar only (6)	4.0 (1.5–10.3)	
		1–2 cigars/day (0)	–	
		> 3 cigars/day (6)	7.6 (2.9–19.6)	
		< 25 years (0)	–	
		≥ 25 years (5)	4.6 (1.6–13.0)	
		No inhalation (3)	3.2 (0.9–11.0)	
		Inhalation (2)	6.5 (1.4–29.2)	
Pipe and cigar				
Doll & Peto (1976) British Doctors' Study 1951–71	Oral cavity (excluding nasopharynx), pharynx, larynx, trachea	Never-smoker	1.0	Age
		Current pipe/cigar only	9.0	Includes former cigarette smokers
Chow *et al*. (1993) US Veterans' Study 1954–80	Nasopharynx	Never-smoker (5)	1.0	Age, year
		Ever pipe/cigar only (2)	1.0 (0.2–5.2)	

Table 2.2.2. Case–control studies on exclusive pipe and/or cigar smoking and cancers of the oral cavity and pharynx

Reference Country and years of study	Study characteristics	Site ICD9 codes	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe only or cigar only					
Zheng *et al*. (1990) China 1988–89	248 cases (men) 248 hospital controls, age 18–80 years, response rate 100/100%	Oral cavity 141,143–145	Never-smoker (58/105) Ever pipe only (47/13) < 8 g tobacco/day 8–15.2 g tobacco/day > 15.2 g tobacco/day	1.0 5.7 (2.4–13.3) 3.5 (1.2–10.1) 4.9 (2.0–12.1) 6.3 (2.6–15.2)	Hospital, age, alcohol, education
	156 cases (women) 156 hospital controls	Oral cavity 141,143–145	Never-smoker (104/140) Ever pipe only (26/5)	1.0 4.9 (1.5–16.0)	
La Vecchia *et al*. (1998) Italy/Switzerland 1984–97	59 cases (men) 801 hospital controls, age < 75 years, response rate 98/97%	Oral cavity, pharynx, oesophagus [codes not given]	Never-smoker (50/788) Current cigar only (7/5) Ever cigar only (9/13) Ever > 3 cigars/day (4/5)	1.0 14.9 (4.0–55.9) 6.8 (2.5–18.5) 8.9 (2.1–36.9)	Age, alcohol, education Same study population as Franceschi *et al.* (1990) (see below)
	36 cases (men)	Oral cavity, pharynx	Ever cigar only	9.0 (2.7–30.0)	
	23 cases (men)	Oesophagus	Ever cigar only	4.1 (0.7–23.0)	
Pipe and cigar					
Blot *et al*. (1988) USA 1984–85	762 cases (men) 837 population controls, age 18–79 years, median 63; response rate 75/76%	Oral cavity, pharynx 141,143–146 148–149	Never-smoker (50/185) Ever pipe/cigar only (52/56) ≥ 40 cigars/week (14/1) ≥ 40 pipefuls/week (12/7)	1.0 1.9 (1.1–3.4) 16.7 (3.7–76.7) 3.1 (1.1–8.7)	Age, race, location, alcohol, respondent status (self/proxy)
Franceschi *et al*. (1990) Italy 1986–89	291 cases (men) 1272 hospital controls, age < 75 years, response rate 98/97%	Oral cavity 140–141, 143–145	Never-smoker (4/289) Ever pipe/cigar only (6/14)	1.0 20.7 (5.6–76.3)	Age, area
		Pharynx 146, 148, 161.1	Never-smoker (2/289) Ever pipe/cigar only (0/2)	 –	

Table 2.2.2 (contd)

Reference Country and years of study	Study characteristics	Site ICD9 codes	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/ comments
Franceschi *et al*. (1992) Italy 1986–90	102 cases (men) 726 hospital controls 104 cases (men) age < 75 years, median 58, response rate 98/97%	Tongue 141 Mouth 143–145,149	Never-smoker (3/153) Current pipe/cigar only (1/6) Never-smoker (3/153) Current pipe/cigar only (5/6)	1.0 3.4 (0.3–39.1) 1.0 21.9 (3.8–125.6)	Age, area, occupation, alcohol Age, area, occupation, alcohol Same study population as as Franceschi *et al.* (1990) (see above)
Fernandez Garrote *et al*. (2001) Cuba 1996–99	200 cases (men/ women) 200 hospital controls, age 25–91 years, median 63; response rate 88/79%	Oral cavity, pharynx [codes not given]	Never-smoker (16/81) Current pipe/cigar only < 4 pipes/cigars/day (6/7) ≥ 4 pipes/cigars/day (11/3)	1.0 4.3 (1.1–16.4) 20.5 (4.7–89.7)	Age, sex, area, education, alcohol *p* for trend < 0.01

Table 2.2.3. Effect of interaction between pipe and/or cigar smoking and alcohol drinking on cancer of the oral cavity and pharynx

Reference Country and years of study	Study characteristics	Site ICD9 codes	Smoking/alcohol category (cases/deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only					
Iribarren *et al*. (1999) Kaiser Permanente Medical Care Program Study 1971–1996	17 774 men, 47 cases, age 30–85 years, median 46	Oral cavity, pharynx 140–149	Never-smoker/< 2 drinks/day (39) Never-smoker/> 3 drinks/day (1) Current cigar/< 2 drinks/day (4) Current cigar/> 3 drinks/day (4)	1.0 0.4 (0.1–2.8) 1.5 (0.5–4.3) 7.6 (2.7–21.6)	
Pipe and cigar					
Blot *et al*. (1988) USA 1984–85	762 cases (men) 837 population controls age 18–79 years, median 63	Oral cavity, pharynx 141, 143–146, 148– 149	Never-smoker/< 1 drink/week Ever pipe/cigar/< 1 drink/week Ever pipe/cigar/1–4 drinks/week Ever pipe/cigar/5–14 drinks/week Ever pipe/cigar/15–29 drinks/week Ever pipe/cigar/≥ 30 drinks/week	1.0 0.6 1.0 3.7 4.7 23.0	Age, race, location, respondent status (self/ proxy)

Table 2.2.4. Cohort studies on exclusive pipe and/or cigar smoking and lung cancer

Reference Study and years of study	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only			
Hammond & Horn (1958) American Cancer Society (9-state) Study 1952–55	Never-smoker (15) Ever pipe only (18) Ever cigar only (7)	1.0 3.0 [1.5–6.0] 1.0 [0.4–2.5]	Age
Kahn (1966) US Veterans' Study 1954–62	Never-smoker (78) Former pipe only (7) Current pipe only (17) Former cigar only (5) Current cigar only (25)	1.0 2.4 [1.1–5.2] 1.8 [1.1–3.1] 1.0 [0.4–2.5] 1.6 [1.01–2.5]	Age
Carstensen *et al*. (1987) Swedish Census Study 1963–79	Never-smoker (23) Current pipe only (59) Current cigar only (11)	1.0 7.2 [4.4–11.7] 7.6 [3.7–15.6]	Age, residence; risk increased with grams of tobacco smoked per day.
Lange *et al*. (1992) Copenhagen City Heart Study 1976–89	Never-smoker (5) Current cigar/cheroot only (47) Current pipe only (16)	1.0 6.0 (2.2–17) 4.1 (1.4–13)	Men; age; 17% lung cancer deaths attributable to cigar/cheroot and pipe smoking
	Never-smoker (7) Current cigar/cheroot only (14)	1.0 4.9 (3.0–12)	Women; age; 10% lung cancer deaths attributable to cigar/cheroot smoking
Tverdal *et al*. (1993) Norwegian Screening Study 1973–88	Never-smoker (4) Current pipe only (19)	1.0 [13.0 (4.4–38.2)]	Age and area
Ben-Shlomo *et al*. (1994) Whitehall Study 1967–87	Never-smoker (24) Current pipe only (8) Current cigar only (1)	1.0 [4.0 (1.8–8.9)] [1.8 (0.2–13.3)]	Age
Wald & Watt (1997) BUPA Study 1975–93	Never-smoker (7) Current pipe/cigar only (6)	1.0 3.2 (1.1–9.5)	Age
Shanks & Burns (1998) CPS-I 1959–72	Never-smoker (191) Current cigar only (73) 1–2 cigars/day 3–4 cigars/day > 5 cigars/day No inhalation Slight inhalation Moderate and deep inhalation	1.0 2.1 (1.6–2.7) 0.9 (0.5–1.7) 2.4 (1.5–3.5) 3.4 (2.3–4.8) 2.0 (1.5–2.6) 1.9 (0.8–3.7) 4.9 (1.8–10.7)	Age

Table 2.2.4 (contd)

Reference Study and years of study	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Iribarren *et al.* (1999) Kaiser Permanente Medical Care Program Study 1971–96	Never-smoker (54) Current cigar only (11) < 5 cigars/day (6) > 5 cigars/day (3)	1.0 2.1 (1.1–4.1) 1.6 (0.7–3.7) 3.2 (1.01–10.4)	Age, race, body-mass index, diabetes, alcohol, occupational exposures
Shapiro *et al.* (2000) CPS-II 1982–94	Never-smoker (269) Former cigar only (36) Current cigar only (88) 1–2 cigars/day (10) > 3 cigars/day (68) < 25 years (8) > 25 years (75) No inhalation (36) Inhalation (37)	1.0 1.6 (1.2–2.4) 5.1 (4.0–6.6) 1.3 (0.7–2.4) 7.8 (5.9–10.3) 2.1 (1.0–4.2) 5.9 (4.5–7.7) 3.3 (2.3–4.7) 11.3 (7.9–16.1)	Age, alcohol, smokeless tobacco
Pipe and cigar			
Doll & Peto (1976) British Doctors' Study 1951–71	Never-smoker Current pipe/cigar only	1.0 5.8	Age
Chow *et al.* (1992) Lutheran Brotherhood Insurance Study 1966–86	Never-smoker (6) Current pipe/cigar only (4) Former pipe/cigar only (1)	1.0 3.5 (1.0–12.6) 1.3 (0.2–10.5)	Age and occupation

Table 2.2.5. Case–control studies on exclusive pipe and/or cigar smoking and lung cancer

Reference Country and years of study	Study charac-teristics	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only				
Lubin *et al.* (1984) 7 areas in Europe 1976–80	6920 cases (men) 13 460 hospital controls	Never-smoker (190/2616)	1.00	Age, study location, hospital
		Ever pipe only (39/197)	2.5 [1.8–3.7]	
		1–19 years (3/36)	1.1 [0.3–3.6]	
		20–29 years (3/43)	1.02 [0.3–3.3]	
		30–39 years (11/54)	2.5 [1.3–4.9]	
		≥ 40 years (22/64)	4.4 [2.7–7.4]	*p* for trend < 0.01
		1–3 pipes/day (14/49)	3.2 [1.8–6.0]	
		4–6 pipes/day (13/79)	2.2 [1.2–4.0]	
		≥ 7 pipes/day (12/68)	2.7 [1.4–5.1]	*p* for trend < 0.01
		Inhalation		
		Never inhaled	1.0	
		Moderately inhaled	1.3	
		Deeply inhaled	1.3	*p* for trend = 0.06 also adjusted for duration
		Current pipe only	1.0	
		1–4 years since quitting	2.0	
		> 5 years since quitting	0.9	*p* for trend = 0.33 also adjusted for duration
		Never-smoker (190/2616)	1.0	Age, study location, hospital
		Ever cigar only (37/145)	2.9 [2.0–4.3]	
		1–19 years (5/30)	2.4 [0.9–6.4]	
		20–29 years (10/29)	4.2 [2.0–8.8]	
		30–39 years (8/36)	2.4 [1.1–5.2]	
		≥ 40 years (14/50)	3.0 [1.6–5.5]	*p* trend < 0.01
		1–3 cigars/day (8/61)	1.6 [0.7–3.3]	
		4–6 cigars/day (12/59)	2.2 [1.2–4.1]	
		≥ 7 cigars/day (17/25)	8.9 [4.7–16.8]	*p* for trend < 0.01
		Inhalation		
		Never inhaled	1.0	
		Moderately inhaled	2.7	
		Deeply inhaled	9.5	*p* for trend < 0.01 also adjusted for duration
		Current cigar only	1.0	
		1–4 years since quitting	0.6	
		> 5 years since quitting	0.7	*p*-value for trend = 0.17 also adjusted for duration

Table 2.2.5 (contd)

Reference Country and years of study	Study characteristics	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/comments
Benhamou *et al*. (1986) France 1976–80	1529 cases (men) 2899 hospital controls [response rate not reported]	Never-smoker (36/650)	1.0	Age, hospital, interviewer
		Ever pipe only (5/56)	1.6 (0.5–4.5)	Same study population as Lubin *et al*. (1984)
		Inhalation		
		No inhalation (5/48)	1.9	
		Sometimes/rarely inhaled (0/6)	–	
		Usually/always inhaled (0/2)	–	
		Ever pipe only < 10 years (0/5)	1.0	
		Ever pipe only > 10 years (5/51)	1.17	
		Never-smoker (36/650)	1.0	Age, hospital, interviewer
		Ever cigar only (9/29)	5.6 (2.3–13.5)	
		Inhalation		
		No inhalation (6/28)	3.9	
		Sometimes/rarely inhaled (1/0)	–	
		Usually/always inhaled (2/1)	36.1	p for trend < 0.01
		Ever cigar only < 15 years (1/9)	1.0	
		Ever cigar only > 15 years (8/20)	3.6	
Damber & Larsson (1986) Sweden 1972–77	579 cases (men) 582 population controls (dead), response rate: 98/96%	Never-smoker (42/208)	1.0	Age; postal questionnaire — answered by relatives of cases and or controls; risk increased with years of smoking and decreased with years of cessation [odds ratios not given]
		Ever pipe only (198/142)	6.9 [4.5–10.5]	
		< 100 g/week	4.7	
		> 100 g/week	11.1	
		Ever cigar only (7/7)	[5.0 (1.5–16.8)]	
Qiao *et al*. (1989) China 1985	107 cases (men) 107 occupational controls, age 35–80 years, response rate: 100/100%	Never-smoker (3/5)	1.0	Age; participants were tin miners (1967–84); interviews with 10/6% proxy
		Ever water pipe only (24/23)	1.9 (0.4–9.4)	
Lubin *et al*. (1992) China 1984–88	544 cases (men) 1043 occupational and population controls, age 35–75 years, response rate: 92/91%	Never-smoker (9/72)	1.0	Age, type of control, proxy, years of work underground
		Ever pipe only (56/151)	1.8 (0.8–4.2)	Smoking of water pipe or Chinese long-stem pipe (extension of Qiao *et al*., 1989)
		1–150 g/month (18/41)	2.1 [0.9–5.1]	
		200 g/month (4/18)	2.6 [0.7–9.3]	
		250 g/month (25/44)	4.1 [1.8–9.6]	
		≥ 300 g/month (9/47)	1.3 [0.5–3.5]	
		1–29 years (7/21)	2.1 [0.7–6.3]	
		30–39 years (13/31)	2.7 [1.1–7.0]	
		40–49 years (24/70)	2.5 [1.1–5.8]	
		≥ 50 years (10/32)	2.1 [0.8–5.6]	

Table 2.2.5 (contd)

Reference Country and years of study	Study characteristics	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/comments
Boffetta *et al.* (1999) Germany, Italy, Sweden 1988–94	5621 cases (men) 7255 hospital controls, response rate 67/38% and above	**Pipe**		
		Nonsmoker (117/1750)	1.0	Age, study centre
		Ever pipe only (61/129)	7.9 (5.3–11.8)	
		< 20 years (3/33)	1.3 (0.4–4.5)	
		20.1–32 years (7/33)	3.4 (1.4–8.0)	
		32.1–44 years (21/33)	13.3 (7.2–24.9)	
		≥ 44.1 years (30/30)	19.1 (10.4–35.1)	p for trend < 0.0001
		< 3.5 g/day (2/10)	2.2 (0.5–10.4)	
		3.6–5.0 g/day (22/54)	7.9 (4.3–14.3)	
		5.1–10.7 g/day (6/18)	4.8 (1.9–12.6)	
		≥ 10.8 g/day (31/47)	12.4 (7.2–21.4)	p for trend = 0.1
		Age at start < 20 (27/48)	9.6 (5.6–16.7)	
		Age at start 20–26 (20/52)	6.3 (3.5–11.2)	
		Age at start ≥ 27 (14/29)	8.2 (4.1–16.3)	p for trend = 0.4
		Nonsmoker (117/1750)	1.0	Age, study centre
		Current pipe only	12.5 (7.7–20.2)	
		Former, quit 1–14 years ago	10.3 (5.1–20.5)	
		Former, quit > 15 years ago	1.4 (0.5–4.0)	
		Cigar/cigarillo		
		Nonsmoker (117/1750)	1.0	Age, study centre
		Ever cigar only (16/42)	5.6 (2.9–10.6)	
		Ever cigarillo only (21/31)	12.7 (6.9–23.7)	
		Ever cigar/cigarillo only (43/77)	9.0 (5.8–14.1)	
		< 13 years (4/21)	3.1 (1.0–9.4)	
		13.1–26 years (5/20)	4.3 (1.6–11.9)	
		26.1–39 years (12/17)	10.3 (4.7–22.7)	
		> 39.1 years (22/19)	20.7 (10.5–41.1)	p for trend = 0.0003
		< 5 g/day (5/22)	3.4 (1.3–9.5)	
		5.1–12 g/day (10/25)	6.2 (2.8–13.7)	
		12.1–15 g/day (5/11)	7.8 (2.6–23.4)	
		≥ 15.1 g/day (23/19)	21.1 (10.7–41.7)	p for trend = 0.01
		Age at start < 20 (20/20)	17.0 (8.6–33.4)	
		Age at start 20–26 (16/23)	10.5 (5.3–21.1)	
		Age at start > 27 (7/34)	3.4 (1.5–8.0)	p for trend = 0.002
		Inhalation		
		Non-inhaler	5.2 (2.7–10.0)	
		Inhaler	28.1 [9.5–83.6]	
		Nonsmoker (117/1750)	1.0	Age, study centre
		Current cigar/cigarillo only	10.6 (5.9–19.1)	
		Former, quit 1–14 years ago	8.8 (4.0–19.5)	
		Former, quit > 15 years ago	6.9 (3.1–15.1)	

Table 2.2.6. Studies on exclusive pipe and/or cigar smoking and cancer of the larynx

Reference Study and years of study	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe only or cigar only			
Kahn (1966) US Veterans' Study 1954–62	Never-smoker (3)	1.0	Age
	Former pipe only (0)	–	
	Current pipe only (0)	–	
	Former cigar only (0)	–	
	Current cigar only (6)	10.3 [2.6–41.3]	
Shanks & Burns (1998) CPS-I 1959–72	Never-smoker (4)	1.0	Age
	Current cigar only (7)	10.0 (4.0–20.6)	
	1–2 cigars/day	6.5 (0.7–23.3)	
	3–4 cigars/day	–	
	> 5 cigars/day	26.0 (8.4–60.7)	
	No inhalation	10.6 (3.9–23.1)	
	Slight inhalation	–	
	Moderate and deep inhalation	53.3 (0.7–296.3)	
Shapiro *et al.* (2000) CPS-II 1982–94	Never-smoker (5)	1.0	Age, alcohol, smokeless tobacco use; excludes cancer at baseline
	Former cigar only (3)	6.7 (1.5–30.0)	
	Current cigar only (4)	10.3 (2.6–41.0)	
	1–2 cigars/day (1)	6.0 (0.7–53.5)	
	> 3 cigars/day (3)	15.0 (3.4–65.9)	
	< 25 years (0)	–	
	> 25 years (4)	13.7 (3.4–54.5)	
	No inhalation (1)	4.2 (0.5–37.1)	
	Inhalation (3)	39.0 (8.4–180.1)	

Table 2.2.7. Case–control study on exclusive pipe and/or cigar smoking and cancer of the larynx

Reference Country and years of study	Study characteristics	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe and cigar				
Franceschi *et al.* (1990) Italy 1986–89	162 cases (men) 1272 hospital controls age < 75 years, response rate 98/97%	Never-smoker (8/289) Ever pipe/cigar only (1/14)	1.0 2.8 (0.3–26.1)	Age, area

Table 2.2.8. Cohort studies on exclusive pipe and/or cigar smoking and cancers of the oesophagus and stomach

Reference Name of study and years of study	Site	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only				
Hammond & Horn (1958) American Cancer Society (9-state) Study 1952–55	Stomach, pancreas, liver, colorectum	Never-smoker (100) Ever pipe only (41) Ever cigar only (63)	1.0 1.0 [0.7–1.4] 1.4 [1.1–1.8]	Age
Kahn (1966) US Veterans' Study 1954–62	Oesophagus	Never-smoker (11) Former pipe only (0) Current pipe only (3) Former cigar only (2) Current cigar only (12)	1.0 – 2.0 [0.6–7.1] 2.4 [0.5–10.9] 5.3 [2.4–12.1]	Age
	Stomach	Never-smoker (96) Former pipe only (4) Current pipe only (16 Former cigar only (8) Current cigar only (23)	1.0 1.1 [0.4–3.0] 1.4 [0.8–2.4] 1.3 [0.6–2.7] 1.2 [0.8–1.9]	
Carstensen *et al*. (1987) Swedish Census Study 1963–79	Oesophagus	Never smoker (5) Current pipe only (6) Current cigar only (2)	1.0 3.6 [1.1–11.8] 6.5 [1.3–33.5]	Age, residence
Tverdal *et al*. (1993) Norwegian Screening Study 1973–88	Stomach	Never-smoker (8) Current pipe only (4)	1.0 [1.5 (0.5–5.1)]	Age and area
Shanks & Burns (1998) CPS-I 1959–72	Oesophagus	Never-smoker (30) Current cigar only (19) 1–2 cigars/day 3–4 cigars/day > 5 cigars/day No inhalation Slight inhalation Moderate and deep inhalation	1.0 3.6 (2.2–5.6) 2.3 (0.7–5.3) 3.9 (1.4–8.6) 5.2 (2.2–10.2) 3.4 (1.9–5.6) 1.9 (0.0–10.6) 14.8 (3.0–43.5)	Age
Shapiro *et al*. (2000) CPS-II 1982–94	Oesophagus	Never-smoker (67) Former cigar only (8) Current cigar only (9) 1–2 cigars/day (4) > 3 cigars/day (5) < 25 years (1) > 25 years (8) No inhalation (5) Inhalation (1)	1.0 1.3 (0.6–2.8) 1.8 (0.9–3.7) 1.8 (0.6–5.0) 1.9 (0.8–4.9) 0.9 (0.1–6.4) 2.2 (1.0–4.7) 1.6 (0.7–4.1) 1.0 (0.1–7.2)	Age, alcohol, smokeless tobacco use

Table 2.2.8 (contd)

Reference Name of study and years of study	Site	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Chao *et al*. (2002) CPS-II 1982–96	Stomach	Never-smoker	1.0	Age, race, education, family history of stomach cancer, use of aspirin and several dietary habits
		Former cigar only (13)	1.3 (0.7–2.2)	
		Current cigar only (25)	2.3 (1.5–3.5)	
		1–4 cigars/day (13)	1.7 (0.95–3.0)	
		≥ 5 cigars/day (12)	4.2 (2.3–7.6)	
		< 39 years of smoking (13)	2.4 (1.4–4.3)	
		≥ 40 years of smoking (10)	2.6 (1.3–4.9)	
		Age at starting		
		≥ 30 years (5)	1.6 (0.7–4.0)	
		20–29 years (12)	2.9 (1.6–5.2)	
		≤ 19 years (6)	2.4 (1.1–5.6)	
		No inhalation (15)	2.1 (1.2–3.6)	
		Inhalation (8)	3.9 (1.9–8.0)	
		Former pipe only (6)	0.7 (0.3–1.6)	
		Current pipe only (16)	1.3 (0.8–2.2)	
Pipe and cigar				
Doll & Peto (1976) British Doctors' Study 1951–71	Oesophagus	Never-smoker	1.0	Age
		Current pipe/cigar only	3.7	
Kneller *et al*. (1991) Lutheran Brotherhood Insurance Study 1966–86	Stomach	Never-smoker (8)	1.0	Age
		Tobacco but never cigarettes (6)	1.5 (0.5–4.4)	

Table 2.2.9. Case–control studies on exclusive pipe and/or cigar smoking and cancers of the oesophagus and stomach

Reference Country and years of study	Study characteristics	Site	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only					
La Vecchia *et al*. (1998) Italy/Switzerland 1984–97	23 cases (men) 801 hospital controls age < 75 years; response rate 98/97%	Oesophagus	Never-smoker (50/788) Ever cigar only	1.0 4.1 (0.7–23.0)	Age, alcohol consumption, education Same study population as Franceschi *et al*. (1990) below
Pipe and cigar					
Wu-Williams *et al*. (1990) USA 1975–82	137 cases (white men) 137 population controls, mean age 47 years, response rate 52% (matched design)	Stomach	Never-smoker (21/35) Ever pipe/cigar only (3/3)	1.0 1.8 (0.3–9.8)	Age, race, area
Franceschi *et al*. (1990) Italy 1986–89	288 cases (men) 1272 hospital controls age < 75 years, response rate 98/97%	Oesophagus	Never-smoker (17/289) Ever pipe/cigar only (7/14)	1.0 6.3 (2.3–19.8)	Age, area
Kabat *et al*. (1993) USA 1981–90	431 cases (white men) 4544 hospital controls [response rate not reported]	SCCE	Never-smoker (15/1054) Ever pipe/cigar only (11/332)	1.0 1.8 (0.8–4.1)	Age, hospital, time period, education, alcohol consumption
		AEC	Never-smoker (25/1054) Ever pipe/cigar only (9/332)	1.0 1.1 (0.5–2.3)	
		ADS	Never-smoker (23/1054) Ever pipe/cigar only (8/332)	1.0 1.0 (0.4–2.2)	

SCCE, squamous-cell carcinoma of the oesophagus; AEC, adenocarcinoma of the oesophagus or cardia; ADS, adenocarcinoma of the distal stomach

Table 2.2.10. Cohort studies on exclusive pipe and/or cigar smoking and colorectal cancer

Reference Name of study and years of study	Site ICD code	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only				
Tverdal *et al*. (1993)	Colon	Never-smoker (9)	1.0	Age and area
Norwegian Screening		Current pipe only (3)	[0.9 (0.2–3.2)]	
Study	Rectum	Never-smoker (7)	1.0	
1973–88		Current pipe only (4)	[1.6 (0.5–5.5)]	
Heineman *et al*. (1995)	Colon	Never-smoker (782)	1.0	Age, calendar year, year of survey,
US Veterans' Study		Current pipe/cigar only (576)	1.3 (1.1–1.4)	socioeconomic status, sedentary job
1954–80		Current pipe < 5/day (22)	1.2 (0.8–1.9)	
		Current pipe 5–9/day (27)	1.2 (0.8–1.7)	
		Current pipe 10–19/day (11)	0.7 (0.4–1.2)	
		Current pipe > 20/day (15)	1.8 (1.1–2.9)	*p* for trend = 0.30
		Current cigar 1–2/day (50)	1.5 (1.1–1.9)	
		Current cigar 3–4/day (34)	0.9 (0.6–1.3)	
		Current cigar 5–8/day (44)	1.4 (1.1–1.9)	
		Current cigar > 9/day (15)	2.2 (1.3–3.7)	*p* for trend = 0.004
	Ascending	Never-smoker (67)	1.0	
	153.0	Current pipe/cigar only (48)	1.2 (0.8–1.7)	
	Transverse	Never-smoker (15)	1.0	
	153.1	Current pipe/cigar only (7)	0.8 (0.3–2.0)	
	Descending	Never-smoker (15)	1.0	
	153.2	Current pipe/cigar only (5)	0.6 (0.2–1.6)	
	Sigmoid	Never-smoker (67)	1.0	
	153.3	Current pipe/cigar only (54)	1.4 (1.0–2.0)	
	Rectum	Never-smoker (201)	1.0	
		Current pipe/cigar only (169)	1.4 (1.2–1.8)	
		Current pipe < 5/day (3)	0.6 (0.2–2.0)	
		Current pipe 5–9/day (11)	1.9 (1.0–3.5)	
		Current pipe 10–19/day (10)	2.3 (1.2–4.4)	
		Current pipe > 20/day (4)	1.8 (0.7–4.8)	*p* for trend = 0.007
		Current cigar 1–2/day (14)	1.6 (0.9–2.7)	
		Current cigar 3–4/day (13)	1.4 (0.8–2.4)	
		Current cigar 5–8/day (13)	1.6 (0.9–2.9)	
		Current cigar > 9/day (1)	0.6 (0.1–4.2)	*p* for trend = 0.12

Table 2.2.10 (contd)

Reference Name of study and years of study	Site ICD code	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Iribarren *et al*. (1999) Kaiser Permanente Medical Care Program Study 1971–96	Colon and rectum	Never-smoker (332) Current cigar only (39)	1.0 1.1 (0.8–1.6)	Age, race, body-mass index, diabetes, alcohol, occupational exposure; excludes cancer of interest at baseline
Pipe and cigar				
Doll & Peto (1976) British Doctors' Study 1951–71	Rectum	Never-smoker Current pipe/cigar only	1.0 1.7	Age
Hsing *et al*. (1998) Lutheran Brotherhood Insurance Study 1966–86	Colon	Never-smoker (16) Ever pipe/cigar only (16)	1.0 1.6 (0.8–3.2)	Age, urban/rural, alcohol
	Colon and rectum	Never-smoker (26) Ever pipe/cigar only (17)	1.0 1.0 (0.5–1.9)	
Knekt *et al*. (1998) Finnish Mobile Clinic Health Examination Study 1966–94	Colon and rectum	Never-smoker (264) Current pipe/cigar only (14)	1.0 1.5 (0.8–2.6)	Age, sex, body-mass index, area, occupation, marital status
	Colon	Never-smoker (144) Current pipe/cigar only (6)	1.0 1.5 (0.6–3.5)	
	Rectum	Never-smoker (120) Current pipe/cigar only (8)	1.0 1.5 (0.7–3.1)	
Chao *et al*. (2000) CPS-II 1982–96	Colon and rectum	Never-smoker (2156) Current pipe/cigar only ≥ 20 years	1.0 1.3 (1.1–1.6)	Age, race, body-mass index, education, exercise, intake of aspirin, multivitamins, alcohol, fibre, vegetables and fatty meats, and family history of colorectal cancer

Table 2.2.11. Cohort studies on exclusive pipe and/or cigar smoking and cancer of the liver and intrahepatic bile ducts

Reference Name of study and years of study	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe only or cigar only			
Carstensen *et al.* (1987) Swedish Census Study 1963–79	Never-smoker (9) Current pipe only (5) Current cigar only (4)	1.0 1.7 [0.6–5.1] 7.2 [2.2–23.4]	Age, residence
Hsing *et al.* (1990a) US Veterans' Study 1954–80	Nonsmoker (37) Current cigar/pipe smoker (47)	1.0 3.1 (2.0–4.8)	Age, year

Table 2.2.12. Case–control study on exclusive pipe and/or cigar smoking and cancer of the gallbladder and extrahepatic bile ducts

Reference Country and years of study	Study characteristics	Site	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe and cigar					
Chow *et al*. (1994) USA 1985–89	49 cases (white men) 97 population controls; age, 30–84 years; response rate: 76/84%	Extrahepatic bile duct	Never-smoker (6/25) Ever pipe/cigar only (2/7)	1.0 1.6 (0.3–9.9)	Adjusted for age and ethnicity (58% proxy for deceased cases)
		Ampulla of Vater	Never-smoker (1/25) Ever pipe/cigar only (2/7)	1.0 7.6 (0.6–100.4)	

Table 2.2.13. Cohort studies on exclusive pipe and/or cigar smoking and cancer of the pancreas

Reference Name of study and years of study	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe only or cigar only			
Kahn (1966) US Veterans' Study 1954–62	Never-smoker (88) Former pipe only (2) Current pipe only (8) Former cigar only (5) Current cigar only (27)	1.0 0.6 [0.2–2.4] 0.7 [0.4–1.5] 0.9 [0.4–2.1] 1.5 [0.99–2.3]	Age
Carstensen *et al*. (1987) Swedish Census Study 1963–79	Never-smoker (20) Current pipe only (19) Current cigar only (1)	1.0 2.8 [1.5–5.2] 1.0 [0.1–7.5]	Age, residence
Tverdal *et al*. (1993) Norwegian Screening Study 1973–88	Never-smoker (5) Current pipe only (2)	1.0 [1.2 (0.2–6.2)]	Age and area
Shanks & Burns (1998) CPS-I 1959–72	Never-smoker (198) Current cigar only (56) 1–2 cigars/day 3–4 cigars/day > 5 cigars/day No inhalation Slight inhalation Moderate and deep inhalation	1.0 1.6 (1.2–2.1) 1.2 (0.7–1.9) 1.5 (0.9–2.5) 2.2 (1.4–3.2) 1.6 (1.1–2.1) 2.2 (0.99–4.1) 2.3 (0.5–6.6)	Age
Iribarren *et al*. (1999) Kaiser Permanente Medical Care Program Study 1971–96	Never-smoker (46) Current cigar only (6)	1.0 1.2 (0.5–2.9)	Age, race, body-mass index, diabetes, alcohol, occupational exposures
Shapiro *et al*. (2000) CPS-II 1982–94	Never-smoker (327) Former cigar only (30) Current cigar only (28) 1–2 cigars/day (6) > 3 cigars/day (18) < 25 years (7) > 25 years (19) No inhalation (12) Inhalation (12)	1.0 1.1 (0.7–1.6) 1.3 (0.9–1.9) 0.6 (0.3–1.4) 1.6 (1.0–2.5) 1.5 (0.7–3.3) 1.1 (0.7–1.8) 0.9 (0.5–1.5) 2.7 (1.5–4.8)	Age, alcohol, smokeless tobacco use
Pipe and cigar			
Doll & Peto (1976) British Doctors' Study 1951–71	Never-smoker Current pipe/cigar only	1.0 0.9	Age
Zheng *et al*. (1993) Lutheran Brotherhood Insurance Study 1966–86	Never-smoker (9) Ever pipe/cigar only (5)	1.0 0.8 (0.3–2.5)	Age, alcohol

Table 2.2.14. Case–control studies on exclusive pipe and/or cigar smoking and cancer of the pancreas

Reference Country and years of study	Study characteristics	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only				
Muscat *et al*. (1997) USA 1985–93	290 cases (men) 572 hospital controls mean age 61 years; response rate 51/63%	Never-smoker (66/157) Ever pipe/cigar only (25/28)	1.0 2.1 (1.2–3.8)	Age, education; trained interviewer
		Nonsmoker (146/334) Ever pipe only (16/20) 1–20 years (6/7) > 20 years (10/13) 1–5 pipes/day (7/10) > 5 pipes/day (9/10)	1.0 1.8 (0.9–5.3) 1.8 (0.6–5.3) 1.6 (0.7–3.7) 1.4 (0.5–3.8) 1.4 (0.9–2.2)	Age, education; referent includes long-term quitters (> 20 years)
		Nonsmoker (146/334) Ever cigar only (15/12) 1–20 years (7/4) > 20 years (8/7) 1–4 cigars/day (8/11) > 4 cigars/day (7/1)	1.0 3.1 (1.4–6.9) 3.9 (1.2–13.6) 2.2 (0.8–7.3) 1.4 (0.6–3.6) 14.1 (1.7–115.7)	Age, education; referent includes long-term quitters (> 20 years)
Pipe and cigar				
Mack *et al*. (1986) USA 1976–81	490 cases (men/women) 490 population controls age < 65 years response rate 68/76%	Never-smoker (97/154) Ever pipe/cigar only (7/13)	1.0 0.9 (0.3–2.3)	Age, sex, race, neighbourhood
Partanen *et al*. (1997) Finland 1984–87	625 cases (men/women) 1700 hospital controls age 40–74 years [response rates not reported]	Never-smoker Ever pipe/cigar only Former pipe/cigar only Current pipe/cigar only	1.0 2.3 (1.3–4.4) 1.3 (0.8–2.0) 2.6 (1.4–4.9)	Adjusted for age and sex; smoking status in 1960; former smokers were those who had quitted before interview.
		Interaction with alcohol Never smoker/never drinker Never smoker/moderate drinker Never smoker/heavy drinker Ever pipe/cigar/never drinker Ever pipe/cigar/moderate drinker Ever pipe/cigar/heavy drinker	 1.0 1.1 (0.7–1.6) 0.8 (0.2–3.0) 2.2 (0.8–6.0) 2.2 (0.8–6.0) 2.2 (0.4–12.2)	 Adjusted for age and sex

Table 2.2.15. Cohort studies on exclusive pipe and/or cigar smoking and cancer of the bladder and kidney

Reference Name of study and years of study	Site	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe only or cigar only				
Hammond & Horn (1958) American Cancer Society (9-State) Study 1952–55	Bladder, kidney, prostate	Never-smoker (38) Ever pipe only (21) Ever cigar only (19)	1.0 1.2 [0.7–2.0] 1.1 [0.6–1.8]	Age
Kahn (1966) US Veterans' Study 1954–62	Bladder	Never-smoker (52) Former pipe only (1) Current pipe only (8) Former cigar only (4) Current cigar only (10)	1.0 0.5 [0.1–3.5] 1.2 [0.6–2.5] 1.1 [0.4–3.0] 0.9 [0.5–1.9]	Age
	Kidney	Never-smoker (39) Former pipe only (1) Current pipe only (6) Former cigar only (2) Current cigar only (6)	1.0 0.7 [0.1–5.0] 1.3 [0.6–3.1] 0.8 [0.2–3.5] 0.8 [0.3–1.8]	
Carstensen *et al*. (1987) Swedish Census Study 1963–79	Bladder	Never-smoker (11) Current pipe only (16) Current cigar only (1)	1.0 4.0 [1.9–8.6] 1.9 [0.2–14.7]	Age, residence
Shanks & Burns (1998) CPS-I 1959–72	Bladder	Never-smoker (102) Current cigar only (25) 1–2 cigars/day 3–4 cigars/day > 5 cigars/day No inhalation Slight inhalation Moderate and deep inhalation	1.0 1.4 (0.9–2.0) 0.8 (0.3–1.7) 1.7 (0.8–3.2) 2.0 (0.97–3.7) 1.6 (1.00–2.4) – 1.5 (0.0–8.4)	Age
Iribarren *et al*. (1999) Kaiser Permanente Medical Care Program Study 1971–96	Bladder	Never-smoker (99) Current cigar only (10)	1.0 1.1 (0.6–2.0)	Age, race, body-mass index, diabetes, alcohol, occupational exposures
	Kidney	Never-smoker (50) Current cigar only (5)	1.0 1.1 (0.4–2.7)	
Shapiro *et al*. (2000) CPS-II, 1982–94	Bladder	Never-smoker (94) Former cigar only (10) Current cigar only (6) 1–2 cigars/day (0) > 3 cigars/day (6) < 25 years (0) > 25 years (5) No inhalation (2) Inhalation (4)	1.0 1.3 (0.7–2.5) 1.0 (0.4–2.3) – 1.9 (0.8–4.4) – 1.1 (0.4–2.7) 0.5 (0.1–2.1) 3.6 (1.3–9.9)	Age, alcohol, smokeless tobacco use

Table 2.2.15 (contd)

Reference Name of study and years of study	Site	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe and cigar				
Doll & Peto (1976) British Doctors' Study 1951–71	Bladder	Never-smoker Current pipe/cigar only	1.0 1.6	Age
Steineck *et al.* (1988) Swedish Twin Registry Study 1967–82	Bladder	Never-smoker (8) Ever pipe/cigar only (16)	1.0 3.3 (1.5–7.4)	Age

Table 2.2.16. Case–control studies on exclusive pipe and/or cigar smoking and cancer of the bladder and kidney

Reference Country and years of study	Study characteristics	Site	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only					
Jensen *et al*. (1987) Denmark 1979–81	389 cases (men/ women), 787 population controls, response rate 94/75%	Bladder	Never-smoker (26/132) Ever pipe only (6/18) Ever cigar only (1/2) Ever cigarillo only (8/39) Ever mixed only (18/55)	1.0 1.9 (0.7–5.4) 2.5 (0.2–28.4) 1.0 (0.4–2.4) 1.9 (0.9–3.8)	Age, sex; mixed includes pipe, cigar and cigarillo combined; study included in Pitard *et al*. (2001)
Jensen *et al*. (1988) Denmark 1979–82	96 cases (men/women) 288 hospital controls age < 80 years, response rate 99/100%	Renal pelvis, ureter	Never-smoker (8/57) Ever pipe only (1/10) Ever cigar only (4/24) Ever pipe/cigar only (3/7)	1.0 2.2 (0.1–97) 1.3 (0.3–6.1) 6.5 (0.4–21.2)	Age, sex
McLaughlin *et al*. (1995) Australia, Europe, USA 1989–91	1774 cases 2359 controls age 20–79 years; response rate 72/75%	Renal cell	Never-smoker (585/846) Ever cigar only (18/34) Ever pipe only (19/29)	1.0 0.8 (0.4–1.4) 0.9 (0.5–1.7)	Age, sex, centre, body-mass index
Pitard *et al*. (2001) Europe 1980–95	2279 cases (men) 5268 controls age < 80 years Pooled analysis	Bladder	Never-smoker (154/1109) Ever pipe only (28/85) 1–39 years (11/52) > 40 years (16/33) Ever cigar only (50/122) 1–29 years (15/62) 30–39 years (12/28) > 40 years (22/32) 0.1–1.5 cigars/day (4/23) > 1.5 cigars/day (8/34) Ever pipe/cigar only (10/46)	1.0 1.9 (1.2–3.1) 1.4 (0.7–2.8) 2.5 (1.3–4.9) 2.3 (1.6–3.5) 1.4 (0.8–2.6) 2.7 (1.3–5.7) 3.8 (2.1–7.1) 1.3 (0.4–4.0) 1.9 (0.8–4.4) 1.3 (0.6–2.6)	Age, centre, occupational exposures *p* for trend = 0.006 *p* for trend < 0.001 *p* for trend = 0.1

Table 2.2.17. Cohort studies on exclusive pipe and/or cigar smoking and prostate cancer

Reference Name of study and years of study	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only			
Kahn (1966) US Veterans' Study 1954–62	Never-smoker (117) Former pipe only (5) Current pipe only (23) Former cigar only (11) Current cigar only (36)	1.0 1.1 [0.4–2.6] 1.5 [0.98–2.4] 1.3 [0.7–2.5] 1.5 [1.03–2.2]	Age
Tverdal *et al*. (1993) Norwegian Screening Study 1973–88	Never-smoker (4) Current pipe only (1)	1.0 [0.7 (0.1–5.9)]	Age and area
Pipe and cigar			
Hsing *et al*. (1990b) Lutheran Brotherhood Insurance Study 1966–86	Never-smoker (19) Ever pipe/cigar only (9)	1.0 1.6 (0.7–3.5)	Age
Hsing *et al*. (1991) US Veterans' Study 1954–80	Never-smoker (1075) Current pipe/cigar only (497)	1.0 1.1 (0.99–1.2)	Age

Table 2.2.18. Case–control study on exclusive pipe and/or cigar smoking and prostate cancer

Reference Country and years of study	Study characteristics	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe and cigar				
Sharpe & Siemiatycki (2001) Canada 1979–85	399 cases (men) 476 population controls, age 45–70 years, response rate 81/72%	Never-smoker (47/76) Ever pipe only (6/6) Ever cigar only (6/7)	1.0 1.2 (0.4–4.1) 1.3 (0.4–4.5)	Age, ethnicity, respondent status, body-mass index, income, alcohol consumption

Table 2.2.19. Cohort studies on exclusive pipe and/or cigar smoking and cancer of the haematopoietic system

Reference Name of study and years of study	Site	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe only or cigar only				
Hammond & Horn (1958)	Lymphoma, leukaemia	Never-smoker (31)	1.0	Age
American Cancer Society		Ever pipe only (15)	1.3 [0.7–2.3]	
(9-state) Study		Ever cigar only (10)	0.7 [0.4–1.5]	
1952–55				
Kinlen & Rogot (1988)	Lymphatic leukaemia	Never-smoker (41)	1.0	Age
US Veterans' Study		Ever pipe only (3)	0.8 (0.2–2.4)	
1954–69		Ever cigar only (11)	2.0 (1.0–3.6)	
	Monocytic myeloid leukaemia	Never-smoker (60)	1.0	
		Ever pipe only (6)	1.2 (0.4–2.6)	
	Acute leukaemia	Ever cigar only (14)	1.8 (1.0–3.0)	
		Never-smoker (40)	1.0	
		Ever pipe only (3)	0.9 (0.2–2.5)	
		Ever cigar only (8)	1.5 (0.7–3.0)	
Heineman *et al*. (1992)	Multiple myeloma	Never-smoker (141)	1.0	Age, calendar year, year of response
US Veterans' Study		Ever pipe/cigar only (95)	1.2 (0.9–1.5)	
1954–80		Ever pipe only		
		< 5 pipes/day (6)	1.9	
		5–9 pipes/day (2)	0.5	
		10–19 pipes/day (3)	1.0	
		> 20 pipes/day (1)	0.6	
		Ever cigar only		
		1–2 cigars/day (8)	1.3	
		3–4 cigars/day (8)	1.2	
		5–8 cigars/day (2)	0.4	
		> 9 cigars/day (2)	1.7	
Tverdal *et al*. (1993)	Leukaemia	Never-smoker (6)	1.0	Age and area
Norwegian Screening Study		Current pipe only (3)	[1.5 (0.4–5.9)]	
1973–88				

Table 2.2.19 (contd)

Reference Name of study and years of study	Site	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Pipe and cigar				
Garfinkel & Boffetta (1990) CPS-I, 1959–65	Lymphatic leukaemia	Never-smoker	1.0	Age, men only
		Ever pipe/cigar only	1.1	
	Myeloid leukaemia	Never-smoker	1.0	
		Ever pipe/cigar only	1.5	
CPS-II, 1982–86	Lymphatic leukaemia	Never-smoker	1.0	
		Ever pipe/cigar only	1.2	
	Myeloid leukaemia	Never-smoker	1.0	
		Ever pipe/cigar only	0.9	

Table 2.2.20. Case–control studies on exclusive pipe and/or cigar smoking and cancers of the haematopoietic system

Reference Country and years of study	Study characteristics	Site	Smoking category (cases/controls)	Relative risk (95% CI)	Variables adjusted for/ comments
Pipe and cigar					
Kabat *et al*. (1988) USA 1969–85	342 cases (men) 5862 hospital controls age 20–80 years, mean 51 years; response rate 95/95%	Leukaemia	Never-smoker (94/1320) Ever pipe/cigar only (23/416)	1.0 0.78 (0.49–1.24)	Not adjusted; relative risk for non-cancer controls
Brown *et al*. (1992a) USA 1981–84	578 cases (white men) 820 population controls age > 30 years; response rate 86/78%	Acute non-lymphocytic leukaemia	Never-smoker (29/197) Ever pipe/cigar only (4/40)	1.0 0.7 (0.2–2.1)	Age, state, alcohol
		Chronic myelogenous leukaemia	Never-smoker (8/197) Ever pipe/cigar only (1/40)	1.0 0.6 (0.1–5.1)	
		Chronic lymphocytic leukaemia	Never-smoker (40/197) Ever pipe/cigar only (13/40)	1.0 1.6 (0.8–3.2)	
		Acute lymphocytic leukaemia	Never-smoker (5/197) Ever pipe/cigar only (1/40)	1.0 0.8 (0.1–7.2)	
Brown *et al*. (1992b) USA 1981–84	622 cases (white men) 820 population controls; age > 30 years; response rate 89/78%	Non-Hodgkin lymphoma	Never-smoker (116/197) Ever pipe/cigar only (29/40)	1.0 1.2 (0.8–2.1)	Age, state
	173 cases (white men) 452 population controls; age > 30 years; response rate 84/78%	Multiple myeloma	Never-smoker (41/105) Ever pipe/cigar only (6/22)	1.0 0.6 (0.2–1.6)	Age

Table 2.2.21. Cohort study on exclusive pipe and/or cigar smoking and brain cancer

Reference Name of study and years of study	Smoking category (cases or deaths)	Relative risk (95% CI)	Variables adjusted for/comments
Tverdal *et al*. (1993) Norwegian Screening Study 1973–88	Never-smoker (11) Current pipe only (2)	1.0 [0.5 (0.1–2.5)]	Age and area

Table 2.2.22. Case–control studies on bidi and other tobacco smoking and cancer of the oral cavity and pharynx

Reference Country and years of study	Cancer site (ICD-9)	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Oral cavity						
Sankaranarayanan	Gingiva			*No. of bidis/day*		Hospital-based; as very few women
et al. (1989a)	(143.0, 143.1)	54	402	Never-smoker	1.0	smoked, only men were analysed.
India		26	64	≤ 10	2.8 (1.6–4.8)	
1983–84		15	55	11–20	1.9 (1.0–3.6)	
		8	20	≥ 21	3.2 (1.3–7.7)	*p* for trend < 0.001
				Age at starting (years)		
		39	62	< 21	1.0	
		10	79	≥ 21	0.2 (0.1–0.4)	*p* for trend < 0.001
				Duration (years)		Multivariate analysis further adjusted for
				Never	1.0	use of pan–tobacco, alcohol and snuff
				≤ 20	2.6 (0.7–9.9)	
				> 20	2.1 (1.2–27.9)	*p* for trend < 0.025
Sankaranarayanan	Tongue			*Duration (years)*		Adjusted for age
et al. (1989b)	(141.1–141.4)	79	232	Never-smoker	1.0	
India	and floor of	17	12	≤ 20	3.9 (1.8–8.7)	
1983–84	mouth (144)	60	67	≥ 21	2.7 (1.7–4.4)	*p* for trend < 0.001
				Lifetime exposure		
		79	232	Never-smoker	1.0	
		44	47	< 480	2.7 (1.6–4.5)	
		33	32	≥ 480	3.4 (1.8–6.2)	
					p for trend < 0.001	
				No. of bidis/day		Multivariate analysis adjusted for pan–
				Never-smoker	1.0	tobacco chewing and bidi and cigarette
				< 10	5.2 (2.5–10.9)	smoking
				11–20	4.1 (1.8–9.5)	
				> 20	7.5 (2.6–21.7)	*p* for trend < 0.001

Table 2.2.22 (contd)

Reference Country and years of study	Cancer site (ICD-9)	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Sankaranarayanan	Buccal mucosa			*No. of bidis/day*		Hospital-based study; adjusted for age
et al. (1990a)	(145.0, 145.1,	125	402	Never-smoker	1.0	
India	145.6) and	51	64	≤ 10	2.4 (1.6–3.7)	
1983–84	labial mucosa	43	55	11–20	2.5 (1.6–3.9)	
	(140.3, 140.4)	17	20	≥ 21	2.8 (1.4–5.6)	*p* for trend < 0.001
				Lifetime exposure		
		125	402	Never-smoker	1.0	
		51	61	< 400	2.7 (1.7–4.1)	
		12	27	400–499	1.4 (0.7–2.9)	
		48	52	≥ 500	2.9 (1.8–4.5)	*p* for trend < 0.001
				Duration (years)		Multivariate analysis adjusted for pan–tobacco chewing, alcohol and snuff
				Never-smoker	1.0	
				≤ 20	2.9 (1.3–6.6)	
				≥ 21	1.7 (1.1–2.6)	*p* for trend < 0.01
Rao *et al*. (1994)	Oral cavity:			*No. of bidis/day*		Hospital-based study
India	lip, anterior	407	440	Nonsmoker	1.0	
1980–84	tongue, upper	163	95	1–10	1.9 (1.4–2.5)	
	and lower	64	41	11–20	1.7 (1.1–2.6)	
	alveolus,	66	52	21–30	1.4 (0.9–2.1)	
	buccal mucosa	10	6	≥ 31	1.8 (0.6–5.6)	*p* for trend < 0.001
	and hard			*Duration (years)*		
	palate,	407	440	Nonsmoker	1.0	
	excluding base	61	64	1–10	1.0 (0.7–1.5)	
	of the tongue	61	48	11–20	1.4 (0.9–2.1)	
	(141.0) and	86	39	21–30	2.4 (1.6–3.6)	
	soft palate	96	43	≥ 31	2.4 (1.6–3.6)	*p* for trend < 0.001
	(145.3)					

Table 2.2.22 (contd)

Reference Country and years of study	Cancer site (ICD-9)	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Rao *et al*. (1994)				*Cessation*		Stratified by 4 age groups and 3 areas of residence
(contd)		231	159	Current smoker	1.4 (1.0–1.8)	
		42	14	Quit 1 year before	2.1 (1.1–4.3)	
		10	3	Quit 2 years before	2.2 (0.5–12.0)	
		11	10	Quit > 2 years before	0.7 (0.2–1.9)	
		414	447	Nonsmoker	1.0	
		15	3	Hookah/chillum	5.0 (1.4–22.0)	
Rao & Desai (1998) India 1980–84	Base of the tongue (141.0) and anterior tongue (141.1–141.4)			**Base of tongue**		Hospital-based study
		91	337	Nonsmoker	1.0	
		360	186	Bidi smoker	5.9 (4.2–8.2)	
				No. of bidis/day[†]		[†]Includes smokers of both bidis and cigarettes.
		129	438	Nonsmoker[‡]	1.0	[‡]Includes smokers of cigarettes and other forms of tobacco
		141	79	1–10	4.3 (3.0–6.7)	
		94	54	11–20	5.2 (3.4–8.5)	
		107	56	21–30	4.8 (3.2–7.7)	
		24	4	≥ 31	14.3 (4.1–50.7)	
				Duration (years)[†]		
		129	438	Nonsmoker[‡]	1.0	
		30	63	1–10	2.2 (1.3–4.1)	
		64	48	11–20	4.5 (3.1–8.7)	
		123	39	21–30	7.7 (4.8–13.0)	
		149	43	≥ 31	5.1 (3.3–8.3)	
				Anterior tongue		
		73	337	Nonsmoker	1.0	
		53	186	Bidi smoker	1.1 (0.7–1.7)	
				No. of bidis/day[†]		
		86	438	Nonsmoker[‡]	1.0	
		25	79	1–10	1.2 (0.7–2.2)	
		11	54	11–20	0.8 (0.8–1.8)	
		18	56	21–30	1.4 (0.7–2.7)	
		1	4	≥ 31	–	

Table 2.2.22 (contd)

Reference Country and years of study	Cancer site (ICD-9)	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Rao & Desai (1998) (contd)				*Duration (years)* †		†Includes smokers of both bidis and cigarettes.
		86	438	Nonsmoker‡	1.0	‡Includes smokers of cigarettes and other forms of tobacco
		7	63	1–10	0.5 (0.2–1.3)	
		16	48	11–20	1.4 (0.7–2.7)	
		12	39	21–30	1.2 (0.6–2.8)	
		20	43	≥ 31	1.6 (0.8–3.4)	
				Bidi smoking		Adjusted for alcohol use, illiteracy, non-vegetarian diet and tobacco chewing
				Base of tongue	4.7 (3.5–6.3)	
				Anterior tongue	1.0 (0.6–1.5)	
				Tongue (base + anterior)	3.3 (2.6–4.3)	
Dikshit & Kanhere (2000) India 1986–92	Oral cavity (140, 141.1–141.5, 143, 144, 145.0–145.2, 145.5–145.9)			*Smoking status*		Population-based; adjusted for age and tobacco-quid chewing
		76	146	Nonsmoker	1.0	
		72	114	Bidi/cigarette smoker†	1.5 (0.9–2.4)	†70–80% smoked only bidis.
Balaram *et al.* (2002) India 1996–99	Oral cavity			*No. of bidis/day*		Hospital-based; frequency-matched for age and sex; adjusted for age, centre, education, alcohol use and chewing habits
				Nonsmoker	1.0	
		55	33	< 20	2.0 (1.1–3.8)	
		73	41	≥ 20	2.5 (1.4–4.4)	
Pharynx						
Wasnik *et al.* (1998) India [years of study not reported]	Oropharynx	72	112	Nonsmoker	1.0	Hospital-based; age- and sex-matched control patients — one cancer and one non-cancer
		5	16	Cigarette smoker	0.7 (0.3–1.9)	
		40	31	Bidi/chillum smoker	2.7 (1.6–4.5)	
		6	20	Bidi/cigarette smoker	3.1 (0.6–15.3)	

Table 2.2.22 (contd)

Reference Country and years of study	Cancer site (ICD-9)	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Rao *et al*. (1999)	Oropharynx			*No. of bidis/day*		Hospital-based
India	(141.0, 145.3,	193	445	Nonsmoker	1.0	
1980–84	146.9)	188	77	1–10	4.3 (3.1–6.5)	
		124	52	11–20	4.9 (3.3–7.9)	
		141	53	21–30	4.7 (3.2–7.2)	
		31	4	≥ 31	12.2 (3.8–42.4)	
				Duration (years)		
		193	445	Nonsmoker	1.0	
		44	62	1–10	2.4 (1.5–4.1)	
		89	46	11–20	4.7 (3.4–8.6)	
		159	38	21–30	7.0 (4.5–11.4)	
		192	40	≥ 31	5.2 (3.4–8.1)	
				Bidi smoking		Adjusted for alcohol use, illiteracy,
				Nonsmoker	1.0	vegetarian/non-vegetarian diet and tobacco
				Smoker	4.7 (3.6–6.3)	chewing
Rao *et al*. (1999)	Hypopharynx			*No. of bidis/day*		Hospital-based; alcohol as an additional risk
India	(148)	242	445	Nonsmoker	1.0	factor
1980–84		126	77	1–10	2.1 (1.5–3.1)	
		81	52	11–20	2.5 (1.6–4.0)	
		112	53	21–30	3.5 (2.4–5.5)	
		25	4	≥ 31	8.3 (2.3–26.0)	
				Duration (years)		
		242	445	Nonsmoker	1.0	
		44	62	1–10	1.8 (1.1–3.1)	
		61	46	11–20	2.7 (1.8–4.9)	
		95	38	21–30	3.3 (2.2–5.7)	
		144	40	≥ 31	3.0 (1.9–4.7)	
				Bidi smoking		Adjusted for alcohol use, illiteracy,
				Nonsmoker	1.0	vegetarian/non-vegetarian diet and tobacco
				Smoker	2.8 (2.1–3.7)	chewing

Table 2.2.22 (contd)

Reference Country and years of study	Cancer site (ICD-9)	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Dikshit & Kanhere (2000) India 1986–92	Oropharynx (posterior tongue, soft palate, uvula, nasopharynx, hypopharynx) (141.0, 141.6, 145.3, 145.4, 146, 147, 148.0–149.0)			*Bidi smoking*		Population-based; adjusted for age and tobacco quid chewing
		59	NR	No	1.0	
		188		Yes	7.3 (4.7–11.2)	
		59	NR	No. of bidis/day		
		63		1–10	4.1 (2.4–7.0)	
		84		11–20	11.4 (6.5–19.9)	
		41		> 20	17.0 (7.7–37.6)	χ^2_{trend} = 3.82 (NS)
				Nonsmoker	1.0	
				Bidi smoker only	7.9 (5.1–12.4)	
				Cigarette smoker only	4.1 (2.0–8.4)	
				Bidi and cigarette smoker	6.2 (2.8–13.4)	

NR, not reported

Table 2.2.23. Cross-sectional studies on bidi and other tobacco smoking and oral lesions

Reference Country	Oral lesion	Smoking category	No. of lesions	Prevalence (%)	Total	Comments
Van der Eb *et al.* (1993) India	Palatal lesions	Nonsmoker	5	3	161	Randomly selected population sample; 9 carcinomas of the hard palate, all among reverse chutta smokers
		Chewing tobacco	0	0	10	
		Cigarette	3	21.4	14	
		Bidi	11	55.0	20	
		Conventional chutta	34	56.7	60	
		Ex-conventional chutta/bidi	6	42.9	14	
		Reverse chutta	139	86.9	160	
		Ex-reverse chutta	16	76.2	21	
		Mixed habits	11	55.0	20	
		Total	225	46.9	480	

Reference Country	Oral lesion	No. of cases	No. of controls	Smoking category	RR (95% CI)	Comments
Macigo *et al.* (1996) Kenya	Oral leukoplakia			**Kiraiku**[†]		Population-based [†]Home-processed hand-rolled products
		42	120	Never-smoker	1.0	
		29	17	Former smoker	4.9 (2.3–10.4)	
		14	4	Current smoker	10.0 (2.9–43.4)	
				Duration (years)		
		24	15	≤ 10	4.6 (2.1–10.2)	
		5	2	> 10	7.1 (1.1–76.6)	
				Years since quitting		
		11	8	≥ 10	3.9 (1.4–11.6)	
		12	7	5–9	4.9 (1.7–14.9)	
		6	2	≤ 4	8.6 (1.4–88.7)	

Table 2.2.24. Intervention studies on tobacco use and oral lesions in India

Place Reference	Tobacco habit	Oral lesion	Sex	Intervention cohort		Control cohort		Rate ratio	Comments
				No.	Incidence rate/1000	No.	Incidence rate/1000		
Bhavnagar District									
Gupta *et al*. (1986b)	Bidi	Leukoplakia	Men	224	41.9	58	47.6	0.88	After 5 years of follow-up
Srikakulam District									
Gupta *et al*. (1986b)	Reverse smoking	Palatal lesions	Men	52	163.3	671	427.7	0.38	After 5 years of follow-up
			Women	428	292.0	1 167	513.9	0.57	
				Person–years	Incidence rate/1000	Person–years	Incidence rate/1000		
Gupta *et al*. (1994)	Reverse smoking	Palatal lesions	Men	7 341	1.1	7 718	6.2		After 10 years of follow-up
			Women	49 522	3.4	11 210	11.4		
				Observed	Expected				
Ernakulam District									
Gupta *et al*. (1990)	Bidi	Leukoplakia	Men	63	142.6			0.4	After 8 years of follow-up
			Women	0	2.6			0.0	
	Cigarette		Men	0	12.8			0.0	
			Women	0	0.0			–	

Table 2.2.24 (contd)

Place Reference	Tobacco habit	Oral lesion	Sex	Intervention cohort			Control cohort		Rate ratio	Comments
				Person–years	Incidence rate/1000		Person–years	Incidence rate/1000		
Gupta *et al.* (1992)	Bidi	Leukoplakia								
			Men	48 265	1.46		15 529	3.02	0.4	
			Women	1 444	–		199	5.86	0.0	
	Cigarette		Men	2 699	–		2 165	1.46	0.0	
			Women	6	–		0	0	–	
				Stopped			All others			
				Person–years	Observed	Expected	Person–years	Observed		
	Bidi	Oral lesions	Men	ca. 3000	8	42.3	ca. 40 000	601		
					Observed	Incidence/ 100 000	Observed	Incidence/ 100 000		
		Leukoplakia			1	24	80	155	0.15	

Table 2.2.25. Case–control studies of bidi and other tobacco smoking and lung cancer

Reference Country and years of study	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Dikshit & Kanhere (2000)	17	146	Nonsmoker	1.0	Population-based; adjusted for age
India	100	81	Bidi smoker only	11.6 (6.4–21.3)	
1986–92	15	20	Cigarette smoker only	7.7 (3.2–18.4)	
	31	13	Bidi and cigarette smoker	24.1 (10.4–56.1)	
Gupta *et al*. (2001)	26	172	Nonsmoker	1.0	Hospital-based; males; relative risks adjusted for age and education
India	208	261	Ever-smoker (any)	5.0 (3.1–8.0)	
1995–97	137	162	Bidi smoker	5.8 (3.4–9.7)	
	78	103	Cigarette smoker	3.9 (2.1–7.1)	
	12	31	Hookah smoker	1.9 (0.9–4.4)	
			Bidis		[†]Average consumption of cigarette equivalents (see text)
			Average no./day[†]		
	11	39	1–4	1.8 (0.8–4.0)	
	46	54	5–9	5.9 (3.2–10.8)	
	67	63	10–19	6.8 (3.9–12.1)	
	13	6	≥ 20	12.3 (4.2–36.1)	
			Duration (years)		
	23	45	0–24	3.7 (1.8–7.7)	
	48	36	25–34	9.6 (4.9–18.7)	
	30	48	35–44	3.7 (1.9–7.2)	
	37	33	≥ 45	6.4 (3.3–12.6)	
			Pack–years		
	41	71	0–9	3.9 (2.1–7.1)	
	57	54	10–19	6.5 (3.6–11.7)	
	26	23	20–29	6.9 (3.4–14.3)	
	13	14	≥ 30	5.3 (2.2–12.9)	
			Hookah		
			Average no./day[†]		
	12	31	1–4	1.9 (0.9–4.4)	
			Duration (years)		
	1	9	0–24	0.5 (0.1–4.4)	
	0	6	25–34	–	
	6	10	35–44	2.7 (0.9–8.5)	
	5	6	≥ 45	4.4 (1.2–16.4)	
			Pack–years		
	12	31	0–9	1.9 (0.9–4.4)	

Table 2.2.26. Case–control studies on bidi and other tobacco smoking and cancer of the larynx and oesophagus

Reference Country and years of study	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Larynx					
Sankaranarayanan			*No. of bidis/day*		Hospital-based
et al. (1990b)	101	402	None	1.0	
India	31	65	≤ 10	1.8 (1.1–2.9)	
1983–84	31	55	11–20	2.1 (1.3–3.5)	
	25	20	≥ 21	5.1 (2.7–9.6)	*p* for trend < 0.001
			Duration (years)		Adjusted for duration of cigarette smoking,
			Never	1.0	frequency of bidi and cigarette smoking and
			≤ 20	1.3 (0.3–6.4)	duration of alcohol use
			≥ 21	7.1 (4.0—12.5)	*p* for trend < 0.001
Rao *et al.* (1999)			*No. of bidis/day*		Hospital-based
India	203	445	Nonsmoker	1.0	
1980–84	93	77	1–10	1.8 (1.2–2.8)	
	38	52	11–20	1.4 (0.8–2.4)	
	76	53	21–30	2.5 (1.7–4.1)	
	11	4	≥ 31	3.8 (0.9–14.1)	
			Duration (years)		
	203	445	Nonsmoker	1.0	
	24	62	1–10	1.2 (0.7–2.3)	
	44	46	11–20	2.3 (1.4–4.3)	
	62	38	21–30	2.3 (1.4–4.1)	
	88	40	≥ 31	2.0 (1.3–3.2)	
			Bidi smoking		Adjusted for alcohol use, illiteracy,
			Nonsmoker	1.0	vegetarian/non-vegetarian diet and tobacco
			Smoker	2.1 (1.6–2.8)	chewing

Table 2.2.26 (contd)

Reference Country and years of study	No. of cases	No. of controls	Smoking category	Relative risk (95% CI)	Comments
Oesophagus					
Sankaranarayanan			*No. of bidis/day*		Hospital-based
et al. (1991)	88	402	None	1.0	
India	45	65	≤ 10	2.8 (1.8–4.5)	
1983–84	45	55	11–20	3.5 (2.2–5.5)	
	24	20	≥ 21	5.2 (2.7–10.0)	p for trend < 0.001
			Duration (years)		Adjusted for the number of bidis and cigarettes
			Never	1.0	smoked daily, alcohol use and pan–tobacco
			≤ 20	2.1 (0.8–5.9)	chewing
			> 20	4.7 (2.8–7.9)	p for trend < 0.001
Nandakumar *et al*.			*All cases*		Hospital-based; age- and sex-matched, adjusted
(1996)	36	139	Nonsmoker	1.0	for tobacco chewing, pan chewing without
India	115	144	Bidi smoker	4.0 (2.3–6.8)	tobacco, alcohol drinking and cigarette smoking
1982–85			*Upper third*		
	4	16	Nonsmoker	1.0	
	11	8	Bidi smoker	7.1 (1.1–46.8)	
			Middle third		
	14	76	Nonsmoker	1.0	
	60	73	Bidi smoker	6.0 (2.5–14.5)	
			Lower third		
	12	37	Nonsmoker	1.0	
	34	48	Bidi smoker	3.9 (1.4–10.7)	
Nayar *et al*. (2000),			*Bidi smoking*		Hospital-based; matched controls; adjusted for
India	83	112	Never-smoker	1.0	betel quid with tobacco and diet (other
1994–97	66	37	Daily smoker	2.0 (1.2–3.3)	vegetables besides leafy greens)

Table 2.2.27. Case–control study of bidi and other tobacco smoking and stomach cancer

Reference Country and years of study	No. of cases	No. of controls	Smoking categories	Relative risk (95% CI)	Comments
Gajalakshmi &			*Current smoker*		Hospital-based; matched on age, sex,
Shanta (1996)	72	40	Bidi	3.2 (1.8–5.7)	religion and mother tongue
India	43	33	Cigarette	2.0 (1.1–3.6)	
1988–90	31	22	Chutta	2.4 (1.2–4.9)	
	13	2	Combination	8.2 (1.7–38.9)	
			Bidis		
			Age at starting smoking (years)		
	10	5	> 30	3.6 (1.0–13.5)	
	27	16	21–30	2.7 (1.2–5.9)	
	35	19	≤ 20	3.7 (1.7–8.3)	*p* for trend < 0.001
			Lifetime exposure		
	21	17	Mild	2.0 (0.9–4.3)	
	17	11	Moderate	5.3 (1.6–18.3)	
	34	12	Heavy	4.5 (1.8–11.3)	*p* for trend < 0.001
			Chuttas		
			Age at starting smoking (years)		
	3	5	> 30		
	12	6	21–30	2.2 (0.3–13.5)	
	16	11	≤ 20	2.4 (0.8–7.2)	
				2.3 (0.9–6.0)	
			Lifetime exposure		
	12	12	Mild	2.8 (0.9–8.4)	
	8	7	Moderate	1.5 (0.5–4.6)	
	8	3	Heavy	4.4 (1.2–16.1)	*p* for trend < 0.05

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2.3 Synergistic carcinogenic effects of tobacco smoke and other carcinogens

2.3.1 *Introduction*

This section addresses the combined effects on cancer risk of cigarette smoking and other agents also associated with risk, excluding smokeless tobacco. The chapter is restricted to studies of smoking and exposures to single agents and does not address modification of risk by diet, whether by specific foods, nutrients or micronutrients.

For many cancers, including lung cancer, multiple causal factors are relevant and persons being exposed to more than one risk factor may be subject to risks beyond those anticipated from the individual agents acting alone. The terminology and methods used to characterize the combined effects of two or more agents have been poorly standardized with substantial blurring of concepts derived from toxicology, biostatistics and epidemiology (Greenland, 1993; Mauderly, 1993). Epidemiologists refer to *effect modification* if effects of multiple agents are interdependent whereas toxicologists assess whether the effects of multiple agents are *synergistic* (positive interdependence) or *antagonistic* (negative interdependence). Statisticians test whether there is *interaction* between independent determinants of cancer risk. For the purposes of this report, epidemiological concepts are followed, such that interdependence of effects is termed *effect modification*, and *synergism* and *antagonism* are used to describe the consequences of the interdependence of disease risk when both risk factors are present (Rothman & Greenland, 1998). The term *interaction* is reserved for the statistical approach for testing whether effect modification is present.

In a toxicological paradigm that extends from exposure through dose and finally to biological effects, there are a number of different points at which smoking might influence the effect of another risk factor. The 1985 Report of the US Surgeon General (US Department of Health and Human Services, 1985) set out a broad conceptual framework for considering the joint effect of smoking with an occupational agent, which can be extended more generally to other risk factors. The levels of potential interaction between agents are multiple, ranging from molecular to behavioural (Table 2.3.1). Current research on the molecular basis of carcinogenesis is improving the understanding of potential points of interaction at the mechanistic level, but approaches to assess effect modification remain largely empirical. Some of the potential points of interaction (Table 2.3.1) would have an impact on the level of exposure, others — including the exposure–dose relationship — on the dose–response relation of exposure with risk, either for smoking or for the modifying factor. Typically, epidemiological data do not provide evidence relevant for assessing each of these potential points of interaction of another risk factor with cigarette smoking. In assessing the presence of synergism or antagonism, a model is assumed to predict the combined effect from the individual effects; in the absence of sufficient biological understanding to be certain of the most appropriate model, the choice is often driven by convention or convenience. There is also a potential for the combined effects to vary over the life-span; as the carcinogenesis process advances, agents are cleared (e.g. chrysotile asbestos fibres are cleared or dissolve in the lung), or exposure to tobacco or the other agent ends. Epidemiological studies generally only capture combined effects over a single interval of time.

In a multi-stage formulation of carcinogenesis, inferences as to the stages at which agents act can be made based on patterns of effect modification, particularly if data are available on the timing of exposure (Doll, 1971; Whittemore, 1977; Thomas & Whittemore, 1988). Effect modification also has implications for prevention, as synergism may increase the disease burden beyond that anticipated from the risk of smoking alone and may place some people, e.g. occupationally exposed workers, at particularly high risk.

The identification of studies addressing effect modification is difficult as authors may not have noted that effect modification was examined and search terms are not sufficiently conclusive. It was also impossible to search all studies involving smoking and potential modifying factors. Consequently, targeted searches were used to find published articles that specifically mentioned interaction, synergism or antagonism. Summary reviews also could be used as a further source of references.

(*a*) *Epidemiological concepts*

The effect of a risk factor for a disease may be estimated on an absolute scale or on a relative scale. In the absolute risk model, the risk (r(x)) of disease associated with some factor (x) can be expressed in a simple linear relationship as:

$$r(\mathrm{x}) = r_0 + \beta \mathrm{x}$$

while in a relative risk relationship, risk is given by:

$$r(\mathrm{x}) = r_0 \times (1 + \beta \mathrm{x}) = r_0 + r_0\beta \mathrm{x}$$

where r_0 is the background rate of disease in the absence of exposure and β describes the increment in risk per unit increment in exposure to x. Under a relative risk characterization of disease risk, the impact of an exposure on disease risk, $r_0\beta$x, depends on the background rate. In the absolute risk model, the effect of exposure on disease risk, βx, does not depend on the level of r_0. The selection of the risk model (i.e. absolute or relative), has substantial implications for interpreting the combined effects of two agents and for extending risks observed in one population to another population that may not have comparable r_0 because of differing patterns of risk factors other than the exposure of interest.

These two models can be extended to address the effects of multiple causes of disease. In the example of two exposures, x_1 and x_2 (e.g. radon and smoking), disease risk ($r(x_1, x_2)$) under a relative risk model is given by:

Additive model: $r(x_1,x_2) = r_0 + r_0\beta_1 x_1 + r_0\beta_2 x_2$

Multiplicative model: $r(x_1,x_2) = r_0 \times (1 + \beta_1 x_1)(1 + \beta_2 x_2) =$

$r_0 + r_0\beta_1 x_1 + r_0\beta_2 x_2 + r_0\beta_1 x_1\beta_2 x_2 =$

$r_0 + r_0\beta_1 x_1 + r_0\beta_2 x_2(1 + \beta_1 x_1)$

Comparison of these two models highlights the differing dependence of the effect of x_2 on r_0 and x_1. In assessing the role of x_2 on disease risk, a multiplicative model implies that the effect of x_2 on disease risk depends not only on r_0, but also on the effect of x_1. In contrast, under the additive model, the effect of x_2 depends on r_0 but not on the effect of x_1.

Epidemiologists describe the effect of exposures in causing disease either as a difference on an absolute scale or as a ratio on a relative scale. The preference has been for ratio measures (e.g. the relative risk that compares risk in the exposed group to risk in a referent group, typically the unexposed group). Effect modification is considered to occur when the combined effect of two or more variables is larger or smaller than the anticipated effect predicted by the independent effects, based on the measure used (Greenland, 1993). Current analytical approaches compare the combined effect to predictions based on either additivity or multiplicativity of the individual effects, that is, using either the absolute risk or relative risk models described above. Thus, a factor may be an effect modifier in the additive model and not in the multiplicative model. Epidemiologists have recognized that the appropriate scale for assessing a combined effect depends on the intent of the analysis (Rothman *et al.*, 1980). For public health purposes, an effect greater than additive is considered as synergistic. Biological mechanisms, if sufficiently understood, may suggest an alternative scale for assessment.

Although epidemiological methods have been proposed for assessing effect modification, no strict criteria for determining its presence have been defined. Rothman (1976) developed a synergy index that quantifies departure from independence of effects. Statistical significance alone is recognized to be an insufficient criterion (Greenland, 1993), and the interpretation of patterns of interdependence remains subjective. Additionally, inadequate statistical power often limits the assessment of effect modification (Greenland, 1983) and interpretation of possible effect modification should also consider the consequences of exposure measurement error, which may differ in degree for smoking and the other agent(s).

The concern about limited power extends specifically to studies of smoking and disease. Particularly limiting is the small number of cases that occur among nonsmokers in the studies of occupational agents.

(*b*) *Statistical concepts*

Statisticians have used the term ‘interaction’ to refer to interdependence as detected by a statistical approach or ‘model’. Interaction, which is equivalent to the epidemiological concept of effect modification, has typically been assessed in a regression framework using product terms of the risk factors of interest to test for effect modification (Thomas & Whittemore, 1988; Rothman & Greenland, 1998). For example, interaction between two risk factors, x_1 (e.g. smoking) and x_2 (e.g. radon exposure) could be assessed using the following model:

$$r(x_1, x_2) = 1 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

In this linear model, the product or interaction term, $\beta_3 x_1 x_2$, estimates the joint contribution of the two agents to the risk. The model provides an estimate of the value of β_3 and a test of the statistical significance of β_3 for the null hypothesis: $\beta_3 = 0$. This modelling approach inherently assumes a mathematical scale on which the interaction is characterized, the usual choices being additive or multiplicative. Most often, primarily because of computational convenience, the multiplicative scale is used. Alternative approaches for assessing interaction have been described (Thomas, 1981; Breslow & Storer, 1985; Lubin & Gaffey, 1988). These choices more flexibly estimate the combined effects of risk factors without imposing the rigidity of a particular scale. Imprecision and bias from measurement error may also limit estimates obtained from such modelling approaches.

(*c*) *Characterizing the burden of cancer attributable to smoking*

In describing the burden of disease, epidemiologists use a quantity referred to as the attributable risk (Rothman & Greenland, 1998). The attributable risk indicates the burden of disease that could be avoided if exposure to the agent of concern were fully prevented. This measure has been widely used for cigarette smoking to estimate the burden of avoidable tobacco-caused disease.

One form of the attributable risk, the population attributable risk (PAR) describes the proportion of disease in a population associated with exposure to an agent. For a factor, x_1, having an associated relative risk RR_1, PAR is calculated as below, where I and I_0 and P_1 and P_0 are the disease rates and probabilities of exposure in the population under current conditions and under some counterfactual set of conditions of differing exposure (for smoking, generally the complete prevention of smoking), respectively:

$$\begin{aligned} \mathrm{PAR}(x) &= \frac{I - I_0}{I} \\ &= \frac{P_1 I_1 + P_0 I_0 - I_0}{P_1 I_1 + P_0 I_0} \\ &= \frac{P_1(\mathrm{RR}_1 - 1)}{P_1(\mathrm{RR}_1 - 1) + 1} \end{aligned}$$

For diseases caused by several agents, the total burden of disease that is theoretically preventable may exceed the observed number of cases, or 100%, if there are synergistic patterns of effect modification on an additive scale. For example, an estimate of smoking-attributable lung cancer cases can be conceptualized as including those cases caused by smoking, and those caused by radon and smoking in smokers. In the above formula, the attributable risk figure for smoking includes those cases caused by smoking alone and radon and smoking acting together; similarly, the attributable risk figure for radon would include those cases caused by radon alone and those caused by radon acting together with smoking. Combining the attributable risk estimates for smoking and radon counts the jointly determined cases twice. This subtlety of the attributable risk statistic is not universally appreciated and there is widespread misperception that the attributable risk should add up to 100% when all the various causes of the cancer are considered.

For two factors, x_1 and x_2, the sum of the individual exposure-specific PAR estimates, PAR(x_1) and PAR(x_2), can exceed 100%. However, when evaluating two factors, these PARs are incorrectly determined by contamination of the referent groups; i.e. the subgroup of individuals with $x_1 = 0$ includes subjects for whom x_2 may be 0 or 1 and the subgroup of individuals with $x_2 = 0$ includes persons for whom x_1 may be 0 or 1.

For joint exposures to x_1 and x_2, PAR is defined as:

$$\mathrm{PAR}_{(x1,x2)} = \frac{P_{1,1}(\mathrm{RR}_{1,1} - 1) + P_{1,0}(\mathrm{RR}_{1,0} - 1) + P_{0,1}(\mathrm{RR}_{0,1} - 1)}{P_{1,1}(\mathrm{RR}_{1,1} - 1) + P_{1,0}(\mathrm{RR}_{1,0} - 1) + P_{0,1}(\mathrm{RR}_{0,1} - 1) + 1}$$

The PAR for two exposures, e.g. smoking and radon, is the sum of components due to smoking in the absence of radon exposure, to radon exposure in the absence of smoking, i.e. in never-smokers, and to the combined effect of radon exposure and smoking. PAR(x_1,x_2), calculated with the above formula, cannot exceed 100%.

Finally, the definition of PAR can be generalized for a continuous exposure, x, with exposure distribution f, as

$$\mathrm{PAR(x)} = \frac{I - I_0}{I} = \frac{\int I(\mathrm{x})\mathrm{f(x)dx} - I_0}{\int I(\mathrm{x})\mathrm{f(x)dx}} = \frac{\int \mathrm{RR(x)f(x)dx} - 1}{\int \mathrm{RR(x)f(x)dx}}$$

where RR(x) is the relative risk for exposure level x, relative to zero exposure.

2.3.2 *Asbestos*

Asbestos, a term referring to a group of fibrous silicates, has long been identified as a cause of lung cancer, and was classified by IARC as *carcinogenic to humans* (Group 1) (IARC, 1987). Many studies of asbestos-exposed workers have addressed the combined effect of asbestos and smoking on lung cancer risk. Data available at the time allowed the Working Group to establish that ‘the relationship between asbestos exposure and smoking indicated a synergistic effect of smoking with regard to lung cancer’ (IARC, 1987). There have been several recent comprehensive reviews on this topic (Erren *et al.*, 1999; Lee, 2001; Liddell, 2001), as well as several frequently-cited earlier reviews (Saracci, 1977; Vainio & Boffetta, 1994). The topic has also been addressed in several reviews on occupational carcinogens in general and smoking (Saracci, 1987; Saracci & Boffetta, 1994).

Tables 2.3.2 and 2.3.3 summarize the characteristics of the principal relevant case–control and cohort studies, respectively, reviewed by Lee (2001), together with one more recent study (Gustavsson *et al.*, 2002). These studies vary widely in design and in the quality and extent of information available on smoking and on asbestos exposure. In the cohort studies, exposure to asbestos was generally at levels that would be considered high in relation to today's occupational standards. Exposure estimates were based on available sources of information including measurements that were generally limited in scope. Types of information included: job and industry, judgement of industrial hygienists, and self-report. The extent of the available information on smoking was also variable and in many of the cohort studies information was collected only at the initiation of follow-up or some other single point in time. In the case–control studies, interviews with the participants or with a surrogate respondent for deceased persons were the principal source of information.

Tables 2.3.4 and 2.3.5, adapted from Lee (2001), provide the relative risks for the four strata created by dichotomous classification of smoking and asbestos exposure. The general pattern of the risk estimates indicated departure from additivity in many of the studies, although the findings of some studies did not indicate synergism (McDonald *et al.*, 1993; McDonald *et al.*, 1999). The extent of departure from additivity varied across studies, from only slightly greater than additive (Gustavsson *et al.*, 2002) to a multiplicative interaction (Hammond *et al.*, 1979).

The three recent reviews include quantitative summaries of the evidence on effect modification. [The Working Group did not attempt to replicate these analyses.]

Erren and colleagues (Erren *et al.*, 1999) identified 17 relevant reports published from 1966 to 1996. Of these, 12 were included in the analysis, which used Rothman's synergy index. The value of the synergy index exceeded unity in all of the 12 studies. After excluding one study and verifying the absence of significant heterogeneity between the studies, the weighted summary value of the synergy index was estimated as 1.66 (95% CI, 1.33–2.06).

Liddell (2001) focused on seven cohort studies and six case–control studies. He also calculated an index of effect modification, termed the relative asbestos effect (RAE), which exceeded unity if the effect was greater in nonsmokers than in smokers. For the cohort studies, the estimate of RAE was 2.04 (95% CI, 1.28–3.25), indicating that the relative risk for asbestos exposure in nonsmokers was twice that in smokers; for the case–control studies, the RAE estimate was 0.83 (95% CI, 0.53–1.30). Liddell set aside the case–control data as being of insufficient quality and found that the data from cohort studies were not consistent with a fully multiplicative interaction. [The Working group noted that Liddell did not test for departure from additivity].

Lee (2001) analysed data from 23 studies, testing for additivity and multiplicativity. The studies reviewed showed strong evidence for departure from additivity. A test of multiplicativity was used that was conceptually comparable to Rothman's synergy index. Although the value of this index varied substantially across studies, the summary value of the synergy index derived by meta-analysis was 0.90 (95% CI, 0.67–1.20), which was consistent with a multiplicative interaction.

The discrepancy between the analyses, findings and conclusions of Erren *et al.* (1999), Lee (2001) and Liddell (2001) lies in the selection of studies and the approaches used to abstract and analyse the evidence. All three reviews document the range of the evidence and the imprecision with which many of the studies assess effect modification.

The Working Group concluded that the evidence supports synergism between asbestos exposure and smoking in causing lung cancer, but notes that the degree of synergism remains uncertain.

2.3.3 *Radon and other ionizing radiation*

The combined effect of radon and smoking has been investigated in cohort studies of underground miners exposed to radon and radon progeny and in case–control studies of lung cancer and exposure to radon in homes. The Working Group for the *IARC Monograph* on radon 'considered that the epidemiological evidence [did] not lead to a firm conclusion concerning the interaction between exposure to radon decay products and tobacco smoking' (IARC, 1988a). The report of the US National Research Council's Biological Effects of Ionizing Radiation (BEIR) VI Committee provided an in-depth review of the combined effect of smoking and radon on lung cancer risk and the following section is largely based on this report (National Research Council, 1999). The cohort and case–control studies cited in that review, together with more recent studies, are included in Tables 2.3.6 and 2.3.7.

The BEIR VI Committee identified five cohort studies of underground miners that provided information on both smoking and exposure to radon progeny (Table 2.3.6). The extent of information available on smoking was variable and smoking was not systematically evaluated across the follow-up of any of the cohorts. Quantitative estimates of exposure to radon progeny were available for all participants. The data had been analysed by Lubin *et al.* (1994) using a mixture model that flexibly assessed effect modification. The two largest studies, the study of Colorado Plateau uranium miners and the study of Chinese tin miners, provided the strongest evidence of effect modification because of the size of the cohorts and the numbers of lung cancer deaths. Both studies provided evidence against the additive model, as did the overall estimate for the mixture parameter, which indicated a synergistic but submultiplicative interaction.

In modelling the risk for lung cancer, the BEIR VI Committee adopted this submultiplicative interaction. Relative to the overall effect of exposure to radon progeny on lung cancer risk, the risk estimate in ever-smokers was proportionally lower by a factor of 0.9 whereas the relative effect in never-smokers was proportionally higher by 1.9.

Hornung and colleagues (Hornung *et al.*, 1998) reported an analysis of the Colorado Plateau study that incorporated updated smoking information obtained in 1986 from surviving cohort members and next of kin of deceased members. The smoking histories, updated for about two-thirds of the original cohort, showed a substantial rise in the proportion of former smokers. Multiple analytical approaches were used to explore effect modification. The general finding was that the interaction between smoking and radon was submultiplicative, but there was no strong evidence against a multiplicative interaction.

Further evidence on smoking and exposure to radon progeny has come from a population-based case–control study conducted in Gejiu City, the site of the Yunnan Tin Corporation (Yao *et al.*, 1994). This study included 460 cases, of whom 368 had been miners, and 1043 controls. Tobacco was smoked by study participants as cigarettes or with water pipes or Chinese long-stem pipes; a mixed pattern of smoking was most common. In contrast to the cohort analysis of the Yunnan tin miners, the case–control data were consistent with a multiplicative model, although the best-fitting model was intermediate between additive and multiplicative.

The joint effect of smoking and exposure to radon progeny could plausibly vary with the sequence of the two exposures. Thomas and colleagues (Thomas *et al.*, 1994) analysed the Colorado Plateau data using a case–control approach to assess temporal modification of the interaction between radon progeny and smoking. They characterized the temporal sequence of the two exposures as: simultaneous; radon before smoking; and radon following smoking. Exposure to radon followed by smoking was associated with an essentially additive effect whereas smoking followed by exposure to radon was associated with a more than multiplicative effect on a relative risk scale. Thomas and colleagues interpreted this finding as suggesting that smoking could act to promote radon-initiated cells.

The data from the Colorado Plateau cohort and Yunnan tin miners cohort have been analysed with mechanistic carcinogenic models, based in the Moolgavkar, Venzon and Knudson two-mutation model (Moolgavkar *et al.*, 1993; Luebeck *et al.*, 1999; Hazelton *et al.*, 2001; Little *et al.*, 2002). Under the assumed models, inferences can be made as to the mutations affected by smoking and exposure to radon progeny. In the most recent analysis of the Colorado Plateau cohort data (Little *et al.*, 2002), the findings of a two-stage model implied action of both factors on the first mutation rate and an action of exposure to radon progeny on intermediate cell death or the differentiation rate. A two-stage model was applied by Hazelton *et al.* (2001) to the Yunnan tin miner cohort data, which included estimates of exposure to smoking, arsenic and radon progeny. Various models were fitted; all showed effects of each of the exposures; radon had the smallest effect and smoking the greatest.

Effect modification has also been assessed in case–control studies of lung cancer in the general population (Table 2.3.7). All studies made estimates of radon concentration in the current and past homes of persons with lung cancer and of appropriate controls. Information on smoking was obtained by interview with the index respondent or with a surrogate for deceased persons. Measurement error is an unavoidable limitation of these studies, as exposure to radon throughout the lifetime is considered relevant to risk for lung cancer in adulthood.

Because most cases of lung cancer occur in smokers, the case–control studies included few never-smokers and consequently effect modification cannot be characterized with great precision. The available studies do not provide evidence for effect modification, considered on the multiplicative scale. [The Working Group noted that the studies have not been systematically analysed for the presence of synergism, assessed as departure from additivity].

The combined effect of smoking and exposure to radiation has been assessed in a few populations exposed to low-linear energy transfer (LET) radiation. These populations included atomic bomb survivors (Prentice *et al.*, 1983; Kopecky *et al.*, 1986), persons receiving therapeutic irradiation for breast cancer (Kaldor *et al.*, 1992; Neugut *et al.*, 1994; Van Leeuwen *et al.*, 1995), and workers subjected to mixed exposure to external gamma radiation and internal emitters (Petersen *et al.*, 1990).

Of the cancer risks associated with exposure to radiation in atomic bomb survivors, relative risks for lung cancer are among the highest (Mabuchi *et al.*, 1991). A series of studies conducted by the Radiation Effects Research Foundation have explored the effect of smoking on lung cancer in the atomic bomb survivors. Kopecky *et al.* (1986) reported an analysis of the combined effects of smoking and radiation in a selected cohort for which information was available on smoking. A total of 351 cases of lung cancer were reported in a cohort of 29 332 exposed survivors. Poisson regression models were used to assess the effects of exposure to radiation (using the T65 radiation dosimetry), and smoking, with control for other factors including age at the time of the bombing. Using an additive model for the excess relative risk, Kopecky *et al.* (1986) found that both exposure to radiation and cigarette smoking were determinants of lung cancer risk; an interaction term for the two exposures was not statistically significant ($p = 0.72$). While Kopecky *et al.* (1986) expressed a preference for the additive model based on these analyses, further analyses by the BEIR IV Committee (National Research Council, 1988) showed that the data were equally compatible with a multiplicative model.

Three studies have examined modification by cigarette smoking of the risk for lung cancer following therapeutic irradiation.

Neugut *et al.* (1994) conducted a case–control study of Connecticut women with a second primary cancer following an initial diagnosis of breast cancer. The cases ($n = 94$) were women with lung cancer as the second primary cancer whereas the controls ($n = 598$) had a second malignancy of a type not associated with smoking or radiation. The pattern of the increased risk associated with both smoking and radiation therapy for the initial breast cancer was consistent with a multiplicative interaction; however, the consistency of the data with different models was not formally assessed.

Van Leeuwen *et al.* (1995) used a nested case–control design to assess risk for lung cancer in relation to radiation and smoking in a cohort of 1939 patients who had received treatment for Hodgkin disease in the Netherlands. The 30 cases identified during an 18-year follow-up were matched to 82 controls. Radiation doses to the region of the lung where the case developed cancer were estimated and information on smoking was obtained from several sources. There was a significantly greater increase in risk among smokers in relation to estimated radiation dose than among nonsmokers. However, in reviewing the findings, Boivin (1995) showed that the pattern of combined effects was consistent with additivity of the excess relative risks. This study was limited by the small number of lung cancer cases and by the potential modifying effects of chemotherapy.

Therapy for small-cell carcinoma of the lung includes aggressive chemotherapy and radiation. Tucker *et al.* (1997) carried out a multi-centre study in North America of 611 persons treated for small-cell carcinoma of the lung and who remained cancer-free for at least two years after the therapy. The risks varied with smoking status with the highest risk being found in those who continued to smoke after the initial diagnosis of lung cancer (relative risk = 21); no second lung cancers were observed in the 13 never-smokers. The authors reported that the interaction was not statistically significant when a model was used to assess interaction.

2.3.4 *Arsenic*

The combined effect of smoking and arsenic on lung cancer risk has been examined in occupational groups exposed to arsenic through work in smelting or metal mining. Table 2.3.8 summarizes the studies included in two relevant reviews (Hertz-Picciotto *et al.*, 1992; Saracci & Boffetta, 1994).

Hertz-Picciotto *et al.* (1992) used data from six studies (Rencher *et al.*, 1977; Pershagen *et al.*, 1981; Enterline, 1983; Pershagen, 1985; Enterline *et al.*, 1987; Järup & Pershagen, 1991) to evaluate the pattern of joint effects. Although the data available from the different studies were not uniform, the analysis indicated a pattern of combined effects that was consistently greater than additive.

2.3.5 *Alcohol drinking*

The combined effects of smoking and alcohol consumption on cancers of the oral cavity, pharynx, larynx and oesophagus have been examined extensively, and to a lesser degree for cancer of the liver (Table 2.3.9). The studies varied in their methods and in the approaches used to assess effect modification, which ranged from descriptive to formal estimation of interaction terms in multivariate models.

(*a*) *Cancers of the upper aerodigestive tract*

For cancers of the oral cavity and pharynx, the evidence comes entirely from case–control studies carried out in Asia, Australia, Europe and the United States. In the majority of the studies, evaluation of effect modification was descriptive, without formal assessment of interaction. Overall, however, the pattern of odds ratios for smoking, across categories of alcohol consumption, is consistent with synergism. In two studies with relatively large numbers of cases and controls, the pattern of increasing cancer risk with increasing alcohol consumption is strong (Mashberg *et al.*, 1993; Kabat *et al.*, 1994). In both studies, the pattern of odds ratios for men and women was consistent with synergism and a test for interaction was statistically significant for both sexes.

Seven case–control studies and one cohort study reported on joint effects of tobacco smoking and alcohol drinking on the risk for oesophageal cancer. Generally, the studies support a positive departure of joint effects from additivity. Since multiple logistic regression models were used for analysing most of these studies, some also were tested for departure from multiplicativity. These tests for interaction are inadequate to assess synergy as defined in this monograph.

Most of the case–control studies of laryngeal cancer provide strong evidence for synergism. The studies were carried out in a number of locations around the world. Only the study in Shanghai (Zheng *et al.*, 1992) did not yield evidence consistent with synergism. In a number of studies, tests for interaction were carried out and reported to be 'non-significant.' These were tests for departure from the multiplicative models, typically multiple logistic regression models, used to analyze the case–control data, and not tests for departure from additivity.

Several studies reported on findings on cancer of the 'mixed upper aerodigestive tract', comprising studies of patients with squamous cell carcinomas, regardless of the specific site within the head and neck region. These studies also provided strong evidence for synergism.

(*b*) *Liver cancer*

Alcohol consumption is an established cause of liver cancer (IARC, 1988b) and of hepatic injury, which may lead to hepatic cirrhosis. Six case–control studies were identified that included information on the joint effect of smoking and alcohol consumption on liver cancer risk. In three studies, odds ratios for smokers were greater if they were also in the higher category of alcohol consumption (Chen *et al.*, 1991; Yu *et al.*, 1991; Kuper *et al.*, 2000). In one study (Kuper *et al.*, 2000), there was a statistically significant and super-multiplicative interaction between heavy smoking and heavy drinking in causing liver cancer.

2.3.6 *Infectious agents*

(*a*) *Hepatitis B*

Two case–control studies were identified that provided evidence on risk for liver cancer associated with smoking by serological status for hepatitis B infection (Table 2.3.10). The results are conflicting; the study conducted in Greece (Trichopoulos *et al.*, 1987) showed generally lower odds ratios in subjects who were seropositive for hepatitis B surface antigen compared with those who were negative for the antigen, whereas the study from China, Province of Taiwan (Chen *et al.*, 1991) showed greater risks in subjects who were positive for hepatitis B surface antigen.

(*b*) *Human papillomavirus*

For cervical cancer (squamous-cell type), evidence suggests that human papillomavirus (HPV) is a necessary factor, and implies that the risk of smoking cannot be estimated in the absence of HPV infection. Because the absolute risk of cervical cancer in the absence of HPV infection, is hence by definition zero, the incremental risk associated with smoking is interpreted as indicating synergism (Table 2.3.11).

(*c*) Helicobacter pylori

A case–control study of stomach cancer in Moscow examined the combined effect of smoking and *H. pylori* infection (Zaridze *et al.*, 2000). In non-infected persons, the odds ratio, comparing ever- to never-smokers was 1.2 (95% CI, 0.8–1.8) whereas in infected persons, the odds ratio was 1.6 (95% CI, 1.0–2.4). The odds ratios did not vary significantly with infection status. No other studies were identified.

2.3.7 *Others*

(*a*) *Nickel*

Only one study addressed the combined effect of occupational exposure to nickel and cigarette smoking. Andersen and colleagues (Andersen *et al.*, 1996) reported the findings of a cohort study of workers (*n* = 4764) at the Falconbridge nickel refinery (Norway). Information on smoking was obtained primarily from medical records at the refinery and from co-workers. Assessment of effect modification was restricted to 1337 men who were in the same birth cohorts as a population comparison group. The results were consistent with a combined effect of nickel exposure and smoking that is multiplicative: the relative risk for unexposed smokers was 6.1; the relative risk for exposed never-smokers was 3.6; and relative risk for exposed smokers was 23.

(*b*) *Silica (silicon dioxide)*

Exposure to silica is common among miners, sand-blasters and many other occupational groups. Crystalline silica has been classified by IARC as *carcinogenic to humans* (Group 1) (IARC, 1997) and is also known to cause silicosis, a fibriotic disorder of the lungs. Workers with silicosis have an increased risk for lung cancer that may be the direct consequence of the silica particles deposited in the lung, or an indirect consequence of the lung fibrosis.

Studies that have investigated the combined effect of smoking with silica exposure are summarized in Table 2.3.12 (Saracci & Boffetta, 1994). Both studies on silica exposure and on silicosis were included. No consistent patterns of effect modification were evident in either group of studies.

(*c*) *Chloromethyl ethers*

The chloromethyl ethers include chloromethyl methyl ether and bis(chloromethyl)-ether; these compounds were used in the chemical industry as intermediates in organic synthesis and in the production of ion exchange resins. The strong association of exposure to this agent with lung cancer was first reported by Figueroa *et al.* (1973) who described 14 cases; three were in never-smokers and the histology for 13 of the cases showed that only one was not a small-cell carcinoma. On follow-up of workers in the plant, nonsmokers were found to comprise a higher proportion of cases than in the general population (Weiss *et al.*, 1979). In a small cohort ($n = 51$) apparently drawn from the same plant (Weiss, 1980), the standardized mortality rate for lung cancer death was markedly higher for never-smokers and former smokers together, compared with current smokers. The authors interpreted this analysis as indicating antagonism between smoking and exposure to chloromethyl ethers. [The Working Group noted the limited information available on the joint effect of smoking and exposure to chloromethyl ethers.]

Table 2.3.1. Examples of levels of interaction between smoking and another agent

Exposure

- Work assignments of smokers and nonsmokers are different.
- Absenteeism rates differ for smokers and nonsmokers.

Exposure–dose relationships for the lung

- Differing patterns of physical activity and ventilation for smokers and nonsmokers
- Differing patterns of lung deposition and clearance in smokers and nonsmokers
- Differing morphometry of target cells in smokers and nonsmokers

Carcinogenesis

- Other carcinogens and tobacco smoke carcinogens act at the same or different steps in a multistage carcinogenic process.
- Smokers and non-smokers differ on other, unmeasured modifying factors.

Table 2.3.2. Characteristics of case–control studies on the combined effect of asbestos exposure and smoking in the causation of lung cancer

Reference[a]	Location	Years of study	Study type and population	Controls	No. of cases[b]	Source of diagnosis
Martischnig *et al.* (1977)	Gateshead, UK	1972–73	Hospital-based; shipbuilding area	Patients	201	Confirmed clinical
Blot *et al.* (1978, 1980, 1982)	Georgia, Virginia, Florida, USA	1970–78	Shipbuilding areas	Patients and decedents, no chronic obstructive pulmonary disease	1072	Death certificates, medical records
Rubino *et al.* (1979)	Balangero, Italy	1946–75	Nested case–control study in chrysotile miners and millers	Alive when case died	12	Death certificates, medical records
Pastorino *et al.* (1984)	Lombardy, Italy	1976–79	Industrial areas	Population	204	Confirmed clinical
Kjuus *et al.* (1986)	Telemark and Vestfold, Norway	1979–83	Hospital-based; industrial and shipbuilding areas	Patients, no chronic obstructive pulmonary disease, other diseases precluding employment in heavy industry	176	Medical records
Garshick *et al.* (1987)	USA	1981–82	Railroad workers	Decedent, no cancer, accident, suicide, unknown cause	1081	Death certificates
De Klerk *et al.* (1991)	Wittenoom, Australia	1979–86	Nested case–control study in crocidolite miners and millers	Alive, no asbestos-related disease	40	Death certificates, medical records
Minowa *et al.* (1991)	Yokosuka, Japan	1979–82	Shipbuilding area	Decedent, no cancer, pneumoconiosis, accident, suicide	96	Confirmed clinical or autopsy
Bovenzi *et al.* (1993)	Trieste, Italy	1979–81, 1985–86	Industrial and shipbuilding area	Decedent, no chronic obstructive pulmonary disease, smoking-related cancer	516	Autopsy records
Gustavsson *et al.* (2002)	Stockholm, Sweden	1985–90	All men aged 40–75 years, residents of Stockholm County	1. Alive 2. Decedent, no tobacco-related disease	1038	Regional cancer register

Adapted from Lee (2001)
[a] Reference from which main results were obtained
[b] Number of cases with data on smoking and asbestos exposure

Table 2.3.3. Characteristics of cohort studies on the combined effect of asbestos exposure and smoking in the causation of lung cancer

Reference[a]	Location	Follow-up period	Study population	No. of cases[b]	Source of diagnosis
Elmes & Simpson (1971)	Belfast, Northern Ireland	1940–66	Insulation workers	19	Death certificates, medical records
Selikoff & Hammond (1975)	New York and New Jersey, USA	1943–74	Insulation workers	47	Death certificates, medical records
Hammond *et al.* (1979)	USA and Canada	1967–76	Insulation workers	276	Death certificates, medical records
Selikoff *et al.* (1980)	New Jersey, USA	1961–77	Amosite asbestos factory workers	50	Death certificates, medical records
Acheson *et al.* (1984)	Uxbridge, UK	1947–79	Amosite asbestos factory workers	22	Death certificates
Berry *et al.* (1985)	East London, UK	1960–70, 1971–80	Asbestos factory workers	79	Death certificates
Hilt *et al.* (1985)	Telemark, Norway	1953–80	Workers in nitric acid production plant	127	Death certificates
Neuberger & Kundi (1990)	Vöcklabruck, Austria	1950–87	Asbestos cement products workers	49	Death certificates, medical records
Hughes & Weill (1991)	New Orleans, USA	1969–83	Asbestos cement products workers	26	Death certificates
Cheng & Kong (1992)	Tianjin, China	1972–87	Chrysotile asbestos products workers	21	Not given (death)
McDonald *et al.* (1993)	Quebec, Canada	1950–92	Chrysotile miners and millers	299	Death certificates
Zhu & Wang (1993)	8 factories, China	1972–86	Chrysotile asbestos products workers	57	Death certificates, medical records
Meurman *et al.* (1994)	North Savo, Finland	1953–91	Anthophyllite miners	55	Cancer registration
Oksa *et al.* (1997)	Finland	1967–94	(1) Asbestos sprayers (2) Asbestosis patients (3) Silicosis patients	3 33 15	Cancer registry

Adapted from Lee (2001)

[a] Reference from which main results were obtained.

[b] Number of cases with data on smoking and exposure to asbestos

Table 2.3.4. Case–control studies on the combined effect of exposure to asbestos and smoking in the causation of lung cancer

Reference	Definition and source of asbestos exposure	Definition of smoking exposure	Relative risk[a]				Interaction[b]
			Not exposed to asbestos or smoking	Exposed to asbestos but not smoking	Exposed to smoking but not asbestos	Exposed to smoking and asbestos	
Martischnig *et al.* (1977)	Yes *vs* no: questionnaire on work history	≥ 15 *vs* 0–14 cigarettes/day	1	1.08	1.78	5.57	> M
Blot *et al.* (1978, 1980, 1982)	Ever *vs* never worked in shipbuilding: interview of patients or proxies about work history	Current or former < 10 years					
		Georgia (*n* = 458)	1	1.28	4.71	7.58	~ M
		Virginia (*n* = 319)	1	1.88	3.09	4.87	~ M
		Florida (*n* = 295)	1	1.80	6.01	7.79	
Rubino *et al.* (1979)	≥ 101 *vs* 100 fibre–years: work history, dust measurements	Smoker *vs* nonsmoker	0	0	1	2.32	
Pastorino *et al.* (1984)	Yes *vs* no: interview of patients or proxies about work history	≥ 10 *vs* 0–9 cigarettes/day	1	2.82	5.47	9.86	I
Kjuus *et al.* (1986)	Heavy or moderate *vs* uncertain or none: interview of patients about asbestos exposure	≥ 10 *vs* 0–9 cigarettes/day	1	2.41	5.41	19.86	~ M
Garshick *et al.* (1987)	Yes *vs* no: work history	> 50 pack–years vs never smoker[c]					
		age < 65 years	1	1.20	5.68	6.82	
		age ≥ 65 years	1	0.98	9.14	8.96	
De Klerk *et al.* (1991)	High *vs* low: work history, dust measurements	Current or former < 10 years *vs* nonsmoker or former ≥ 10 years	1	2.24	3.44	9.57	> M
Minowa *et al.* (1991)	Definite or suspected *vs* none: interview of proxies about work history	Current or former < 10 years *vs* never-smoker or former > 10 years	1	–[d]	3.38	8.28	

Table 2.3.4 (contd)

Reference	Definition and source of asbestos exposure	Definition of smoking exposure	Relative risk[a]				Inter-action[b]
			Not exposed to asbestos or smoking	Exposed to asbestos but not smoking	Exposed to smoking but not asbestos	Exposed to smoking and asbestos	
Bovenzi *et al.* (1993)	Definite or possible *vs* none: interview of proxies about work history	Ever- *vs* never-smoker	1	1.83	10.13	15.89	
Gustavsson *et al.* (2002)	≥ 2.5 fibre–years *vs* none: reported work histories evaluated by an industrial hygienist and linked to workplace measurements	Current smoker *vs* never-smoker	1	10.2	21.7	43.1	

Adapted from Saracci & Boffetta (1994); Lee (2001)

[a] 0 indicates no cases in this category; 1 indicates reference group.

[b] Interaction term taken from Saracci & Boffetta (1994); numbers in parentheses are based on the assumption of a relative risk due to smoking of 10; A, additive; I, intermediate; M, multiplicative

[c] Fitted logistic regression assuming multiplicative model

[d] Not applicable because of zero division in odds ratio calculation

Table 2.3.5. Cohort studies on the combined effects of asbestos exposure and smoking in the causation of lung cancer

Reference	Definition and source of asbestos exposure	Definition of smoking exposure	Reference group[a]	Relative risk				Inter-action[c]
				Not exposed to asbestos or smoking	Exposed to asbestos but not smoking	Exposed to smoking but not asbestos[b]	Exposed to smoking and asbestos	
Elmes & Simpson (1971)	Study group: inferred from nature of population studied	Smoker *vs* nonsmoker	External	1	0[d]	(7.13)	112.94	
Selikoff & Hammond (1975)	Study group: inferred from nature of population studied	Ever *vs* never-smoker	External	1	8.44	(7.13)	73.71	(> M)
Hammond *et al.* (1979)	Study group: inferred from nature of population studied	Ever *vs* never-smoker	External	1	5.17	10.85	53.24	M
Selikoff *et al.* (1980)	Study group: inferred from nature of population studied	Ever *vs* never-smoker	External	1	25.00	(7.13)	33.44	I
Acheson *et al.* (1984)	Medium or heavy *vs* background: work history and dust measurements	Ever *vs* never-smoker	Internal External	0 1	1 6.07	0 (7.13)	2.57 15.53	(~ M)
Berry *et al.* (1985)	Severe *vs* low to moderate: work history	Ever *vs* never-smoker						
		(1960–70)	Internal					
		Men		1	0	1.15	1.93	(> M)
		Women		0	1	0	2.26	(> M)
		(1971–80)	External					
		Men		1	0	(7.13)	19.33	(A)
		Women		1	15.00	(7.13)	33.97	(I)
Hilt *et al.* (1985)	Exposed *vs* population controls: work history	Ever *vs* never-smoker	Internal	1	0	5.84	25.20	> M
Neuberger & Kundi (1990)	All workers: work history and dust measurements	Cigarettes/day smoked					[e]	
Hughes & Weill (1991)	Study group: work history and dust measurements	Ever *vs* never-smoker	External	1	0	(7.13)	~ 13	

Table 2.3.5 (contd)

Reference	Definition and source of asbestos exposure	Definition of smoking exposure	Reference group[a]	Relative risk				Inter-action[c]
				Not exposed to asbestos or smoking	Exposed to asbestos but not smoking	Exposed to smoking but not asbestos[b]	Exposed to smoking and asbestos	
Cheng & Kong (1992)	Yes *vs* no: work history and dust measurements	Cigarette smoker *vs* nonsmoker	Internal	1	5.44	1.57	8.73	M
McDonald *et al.* (1993)	≥ 60 *vs* < 60 million particles per cubic foot × years: work history and dust measurements	Ever *vs* never-smoker	Internal External	1 1	1.65 4.07	4.46 (7.13)	4.51 11.13	
Zhu & Wang (1993)	Yes *vs* no: work history and dust measurements	Smoker *vs* nonsmoker	Internal	1	3.78	1.83	11.06	
Meurman *et al.* (1994)	Heavy *vs* moderate: work history	Cigarette smoker *vs* nonsmoker	Internal External	1 1	0.83 3.21	6.27 (7.13)	6.16 23.87	
Oksa *et al.* (1997)	Study group: medical interview	Ever-smoker *vs* never-smoker	External					
		Asbestos sprayers		1	0	(7.13)	74.77	
		Patients with asbestosis		1	0	(7.13)	81.72	
		Patients with silicosis		1	0	(7.13)	22.34	

Adapted from Saracci & Boffetta (1994); Lee (2001)
[a] Internal: internal data for all four comparison groups; external: external reference group for asbestos-exposed groups
[b] The value of 7.13, shown in parentheses, is a value assumed by Lee (2001) and taken from the British Doctors' Study (see Section 2.0).
[c] Interaction term taken from Saracci & Boffetta (1994); numbers in parentheses are based on the assumption of a relative risk due to smoking of 10; A, additive; I, intermediate; M, multiplicative
[d] Only five nonsmokers at risk
[e] Graph showing that the observed number of deaths was close to that expected according to the workers' smoking habits, indicating that 'exposure to chrysotile does not increase lung cancer'

Table 2.3.6. Cohort studies on the combined effect of smoking and exposure to radon progeny in the causation of lung cancer

Reference[a]	Place of study	Years of study	Study population	Total cases/ cohort	Cases/cohort included	*p* value		Mixture	
						Multiplicative	Additive	λ	*p* value[b]
Radford & St Clair Renard (1984)	Sweden	1951–91	Iron miners	79/1294	51/1415	0.43	0.31	–0.3	0.38
Hornung & Meinhardt (1987)	Colorado, USA	1950–87	Uranium miners	329/3347	292/2205	0.58	0.04	0.7	0.49
Morrison *et al.* (1988)	Newfoundland, Canada	1950–84	Fluorspar miners	118/2088	25/1002	0.53	0.67	–0.1	0.85
Samet *et al.* (1991)	New Mexico, USA	1943–85	Uranium miners	69/3469	52/2602	0.15	0.11	0.4	0.16
Xuan *et al.* (1993)	Yunnan, China	1976–87	Tin miners	980/17 143	907/13 047	0.02	0.08	–0.3	0.39

Adapted from Lubin *et al.* (1994); NRC (1988)
[a] Most recent reference in 1994
[b] Refers to fit of mixture model versus full model.

Table 2.3.7. Case–control studies on the combined effect of smoking and radon exposure at home in the causation of lung cancer

Reference	Study location Years of study	No. of cases: Never-smoker/total	Findings
Axelson *et al.* (1988)	Sweden 1960–81	15/177	Increased risk for non- and occasional smokers vs. regular smokers in rural areas
Svensson *et al.* (1989)	Sweden 1983–85	35/210	Greater risk for smokers than never-smokers
Blot *et al.* (1990)	China 1985–87	123/308	Nonsignificantly greater risk in smokers ($p = 0.15$)
Schoenberg *et al.* (1990)	USA 1982–83	61/433	Exposure response strongest in light smokers; inverse in heaviest smokers
Ruosteenoja (1991)	Finland 1980–85	4/238	No pattern observed when heavier smokers compared with light smokers
Pershagen *et al.* (1994)	Sweden 1980–84	178/1360	Higher excess relative risk in current smokers than in never-smokers. Additivity rejected by data ($p = 0.02$)
Darby *et al.* (1998)	UK 1988–93	26/982	No evidence for heterogeneity of excess relative risk
Pisa *et al.* (2001)	Italy 1987–93	14/138	Interaction described as multiplicative, but analyses of interaction not significant
Wang *et al.* (2002)	China 1994–98	765/2009	No evidence for heterogeneity of excess relative risk

Adapted from NRC (1988)

Table 2.3.8. Studies on the combined effects of smoking and occupational exposure to arsenic on lung cancer

Reference Country and years of study	Study design	Source population	Exposure assessment (tobacco or arsenic)	No. of cases/ deaths	Smoking categories	Relative risks Exposure categories			Interaction/ excess risk (%)[a]	Comments
Rencher *et al.* (1977) USA 1959–69	Proportional mortality cohort	522 workers at Utah copper smelter who died in 1959–69	Smoking history obtained from work supervisors of deceased employees	31 deaths	 Nonsmoker Smoker	*Mine* 1.0 4.7	*Concentrator* 1.1 4.7	*Smelter* 4.7 13.1	69	
Pershagen *et al.* (1981) Sweden 1928–77	Nested case– control	Cohort of 3958 workers at Ronnskar smelter employed for at least 3 months		76 deaths, 152 deceased controls	 Nonsmoker Smoker	*No* 1.0 4.9	*Yes* 3.0 14.6		M; 131	Overlap of 41 cases with Pershagen (1985) and all 76 cases with Järup & Pershagen (1991)
Welch *et al.* (1982) USA 1938–77	Cohort	1800 workers from Anaconda, MT, smelter: heavy exposure and a 20% random sample of other exposure categories	Arsenic categories based on quantified exposure estimates for one point in time	80 deaths	 Nonsmoker Smoker Nonsmoker Smoker	*Low* 1.0 1.3 *High* 3.0 3.8	*Medium* 0.9 3.3 *Very high* 6.6 8.5		M	Multiplicative interaction for (high + very high) vs low exposure
Pinto *et al.* (1978); Enterline (1983) USA 1949–73	Cohort	527 workers from Tacoma,WA, smelter who lived beyond age 65 and retired in 1949–73		32 deaths	 Nonsmoker Smoker	*No* 1.0 7.2	*Yes* 5.1 20.7		(I); 91	

Table 2.3.8 (contd)

Reference Country and years of study	Study design	Source population	Exposure assessment (tobacco or arsenic)	No. of cases/ deaths	Smoking categories	Relative risks Exposure categories			Interaction/ excess risk (%)[a]	Comments
Pershagen (1985) Sweden 1961–79	Case–control	Residents in region where the Ronnskar smelter is located		212 deaths, 424 deceased controls		*None*	*Residential*		Residential: 92 Mining: 105 Smelting: 71	Overlap of 52 cases with Järup & Pershagen (1991)
					Nonsmoker	1.0	2.3			
					Smoker	8.3	17.5			
						Mining	*Smelting*			
					Nonsmoker	10.4	8.4			
					Smoker	35.2	26.2			
Enterline *et al.* (1987) USA 1949–80	Nested case–control	Cohort of 2288[b] workers employed at 6 copper smelters for ≥ 3 years in 1946–76, terminating employment at age > 44 and after 1949	Arsenic exposure very low compared with other smelters	55 cases, 126 controls		*None*	*Mean exposure*		64	Included cases from study by Rencher *et al.* (1977). Fitted logistic model; mean exposure level over the six plants calculated as cumulative time-weighted average of 281.03 μg/m^3-years.
					Nonsmoker	1.0	2.1			
					Smoker for 20 years	2.4	5.1			
Taylor *et al.* (1989) China 1971–84	Retrospective nested case–control	Past and present workers at Yunnan Tin Corporation	Arsenic categories based on quantified exposure estimates	107 cases, 107 controls		*Low*	*Medium*	*High*	~ A	Cases alive in 1985 Tobacco smoked in a water pipe; very few nonsmokers; interaction calculated for heavy *vs* light smokers and high *vs* low exposure
					Light	1.0	3.2	5.0		
					Medium	1.0	4.9	4.4		
					Heavy	1.4	8.9	4.9		
Tsuda *et al.* (1990) Japan 1972–89	Cohort	141 certified arsenic poisoning patients	Employment in arsenic mines	8 deaths	SMR	*No*	*Yes*		(> M)	Standardized mortality ratio using sex- and age-specific mortality rate of all Japanese in 1975, 1980 or 1985
					Nonsmoker	0	264			
					Smoker	0	1247			
Järup & Pershagen (1991) Sweden 1928–81	Nested case–control	Cohort of 3916 workers at Ronnskar smelter employed at least 3 months from 1928–67	Smokers of > 10 g tobacco/ day; cumulative arsenic exposure	107 cases, 214 deceased controls excluding smoking-related causes		*Low*	*Medium*	*High*	Low: A Medium: ~ A High: I; 127	
					Nonsmoker	1.0	1.4	5.6		
					Smoker	40.1	9.4	29.2		

Adapted from Hertz-Picciotto *et al.* (1992); Saracci & Boffetta (1994)

[a] Terms for interaction were taken from Saracci and Boffetta (1994); terms in parentheses are based on the assumption that the relative risk is 10. A, additive; I, intermediate; M, multiplicative; the numbers are the percentage by which observed exceeds predicted excess relative risk and are taken from Hertz-Picciotto *et al.* (1992).

[b] Original paper reported 5392 workers in the six plants considered.

Table 2.3.9. Studies with information on interaction of smoking and alcohol in the causation of cancer at various sites

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Oral cavity							
Choi & Kahyo (1991)	Seoul, Republic of Korea, 1986–89	Cases: 113 men, 44 women (oral cavity) Controls: 339 men, 132 women; hospital controls, matched on age, sex and admission date	Alcohol (soju) in mL/day: Light: < 8100 Medium: 8100–16 200 Heavy: > 16 200	Non-drinker	Nonsmoker	1.0	Stratified analysis; ORs extrapolated from figure [no formal test for interaction]
					≤ 1 pack/day	0.5	
					> 1 pack/day	1	
				Light drinker	Nonsmoker	0.1	
					≤ 1 pack/day	0.5	
					> 1 pack/day	1.1	
				Medium drinker	Nonsmoker	1.5	
					≤ 1 pack/day	1.5	
					> 1 pack/day	1.8	
				Heavy drinker	Nonsmoker	1	
					≤ 1 pack/day	2	
					> 1 pack/day	5.04	
Zheng *et al.* (1997)	Beijing, China, 1988–89	Cases: 111 cases (tongue) Controls: 111 hospital controls, matched by age and sex	Alcohol: lifetime consumption	Never-drinker	Nonsmoker	1.0	Logistic regression model; risk estimates adjusted for education level. *p < 0.05 [No formal test for interaction]
					≤ 20 pack–years	1.2	
					> 20 pack–years	7.6*	
				≤ 255 kg	Nonsmoker	1.9	
					≤ 20 pack–years	1.6	
					> 20 pack–years	23.3*	
				> 255 kg	Nonsmoker	2.4	
					≤ 20 pack–years	3.0	
					> 20 pack–years	4.1	
Schlecht *et al.* (1999)	Brazil, 1986–89	Cases: 373 incident cases (oral cavity) Controls: 746 hospital controls, matched on hospital, trimester of admission, age and sex	Alcohol: lifetime consumption	0–10 kg	0–5 pack–years	1.0	Logistic regression model that included an interaction term; risk estimates adjusted for race, beverage temperature, religion, wood stove use and consumption of spicy foods; no statistical evidence for effect modification [p not stated]
					6–42 pack–years	2.9 (1.2–6.8)	
					> 42 pack–years	7.8 (2.9–21.0)	
				11–530 kg	0–5 pack–years	1.2 (0.4–3.4)	
					6–42 pack–years	6.2 (2.7–14.1)	
					> 42 pack–years	11.2 (4.8–26.3)	
				> 530 kg	0–5 pack–years	2.3 (0.6–9.1)	
					6–42 pack–years	19.5 (2.6–147)	
					> 42 pack–years	20.3 (9.0–45.3)	
Pharynx							
Olsen *et al.* (1985)	Denmark, 1980–82	Cases: 32 incident cases (hypopharynx) Controls: 1141 population controls, matched on sex, residence and age	Tobacco: g of tobacco/week	< 150 g/week	< 10 g/week	1.0	Stratified analysis [no formal test for interaction]
					≥ 10 g/week	3.0 (1.3–6.9)	
				≥ 150 g/week	< 10 g/week	1.7 (0.5–5.9)	
					≥ 10 g/week	5.2 (2.0–13.6)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Choi & Kahyo (1991)	Seoul, Republic of Korea, 1986–89	Cases: 133 men, 19 women (pharynx) Controls: 399 men, 57 women; hospital controls, matched on age, sex and admission date	Alcohol (soju) in mL/day: Light: < 8100 Medium: 8100–16 200 Heavy: > 16 200	Nondrinker	Nonsmoker	1.0	Stratified analysis; ORs extrapolated from figure [no formal test for interaction]
					≤ 1 pack/day	0.8	
					> 1 pack/day	1.0	
				Light drinker	Nonsmoker	1.1	
					≤ 1 pack/day	0.9	
					> 1 pack/day	1.3	
				Medium drinker	Nonsmoker	1.0	
					≤ 1 pack/day	1.5	
					> 1 pack/day	1.2	
				Heavy drinker	Nonsmoker	1.0	
					≤ 1 pack/day	2.0	
					> 1 pack/day	6.7	
Schlecht *et al.* (1999)	Brazil, 1986–89	Cases: 217 incident cases (pharynx) Controls: 434 hospital controls, matched on hospital, trimester of admission, age and sex	Alcohol: lifetime consumption	0–10 kg	0–5 pack–years	1.0	Logistic regression model that included an interaction term; risk estimates were adjusted for race, beverage temperature, religion, wood stove use and consumption of spicy foods; interaction term statistically significant ($p = 0.007$)
					6–42 pack–years	2.4 (0.2–24.0)	
					> 42 pack–years	69.4 (6.9–694)	
				11–530 kg	0–5 pack–years	6.2 (0.7–56.6)	
					6–42 pack–years	21.7 (2.6–180)	
					> 42 pack–years	43.0 (4.9–340)	
				> 530 kg	0–5 pack–years	22.3 (2.1–238)	
					6–42 pack–years	66.3 (1.7–2556)	
					> 42 pack–years	77.3 (9.2–625)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Oesophagus							
Case–control studies							
Franceschi *et al.* (1990)	Northern Italy, 1986–89	Cases: 288 men, < 75 years old Controls: men < 75 years old, admitted to same hospitals for acute illness	*Tobacco*: Light: ex-smoker who quit ≥ 10 years ago or smoker of 1–14 cigs/ day for < 30 years Moderate: 30–39 years duration regardless of amount, 15–24 cigs/day regardless of duration, 1–24 cigs/day for ≥ 40 yrs, or ≥ 15 cigs/day for < 30 yrs Heavy: ≥ 25 cigs/day for > 40 yrs *Alcohol*: 1 drink = 150 mL wine = 330 mL beer = 30 mL spirits	< 35 drinks/week	Nonsmoker	1.0	Regression model; risk estimates adjusted for age, area of residence and years of education [no formal test for interaction]
					Light smoker	1.1	
					Moderate smoker	2.7	
					Heavy smoker	6.4	
				35–59 drinks/week	Nonsmoker	0.8	
					Light smoker	7.9	
					Moderate smoker	8.8	
					Heavy smoker	11.0	
				≥ 60 drinks/week	Nonsmoker	7.9	
					Light smoker	9.4	
					Moderate smoker	16.7	
					Heavy smoker	17.5	
Barón *et al.* (1993)	Italy, 1989–91	Cases: 271 men Controls: 1754 men, hospital controls, matched on age and area of residence	Tobacco: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/ day for < 30 years Moderate: 15–24 cigs/day regardless of duration or 30–39 years duration regardless of amount, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for ≥ 40 years	< 35 drinks/week	Nonsmoker	1.0	Regression model; risk estimates adjusted for area of residence, age, education and profession [no formal test for interaction]
					Light smoker	2.1	
					Moderate smoker	4.4	
					Heavy smoker	8.4	
				35–59 drinks/week	Nonsmoker	2.2	
					Light smoker	4.4	
					Moderate smoker	9.7	
					Heavy smoker	18.5	
				≥ 60 drinks/week	Nonsmoker	2.6	
					Light smoker	5.5	
					Moderate smoker	11.4	
					Heavy smoker	21.8	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Brown *et al.* (1994a)	Georgia, Michigan, New Jersey, USA, 1986–89	Cases: 373 men (squamous-cell carcinoma) (124 white, 249 black) Controls: 1364 men, community controls (750 white, 614 black)	Tobacco: Light: nonsmoker, former smoker or current smoker of < 1 pack/day Heavy: current smoker of ≥ 1 pack/day	White men			Logistic regression model; risk estimates adjusted for age, geographical area and income. For both races, interaction between smoking and drinking was not significant [*p* value not provided]. Significant interaction (*p* = 0.02) between race and smoking/drinking variable
				0–7 drinks/week	Light smoker	1.0	
					Heavy smoker	3.3 (1.0–19.8)	
				8–14 drinks/week	Light smoker	1.8 (0.5–6.1)	
					Heavy smoker	8.7 (2.4–32.4)	
				15–35 drinks/week	Light smoker	4.6 (1.7–12.8)	
					Heavy smoker	22.1 (7.8–62.3)	
				36–84 drinks/week	Light smoker	19.7 (7.2–53.4)	
					Heavy smoker	28.5 (10.1–80.2)	
				≥ 85 drinks/week	Light smoker	29.0 (7.2–116.5)	
					Heavy smoker	35.4 (10.0–125.5)	
				Black men			
				0–7 drinks/week	Light smoker	1.0	
					Heavy smoker	4.5 (1.4–14.6)	
				8–14 drinks/week	Light smoker	5.7 (2.0–15.8)	
					Heavy smoker	14.2 (4.1–49.1)	
				15–35 drinks/week	Light smoker	10.6 (4.1–27.2)	
					Heavy smoker	36.8 (13.9–97.2)	
				36–84 drinks/week	Light smoker	39.5 (14.5–107.8)	
					Heavy smoker	42.1 (15.8–112.6)	
				≥ 85 drinks/week	Light smoker	31.0 (9.8–98.5)	
					Heavy smoker	149.2 (39.2–567.4)	
Brown *et al.* (1994b)	Georgia, Michigan, New Jersey, USA, 1986–89	Cases: 174 white men (adenocarcinoma) Controls: 750 men, community controls, frequency-matched on age and race		< 8 drinks/week	< 1 pack/day	1.0	Unconditional logistic regression model; risk estimates adjusted for age, area, and income; not possible to distinguish statistically between additive, multiplicative and intermediate models. [No formal test for interaction]
					≥ 1 pack/day	2.4 (1.5–3.8)	
				≥ 8 drinks/week	< 1 pack/day	2.4 (1.1–5.1)	
					≥ 1 pack/day	3.8 (2.2–6.4)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Castelletto *et al.* (1994)	La Plata, Argentina, 1986–89	Cases: 131 incident cases Controls: 262 hospital controls, matched for age and hospital		0 mL/day	Nonsmoker	1.0	Logistic regression model; risk estimates adjusted for age, sex, hospital and education. Test for interaction between alcohol and tobacco not significant ($p = 0.45$)
					1–14 cigs/day	2.5 (0.4–16.5)	
					≥ 15 cigs/day	0.7 (0.1–6.5)	
				1–99 mL/day	Nonsmoker	1.6 (0.6–4.2)	
					1–14 cigs/day	4.3 (1.4–13.2)	
					≥ 15 cigs/day	3.7 (1.3–11.0)	
				100–199 mL/day	Nonsmoker	1.2 (0.1–12.0)	
					1–14 cigs/day	3.7 (1.3–11.0)	
					≥ 15 cigs/day	11.8 (3.7–37.7)	
				≥ 200 mL/day	Nonsmoker	5.7 (1.1–28.6)	
					1–14 cigs/day	5.0 (0.6–39.1)	
					≥ 15 cigs/day	19.0 (5.4–66.9)	
Hu *et al.* (1994)	Heilongjiang Province, China, 1985–1989	Cases: 196 incident cases Controls: 392 hospital controls (non-neoplastic, non-oesophageal disease), matched on age, gender and area of residence		≤ 57 L liquor/year	Nonsmoker	1.0	Regression model that does not assume multiplicative effects; synergistic effect that accounts for 38% of the excess risk [no formal test for interaction]: when using data in continuous form, interaction terms in the regression models were not significant.
					1–30 cigs/day	1.8	
					≥ 31 cigs/day	4.5	
				> 57 L liquor/year	Nonsmoker	1.0	
					1–30 cigs/day	5.3	
					≥ 31 cigs/day	7.9	
Zambon *et al.* (2000)	Northern Italy, 1992–97	Cases: 275 men (incident squamous-cell carcinoma) Controls: 593 men, hospital controls	Alcohol: 1 drink = 125 mL wine = 330 mL beer = 30 mL spirits	0–20 drinks/week	Nonsmoker	1.0	Logistic regression model; risk estimates adjusted for area of residence, age and education; risk increase for the highest joint level of alcohol drinking and current smoking compatible with a multiplicative model (departure from multiplicativity $\beta = 0.15$, $p = 0.27$)
					1–14 cigs/day	–	
					15–24 cigs/day	3.3 (0.4–31.1)	
					≥ 25 cigs/day	–	
				21–34 drinks/week	Nonsmoker	2.1 (0.2–23.5)	
					1–14 cigs/day	18.9 (2.2–161.8)	
					15–24 cigs/day	35.3 (4.3–288.9)	
					≥ 25 cigs/day	44.1 (5.5–352.9)	
				35–59 drinks/week	Nonsmoker	8.9 (1.0–77.8)	
					1–14 cigs/day	36.5 (4.4–305.7)	
					15–24 cigs/day	57.2 (7.2–456.9)	
					≥ 25 cigs/day	66.8 (7.8–573.3)	
				≥ 60 drinks/week	Nonsmoker	56.1 (6.2–508.0)	
					1–14 cigs/day	40.3 (4.6–355.4)	
					15–24 cigs/day	117.6 (15.0–923.1)	
					≥ 25 cigs/day	130.3 (15.2–980.1)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Cohort study							
Kinjo *et al.* (1998)	Japan, 1966–81	Six-prefecture study (see Table 2.1) 440 deaths		≤ 3 times/week	Nonsmoker	1.0	Risk estimates adjusted for attained age, prefecture, occupation and sex. Joint effect of alcohol drinking and smoking was more than additive. Data available for interaction of tobacco and alcohol stratified by tea consumption (hot/not hot)
					≥ 1 cig/day	1.6 (1.1–2.1)	
				≥ 4 times/week	Nonsmoker	1.0 (0.4–2.0)	
					≥ 1 cig/day	3.9 (2.7–5.4)	
Larynx							
Wynder *et al.* (1976)	New York City, Houston, Los Angeles, Birmingham, Miami, New Orleans, USA, 1970–73	Cases: 258 men, 56 women Controls: 516 men, 168 women; hospital controls, matched on gender, year of interview, hospital status and age at diagnosis	*Tobacco*: 1 cigar = 5 cig. 1 pipe = 2.5 cig. *Alcohol*: 1 unit = 1 oz spirits = 4 oz wine = 6 oz beer	Men Nondrinker	Nonsmoker	1.0	Stratified analysis [no formal test for interaction]
					1–15 cigs/day	3.0 (1.0–9.1)	
					16–34 cigs/day	6.0 (2.2–16.1)	
					≥ 35 cigs/day	7.0 (2.5–19.4)	
				1–6 units/day	Nonsmoker	–	
					1–15 cigs/day	4.0 (1.0–15.6)	
					16–34 cigs/day	6.7 (2.3–19.7)	
					≥ 35 cigs/day	10.3 (3.6–29.8)	
				≥ 7 units/day	Nonsmoker	–	
					1–15 cigs/day	3.3 (0.9–12.8)	
					16–34 cigs/day	13.8 (5.1–37.7)	
					≥ 35 cigs/day	22.1 (7.8–62.1)	
Burch *et al.* (1981)	Ontario, Canada, 1977–79	Cases: 204 incident cases Controls: 204 community controls, matched on neighbourhood, sex and age	*Tobacco*: lifetime cigarette consumption *Alcohol*: lifetime oz ethanol consumption	0 oz	Nonsmoker	1.0	Logistic regression model; coefficient for the interaction term (–0.10) not significant (SE = 0.11, $p = 0.177$)
					< 150 000 cigs	2.0	
					150 000–299 000 cigs	3.9	
					≥ 300 000 cigs	7.6	
				< 10 000 oz	Nonsmoker	2.0	
					< 150 000 cigs	3.5	
					150 000–299 000 cigs	6.3	
					≥ 300 000 cigs	11.1	
				10 000–25 000 oz	Nonsmoker	3.9	
					< 150 000 cigs	6.3	
					150 000–299 000 cigs	10.1	
					≥ 300 000 cigs	16.3	
				≥ 26 000 oz	Nonsmoker	7.7	
					< 150 000 cigs	11.2	
					150 000–299 000 cigs	16.3	
					≥ 300 000 cigs	23.7	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Flanders & Rothman (1982)	7 cities and 2 states in the USA, 1969–71	Cases: 87 men Controls: 956 men with cancers of other sites (excluding oral cavity, pharynx, oesophagus, stomach, lung, small intestine, colon, pancreas, bronchus, pleura, bladder and kidney)	Tobacco and alcohol: lifetime consumption in units 1 tobacco unit = 1 cigarette = 0.2 cigars = 0.4 pipefuls 1 alcohol unit = 1.5 oz spirits = 6 oz wine = 12 oz beer			Index of interaction[†]	[†]A value of 1.0 indicates no synergy.
				0–49 units	0–49 units	–	
					50–549 units	–	
					550–899 units	–	
					≥ 900 units	–	
				50–349 units	0–49 units	–	
					50–549 units	0.1	
					550–899 units	1.8	
					≥ 900 units	1.1	
				350–699 units	0–49 units	–	
					50–549 units	6.1	
					550–899 units	0.7	
					≥ 900 units	1.6	
				≥ 700 units	0–49 units	–	
					50–549 units	3.0	
					550–899 units	0.7	
					≥ 900 units	1.3	
			Daily consumption	0 units	0 unit	–	
					1–14 units	–	
					15–34 units	–	
					≥ 35 units	–	
				1–9 units	0 unit	–	
					1–14 units	2.3	
					15–34 units	1.2	
					≥ 35 units	1.7	
				≥ 9 units	0 unit	–	
					1–14 units	1.8	
					15–34 units	3.0	
					≥ 35 units	3.9	
Herity *et al.* (1982)	Dublin, Ireland	Cases: 59 men Controls: 152 men, hospital controls		Non-/light drinker	Non-/light smoker	1.0	Stratified analysis; synergistic effect between alcohol and tobacco, index of interaction = 2.5
					Heavy smoker	3.3 (1.2–9.1)	
				Heavy drinker	Non-/light smoker	4.0 (1.6–9.9)	
					Heavy smoker	14.0 (6.3–31.0)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)		Comments
						LL	FL	
Walter & Iwane (1983)	7 cities and 2 states in the USA, 1969–71	Cases: 87 men Controls: 956 men with cancers of other sites (excluding oral cavity, pharynx, oesophagus, stomach, lung, small intestine, colon, pancreas, bronchus, pleura, bladder and kidney	Tobacco and alcohol: lifetime consumption in units 1 tobacco unit = 1 cigarette = 0.2 cigars = 0.4 pipefuls 1 alcohol unit = 1.5 oz spirits = 6 oz wine = 12 oz beer	0–49 units	0–49 units	1.0	1.0	Reanalysis of the data from Flanders and Rothman (1982); risk estimates adjusted for age LL = log linear model; FL = Flanders and Rothman model
					50–549 units	1.7	1.5	
					550–899 units	2.6	3.5	
					≥ 900 units	5.4	7.9	
				50–349 units	0–49 units	1.5	1.1	
					50–549 units	2.5	1.9	
					550–899 units	3.8	4.7	
					≥ 900 units	7.9	11.1	
				350–699 units	0–49 units	2.0	2.5	
					50–549 units	3.3	4.0	
					550–899 units	5.1	6.8	
					≥ 900 units	10.5	13.3	
				≥ 700 units	0–49 units	3.0	6.1	
					50–549 units	5.0	9.3	
					550–899 units	7.9	12.1	
					≥ 900 units	16.2	18.5	
Brownson & Chang (1987)	Missouri, USA, 1972–84	Cases: 63 white men Controls: 200 white men with colon cancer	Smoking (yes/no) Drinking (yes/no)	No alcohol	No smoking	1.0		Logistic regression model; risk estimates adjusted for age. Synergy index used to measure interaction between smoking and alcohol = 1.77 (77% greater than predicted additivity).
					Smoking	3.4		
				Alcohol	No smoking	2.4		
					Smoking	7.7		
De Stefani *et al.* (1987)	Uruguay, 1985–86	Cases: 107 men, aged 30–89 years Controls: 290 men, hospital controls		0–64 mL/day	0–15 cigs/day	1.0		Stratified analysis [no formal test for interaction]
					≥ 16 cigs/day	20.6		
				≥ 65 mL/day	0–15 cigs/day	16.7		
					≥ 16 cigs/day	123.4		

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Guénel *et al.* (1988)	Curie Institute, Paris, 1975–85	Cases: 411 men, ≥ 25 years old Controls: 4135 men, community controls, ≥ 25 years old	Tobacco: g tobacco/day	*Glottis (n = 197)*			Stratified analysis; risk estimates adjusted for age. To test deviation from the multiplicative model, a logistic model with cross-product variables alcohol × tobacco was compared to the simple multiplicative model: Glottis: chi-squared =10.2, $p = 0.33$ (9 degrees of freedom); Supraglottis: chi-squared = 4.78, $p = 0.85$ (9 degrees of freedom) [This indicated that the multiplicative model fits well.]
				0–39 g/day	0–9 g/day	1.0	
					10–19 g/day	0.4 (0.2-4.5)	
					20–29 g/day	9.3 (4.9-36.4)	
					≥ 30 g /day	19.2 (7.7-58.4)	
				40–99 g/day	0–9 g/day	1.6 (0.6-4.1)	
					10–19 g/day	2.9 (1.1-8.0)	
					20–29 g/day	12.3 (4.3-27.5)	
					≥ 30 g /day	27.4 (8.4-64.4)	
				100–159 g/day	0–9 g/day	2.8 (1.2-15.2)	
					10–19 g/day	15.1 (5.2-43.4)	
					20–29 g/day	26.4 (7.8-62.3)	
					≥ 30 g /day	48.9 (16.9-132.8)	
				≥ 160 g/day	0–9 g/day	5.1 (2.3-53.8)	
					10–19 g/day	40.9 (10.3-191.5)	
					20–29 g/day	125.3 (34.1-367.4)	
					≥ 30 g /day	289.4 (83.0-705.8)	
				Supraglottis (n = 214)			
				0–39 g/day	0–9 g/day	1.0	
					10–19 g/day	3.4 (0.6–20.9)	
					20–29 g/day	32.3 (4.4–82.1)	
					≥ 30 g /day	46.8 (6.7–152.6)	
				40–99 g/day	0–9 g/day	2.6 (0.3–10.4)	
					10–19 g/day	27.5 (2.1–49.8)	
					20–29 g/day	48.5 (6.7–101.0)	
					≥ 30 g /day	132.3 (16.6–283.8)	
				100–159 g/day	0–9 g/day	7.3 (1.6–57.3)	
					10–19 g/day	75.4 (8.4–187.0)	
					20–29 g/day	180.7 (27.3–415.2)	
					≥ 30 g /day	530.6 (77.7–1175.7)	
				≥ 160 g/day	0–9 g/day	50.6 (8.4–280.2)	
					10–19 g/day	115.5 (22.8–671.0)	
					20–29 g/day	647.7 (106.4–1749.1)	
					≥ 30 g /day	1094.2 (185.8–2970.7)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Tuyns *et al.* (1988)	France, Italy, Spain, Switzerland	Cases: 1147 men Controls: 3057 men, population controls, individually matched on area and frequency-matched on age		*Endolarynx*			Logistic regression model
				0–40 g/day	0–7 cigs/day	1.0	
					8–15 cigs/day	6.7	
					16–25 cigs/day	12.7	
					≥ 26 cigs/day	11.5	
				41–80 g/day	0–7 cigs/day	1.7	
					8–15 cigs/day	5.9	
					16–25 cigs/day	12.2	
					≥ 26 cigs/day	18.5	
				81–120 g/day	0–7 cigs/day	2.3	
					8–15 cigs/day	10.7	
					16–25 cigs/day	21.0	
					≥ 26 cigs/day	23.6	
				≥ 121 g/day	0–7 cigs/day	3.8	
					8–15 cigs/day	12.2	
					16–25 cigs/day	31.6	
					≥ 26 cigs/day	43.2	For multiplicative model, chi-squared = 5.8 (9 degrees of freedom)
				Hypopharynx/epilarynx			
				0–40 g/day	0–7 cigs/day	1.0	
					8–15 cigs/day	4.7	
					16–25 cigs/day	13.9	
					≥ 26 cigs/day	4.9	
				41–80 g/day	0–7 cigs/day	3.0	
					8–15 cigs/day	14.6	
					16–25 cigs/day	19.5	
					≥ 26 cigs/day	18.4	
				81–120 g/day	0–7 cigs/day	5.5	
					8–15 cigs/day	27.5	
					16–25 cigs/day	48.3	
					≥ 26 cigs/day	37.6	
				≥ 121 g/day	0–7 cigs/day	14.7	
					8–15 cigs/day	71.6	
					16–25 cigs/day	67.8	
					≥ 26 cigs/day	135.5	For multiplicative model, chi-squared = 14.5 (9 degrees of freedom)

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Falk *et al.* (1989)	Texas, USA, 1975–80	Cases: 151 living white men, aged 30–79 years Controls: 235 living white men, community controls		< 4 drinks/week	Nonsmoker 1–10 cigs/day 11–20 cigs/day 21–39 cigs/day ≥ 40 cigs/day	1.0 2.9 (2.2–3.9) 5.2 (2.5–10.7) 8.0 (5.8–11.0) 10.2 (8.6–12.2)	Logistic regression model; risk estimates adjusted for age Goodness-of-fit for additive model: chi-squared = 4.44, $p = 0.73$ Goodness-of-fit for multiplicative model: chi-squared = 4.09, $p = 0.77$
				≥ 4 drinks/week	Nonsmoker 1–10 cigs/day 11–20 cigs/day 21–39 cigs/day ≥ 40 cigs/day	1.8 (1.5–2.1) 4.6 (3.1–6.7) 6.5 (3.5–12.0) 10.5 (7.8–14.2) 15.4 (10.9–21.9)	
Franceschi *et al.* (1990)	Northern Italy, 1986–89	Cases: 162 men < 75 years old Controls: Men < 75 years old admitted to same hospitals for acute illness	*Tobacco*: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 30–39 years duration regardless of amount, 15–24 cigs/day regardless of duration, 1–24 cigs/day for ≥ 40 years, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for > 40 years *Alcohol*: 1 drink = 150 mL wine = 330 mL beer = 30 mL spirits	< 35 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	1.0 0.9 4.5 6.1	Regression model; risk estimates adjusted for age, area of residence and years of education. [No formal test for interaction]
				35–59 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	1.6 5.0 7.1 10.4	
				≥ 60 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	– 5.4 9.5 11.7	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Choi & Kahyo (1991)	Seoul, Republic of Korea, 1986–89	Cases: 94 men, 6 women Controls: 282 men, 18 women; hospital controls, matched on age, sex and admission date	Alcohol (soju) in mL/day: Light: < 8100 Medium: 8100–16 200 Heavy: > 16 200	Non-drinker	Nonsmoker	1.0	Stratified analysis; ORs extrapolated from figure [No formal test for interaction]
					≤ 1 pack/day	2	
					> 1 pack/day	4	
				Light drinker	Nonsmoker	0.5	
					≤ 1 pack/day	0.8	
					> 1 pack/day	1.0	
				Medium drinker	Nonsmoker	1.5	
					≤ 1 pack/day	3	
					> 1 pack/day	2.5	
				Heavy drinker	Nonsmoker	0.5	
					≤ 1 pack/day	4	
					> 1 pack/day	20.7	
Freudenheim *et al.* (1992)	New York, USA, 1975–85	Cases: 250 incident (white) cases Controls: 250 (white) neighbourhood controls, matched on age	Alcohol: Drink–years = drinks/month multiplied by number of years of drinking	≤ 1243 drink–years	≤ 24 pack–years	1.0	Logistic regression model; risk estimates adjusted for education; interaction between tobacco and alcohol [no formal test for interaction]
					> 24 pack–years	2.7 (1.4–5.2)	
				> 1243 drink–years	≤ 24 pack–years	0.98 (0.5–2.1)	
					> 24 pack–years	5.8 (3.3–10.4)	
Zheng *et al.* (1992)	Shanghai, 1988–90	Cases: 201 incident cases Controls: 414 community controls, frequency-matched on sex and age	Alcohol lifetime consumption	Men Non-drinker	0–9 pack–years	1.0	Stratified analysis; risk estimates adjusted for age and education [no formal test for interaction]
					10–29 pack–years	3.1 (1.1–8.7)	
					≥ 30 pack–years	35.7 (13.6–93.9)	
				< 300 kg	0–9 pack–years	1.0 (0.2–5.5)	
					10–29 pack–years	3.8 (1.1–12.1)	
					≥ 30 pack–years	12.1 (3.8–38.6)	
				300–899 kg	0–9 pack–years	7.5 (1.4–38.8)	
					10–29 pack–years	3.7 (1.1–12.0)	
					≥ 30 pack–years	23.2 (8.3–65.0)	
				≥ 900kg	0–9 pack–years	2.5 (0.2–27.0)	
					10–29 pack–years	7.4 (1.0–55.0)	
					≥ 30 pack–years	25.1 (9.6–70.0)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Barón *et al.* (1993)	Italy, 1989–91	Cases: 224 men Controls: 1754 men, hospital controls, matched on age and residence	Tobacco: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 15–24 cigs/day regardless of duration or 30–39 years duration regardless of amount, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for ≥ 40 years	< 35 drinks/week	Nonsmoker	1.0	Regression model; risk estimates adjusted for area of residence, age, education and profession [no formal test for interaction]
					Light smoker	1.3	
					Moderate smoker	5.2	
					Heavy smoker	11.2	
				35–59 drinks/week	Nonsmoker	1.3	
					Light smoker	1.7	
					Moderate smoker	6.8	
					Heavy smoker	14.6	
				≥ 60 drinks/week	Nonsmoker	1.9	
					Light smoker	2.5	
					Moderate smoker	9.9	
					Heavy smoker	21.3	
Dosemeci *et al.* (1997)	Turkey, 1979–84	Cases: 832 men Controls: 829 men, hospital controls with selected cancers		Never-drinker	Nonsmoker	1.0	Stratified analysis; risk estimates also provided for glottis, supraglottis and other sites [no formal test for interaction]
					1–20 cigs/day	3.0 (2.2–4.1)	
					≥ 21 cigs/day	6.2 (3.9–9.9)	
				1–20 drink–years	Nonsmoker	–	
					1–20 cigs/day	5.6 (3.2–9.8)	
					≥ 21 cigs/day	6.0 (2.5–14.3)	
				≥ 21 drink–years	Nonsmoker	–	
					1–20 cigs/day	5.2 (1.9–15.1)	
					≥ 21 cigs/day	12.2 (3.1–57.6)	
Schlecht *et al.* (1999)	Brazil, 1986–89	Cases: 194 incident cases Controls: 388 hospital controls, matched on hospital, trimester of admission, age and sex	Alcohol: lifetime consumption	0–10 kg	0–5 pack–years	1.0	Logistic regression model that included an interaction term; risk estimates adjusted for race, beverage temperature, religion, wood stove use and consumption of spicy foods. No statistical evidence for effect modification ($p = 0.945$)
					6–42 pack–years	13.5 (2.7–66.8)	
					> 42 pack–years	11.4 (2.1–62.0)	
				11–530 kg	0–5 pack–years	1.2 (0.1–14.4)	
					6–42 pack–years	16.1 (3.4–76.2)	
					> 42 pack–years	22.0 (4.5–107)	
				> 530 kg	0–5 pack–years	5.5 (0.4–71.5)	
					6–42 pack–years	36.9 (0.7–1800)	
					> 42 pack–years	43.1 (9.1–208)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Mixed upper aerodigestive tract (ADT)							
Case–control studies							
Franceschi *et al.* (1990)	Northern Italy, 1986–89	Cases: 157 men < 75 years old Controls: 1272 men < 75 years old, admitted to same hospitals for acute illness	*Tobacco*: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 30–39 years duration regardless of amount, 15–24 cigs/day regardless of duration, 1–24 cigs/day for ≥ 40 yrs, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for > 40 yrs *Alcohol*: 1 drink = 150 mL wine = 330 mL beer = 30 mL spirits	< 35 drinks/week	Nonsmoker	1.0	Logistic regression model; risk estimates adjusted for age, area of residence, education and occupation [no formal test for interaction]
					Light smoker	3.1	
					Moderate smoker	10.9	
					Heavy smoker	17.6	
				35–59 drinks/week	Nonsmoker	1.6	
					Light smoker	5.4	
					Moderate smoker	26.6	
					Heavy smoker	40.2	
				≥ 60 drinks/week	Nonsmoker	2.3	
					Light smoker	10.9	
					Moderate smoker	36.4	
					Heavy smoker	79.6	
Maier *et al.* (1992)	Germany, 1987–88	Cases: 200 men (squamous-cell cancer of the head and neck) Controls: 800 men, outpatient clinic controls	Tobacco: 1 tobacco–year = daily consumption of 20 cigarettes, 4 cigars, or 5 pipes for 1 year	< 25 g/day	< 5 tobacco-years	1.0	Logistic regression model; combined consumption of alcohol and tobacco increased the risk in a multiplicative manner. [No formal test for interaction]
					5–50 tobacco-years	5.7 (1.9–17.3)	
					> 50 tobacco-years	23.3 (6.6–82.5)	
				25–75 g/day	< 5 tobacco-years	2.3 (0.6–8.8)	
					5–50 tobacco-years	14.6 (4.8–43.9)	
					> 50 tobacco-years	52.8 (15.8–176.6)	
				> 75 g/day	< 5 tobacco-years	10.3 (1.9–55.8)	
					5–50 tobacco-years	153.2 (44.1–532)	
					> 50 tobacco-years	146.2 (37.7–566)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Barón *et al.* (1993)	Italy, 1989–91	Cases: 308 men (oral or pharyngeal cancer) Controls: 1754 men, hospital controls, matched on age and area of residence	Tobacco: Light: ex-smoker who quit ≥ 10 years ago or smokers of 1–14 cigs/day for < 30 years Moderate: 15–24 cigs/day regardless of duration or 30–39 years duration regardless of amount, or ≥ 15 cigs/day for < 30 years Heavy: ≥ 25 cigs/day for ≥ 40 years	< 35 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	1.0 6.4 5.4 32.1	Regression model; risk estimates adjusted for area of residence, age, education and profession [no formal test for interaction]
				35–59 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	3.6 23.0 91.4 115.6	
				≥ 60 drinks/week	Nonsmoker Light smoker Moderate smoker Heavy smoker	9.5 60.8 241.3 304.9	
Kune *et al.* (1993)	Melbourne, Australia, 1982	Cases: 41 men, incident cases (19 oral, 22 pharynx) Controls: 398 men, community controls		≤ 200 g/week	Non/former smoker Current smoker	1.0 25.2 (3.1–204)	Logistic regression model; more than additive interaction [no formal test for interaction]
				> 200 g/week	Non/former smoker Current smoker	42.7 (5.5–330) 111.8 (15.5–865)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Mashberg *et al.* (1993)	New Jersey, USA, 1972–83	Cases: 359 [men] (oral cavity-oropharynx) Controls: 2280 [men], hospital controls	Alcohol: 1 whisky equivalent (WE) = 10.24 g ethanol	0–1 WE/day	0–5 cigs/day	1.0	Logistic regression model; risk estimates adjusted for age; results suggest multiplicative interaction [no formal test for interaction] *$p < 0.05$
					6–15 cigs/day	10.8	
					16–25 cigs/day	7.6	
					26–35 cigs/day	–	
					≥ 36 cigs/day	3.2	
				2–5 WE/day	0–5 cigs/day	2.7	
					6–15 cigs/day	24.2*	
					16–25 cigs/day	29.7*	
					26–35 cigs/day	5.3	
					≥ 36 cigs/day	10.2*	
				6–10 WE/day	0–5 cigs/day	11.9	
					6–15 cigs/day	50.9*	
					16–25 cigs/day	28.9*	
					26–35 cigs/day	61.9*	
					≥ 36 cigs/day	26.8*	
				11–21 WE/day	0–5 cigs/day	12.5*	
					6–15 cigs/day	30.9*	
					16–25 cigs/day	44.8*	
					26–35 cigs/day	79.5*	
					≥ 36 cigs/day	98.4*	
				≥ 22 WE/day	0–5 cigs/day	8.3	
					6–15 cigs/day	27.5*	
					16–25 cigs/day	61.7*	
					26–35 cigs/day	70.3*	
					≥ 36 cigs/day	32.0*	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Kabat *et al.* (1994)	8 cities in the USA, 1977–90	Cases: 1097 men, 463 women, incident cases (oral cavity, pharynx) Controls: 2075 men, 873 women; hospital controls		*Men*			Logistic regression model; risk estimates adjusted for age, years of schooling, race, time period and type of hospital
				Nondrinker	Nonsmoker	1.0	
					Former smoker	1.1 (0.7–1.6)	
					1–20 cigs/day	1.5 (0.9–2.5)	
					21–30 cigs/day	2.2 (1.1–4.3)	
					≥ 31 cigs/day	2.0 (1.1–3.7)	
				1–3.9 oz/day	Nonsmoker	1.6 (0.9–2.7)	
					Former smoker	1.7 (1.1–2.6)	
					1–20 cigs/day	5.8 (3.7–9.1)	
					21–30 cigs/day	6.8 (3.6–12.7)	
					≥ 31 cigs/day	6.9 (3.9–12.4)	
				4–6.9 oz/day	Nonsmoker	1.2 (0.4–3.7)	
					Former smoker	3.1 (1.9–5.2)	
					1–20 cigs/day	5.9 (3.5–10.0)	
					21–30 cigs/day	15.8 (7.4–33.8)	
					≥ 31 cigs/day	18.8 (10.0–35.4)	
				≥ 7 oz/day	Nonsmoker	2.9 (1.1–8.1)	
					Former smoker	5.1 (3.3–7.8)	
					1–20 cigs/day	11.9 (7.7–18.4)	Test for interaction: chi-squared with 12 degrees of freedom = 24.6, $p = 0.02$
					21–30 cigs/day	13.5 (7.9–23.2)	
					≥ 31 cigs/day	20.1 (12.9–31.5)	
				Women			
				Nondrinker	Nonsmoker	1.0	
					Former smoker	1.3 (0.9–2.0)	
					1–20 cigs/day	2.9 (1.9–4.3)	
					≥ 21 cigs/day	3.8 (2.3–6.2)	
				1–3.9 oz/day	Nonsmoker	0.7 (0.3–1.4)	
					Former smoker	2.1 (1.2–3.8)	
					1–20 cigs/day	5.8 (3.5–9.8)	
					≥ 21 cigs/day	22.3 (9.6–51.8)	
				≥ 4 oz/day	Nonsmoker	3.5 (0.9–13.4)	
					Former smoker	2.7 (0.95–7.9)	
					1–20 cigs/day	17.6 (8.1–37.5)	Test for interaction: chi-squared with 6 degrees of freedom = 18.7, $p = 0.005$
					≥ 21 cigs/day	26.7 (12.3–58.6)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
André *et al.* (1995)	Doubs region, France, 1986–89	Cases: 299 men ≥ 35 years old (oral cavity, oropharynx and larynx) Controls: 645 men, population controls ≥ 35 years old	Tobacco: g of tobacco/day	0–40 g/day	0–7 g/day	1	Logistic regression model; risk estimates adjusted for age and environment [no formal test for interaction]
					8–19 g/day	7.1 (1.9–26.1)	
					≥ 20 g/day	10.9 (2.9–40.8)	
				41–100 g/day	0–7 g/day	4.9 (1.3–18.2)	
					8–19 g/day	25.3 (7.7–82.9)	
					≥ 20 g/day	42.8 (13.1–140)	
				> 100 g/day	0–7 g/day	62 (12.2–316)	
					8–19 g/day	194 (49.4–760)	
					≥ 20 g/day	199 (56.5–699)	
Muscat *et al.* (1996)	New York, Illinois, Michigan, Pennsylvania, 1981–90	Cases: 697 men, 322 women (oral neoplasia) Controls: 619 men, 304 women, hospital controls, matched on gender, age, race and date of admisssion	Tobacco: cumulative tar	*Men*			Reference category was never-smokers for all drinking categories. Logistic regression model; estimates adjusted for age and education; further modelling of data revealed a significant interaction between smoking and alcohol consumption for both men and women. [No formal test for interaction presented]
				0 to < 1 drink/week	< 1.4 kg	0.7 (0.3–1.8)	
					1.4–3.5 kg	0.3 (0.1–1.1)	
					> 3.5–6.8 kg	1.0 (0.5–2.6)	
					> 6.8 kg	1.0 (0.4–2.8)	
				Occasional drinker	< 1.4 kg	0.9 (0.3–2.3)	
					1.4–3.5 kg	0.5 (0.2–1.5)	
					> 3.5–6.8 kg	1.2 (0.4–3.7)	
					> 6.8 kg	1.6 (0.6–4.7)	
				1–4 drinks/day	< 1.4 kg	1.0 (0.4–2.1)	
					1.4–3.5 kg	1.5 (0.7–3.2)	
					> 3.5–6.8 kg	1.8 (0.8–3.8)	
					> 6.8 kg	2.5 (1.1–5.2)	
				> 4 drinks/day	< 1.4 kg	2.1 (0.7–5.9)	
					1.4–3.5 kg	2.7 (1.1–6.6)	
					> 3.5–6.8 kg	4.7 (2.0–11.3)	
					> 6.8 kg	6.1 (2.6–14.4)	
				Women			
				0 to < 1 drink/week	< 1.4 kg	1.2 (0.6–2.4)	
					1.4–3.5 kg	3.0 (1.3–7.0)	
					> 3.5–6.8 kg	2.0 (1.0–4.0)	
					> 6.8 kg	2.4 (0.8–6.9)	
				Occasional drinker	< 1.4 kg	1.4 (0.5–4.3)	
					1.4–3.5 kg	1.2 (0.4–3.6)	
					> 3.5–6.8 kg	5.8 (1.7–20.3)	
					> 6.8 kg	16.7 (1.8–152.6)	
				1–4 drinks/day	< 1.4 kg	5.9 (1.7–20.5)	
					1.4–3.5 kg	9.5 (2.8–32.0)	
					> 3.5–6.8 kg	14.0 (4.1–48.5)	
					> 6.8 kg	18.6 (4.0–86.8)	
				> 4 drinks/day	< 1.4 kg	1.0 (0.01–27.9)	
					1.4–3.5 kg	4.3 (0.1–116.9)	
					> 3.5–6.8 kg	6.5 (0.1–174.2)	
					> 6.8 kg	2.4 (0.0–55.1)	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Lewin *et al.* (1998)	Sweden, 1988–90	Cases: 605 men (squamous-cell carcinoma of the head and neck) Controls: 756 men, population controls		< 10 g/day	Nonsmoker	1.0	Logistic regression model; risk estimates adjusted for age and health care area; joint effect of high alcohol intake and current smoking is nearly multiplicative. [No formal test for interaction]
					Former smoker	2.4 (1.4–4.1)	
					Current smoker	6.3 (3.7–10.5)	
				10–19 g/day	Nonsmoker	1.2 (0.5–3.1)	
					Former smoker	2.2 (1.2–4.1)	
					Current smoker	10.4 (5.9–18.3)	
				≥ 20 g/day	Nonsmoker	4.2 (1.8–9.7)	
					Former smoker	5.4 (2.8–10.2)	
					Current smoker	22.1 (13.0–37.8)	
Cohort study							
Chyou *et al.* (1995)	Hawaii, USA 1965–68	American Men of Japanese Ancestry Study (see Section 2.1.1) 92 incident cases of cancer of the upper aerodigestive tract		Non-drinker	Nonsmoker	1.0	Proportional hazards regression model; risk estimates adjusted for age; none of the tests for interaction were statistically significant ($p > 0.05$).
					≤ 20 cigs/day	3.0 (0.8–11.3)	
					> 20 cigs/day	3.2 (0.8–13.4)	
				< 14 oz/month	Nonsmoker	1.3 (0.3–6.3)	
					≤ 20 cigs/day	1.9 (0.5–7.7)	
					> 20 cigs/day	4.6 (1.2–17.8)	
				≥ 14 oz/month	Nonsmoker	6.5 (1.7–26.0)	
					≤ 20 cigs/day	10.7 (3.2–35.4)	
					> 20 cigs/day	14.4 (4.4–47.4)	
					Duration		
				Non-drinker	Nonsmoker	1.0	
					< 30 years	2.0 (0.4–8.8)	
					≥ 30 years	4.2 (1.1–15.5)	
				< 14 oz/month	Nonsmoker	1.3 (0.3–6.3)	
					< 30 years	2.4 (0.6–9.7)	
					≥ 30 years	3.3 (0.9–12.6)	
				≥ 14 oz/month	Nonsmoker	6.5 (1.6–25.9)	
					< 30 years	9.2 (2.7–31.9)	
					≥ 30 years	14.2 (4.4–46.3)	
Liver							
Austin *et al.* (1986)	Alabama, Florida, Massachussetts, North Carolina, Pennsylvania, USA	Cases: 85 cases Controls: 159 hospital controls, matched on gender, age and race		*HBsAg-negative subjects*:			Logistic regression model; information not provided on HBsAg-positive subjects. Test for interaction not statistically significant ($p = 0.50$)
				Nondrinker	Nonsmoker	1.0	
					Former smoker	1.0	
					Current smoker	1.1	
				Occasional drinker	Nonsmoker	1.3	
					Former smoker	1.6	
					Current smoker	4.7	
				Regular drinker	Nonsmoker	3.2	
					Former smoker	1.0	
					Current smoker	3.4	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Chen *et al.* (1991)	China, Province of Taiwan, 1985–87	Cases: 200 incident cases (men) Controls: 200 population controls		Not habitual drinker	Nonsmoker	1.0	Logistic regression model; interaction between smoking and drinking not significant under the multiplicative model [numbers not provided]
					1–10 cigs/day	1.0	
					11–20 cigs/day	1.8	
					> 20 cigs/day	2.7	
				Habitual drinker	Nonsmoker	2.9	
					1–10 cigs/day	3.2	
					11–20 cigs/day	6.2	
					> 20 cigs/day	11.7	
Yu *et al.* (1991)	Los Angeles County, USA, 1984–90	Cases: 74 incident cases Controls: 162 population controls		≤ 29 drink–years	Nonsmoker	1.0	Logistic regression model [no formal test for interaction]
					Former smoker	1.4 (0.3–6.0)	
					Current smoker	3.7 (0.9–15.5)	
				≥ 30 drink–years	Nonsmoker	4.2 (0.8–22.2)	
					Former smoker	4.8 (1.3–17.4)	
					Current smoker	5.4 (1.4–21.0)	
Tanaka *et al.* (1992)	Fukuoka, Japan, 1985–89	Cases: 168 men, 36 women Controls: 291 men, 119 women, hospital controls, frequency-matched on age and sex All subjects aged 40–69 years		< 9.8 drink–years	< 18.4 pack–years	1.0	Logistic regression model; risk estimates adjusted for sex, age, HBsAg status, history of blood transfusion and family history. Lowest drinking category used as reference. [No formal test for interaction]
					18.4–31.9 pack–years	1.0	
					≥ 32 pack–years	1.0	
				9.8–54.1 drink–years	< 18.4 pack–years	0.8	
					18.4–31.9 pack–years	1.2	
					≥ 32 pack–years	1.0	
				≥ 54.2 drink–years	< 18.4 pack–years	0.8	
					18.4–31.9 pack–years	2.1	
					≥ 32 pack–years	1.8	

Table 2.3.9 (contd)

Reference	Place, year	Study population	Definition of tobacco/alcohol exposure	Alcohol categories	Smoking categories	Relative risk (95% CI)	Comments
Mukaiya *et al.* (1998)	Sapporo, Japan, 1991–93	Cases: 104 men Controls: 104 men, hospital controls, matched on age	Alcohol: Nondrinker and ex-drinker for ≥ 10 years Current drinker and ex-drinker for < 10 years	Nondrinker	Nonsmoker Former smoker Current smoker	1.0 9.4 15.4 *p* for trend = 0.006	Stratified analysis [no formal test for interaction]
				Current drinker	Nonsmoker Former smoker Current smoker	9.8 17.3 17.9 *p* for trend = 0.29	
Kuper *et al.* (2000)	Athens, Greece, 1995–98	Cases: 333 incident cases Controls: 360 hospital controls		0–40 glasses/week	Nonsmoker < 3 packs/day ≥ 2 packs/day	1.0 2.1 (1.0–4.6) 1.7 (0.6–5.3)	Logistic regression model; risk estimates adjusted for age, gender, years of schooling and coffee drinking. Strong, statistically significant ($p = 0.0001$) and apparently super-multiplicative interaction between heavy smoking and heavy drinking in the causation of hepatocellular carcinoma. Effect stronger in HBV and/or HCV negative subjects, further confirmed by case–case analysis
				≥ 40 glasses/week	Nonsmoker < 3 packs/day ≥ 2 packs/day	4.2 (0.7–25.9) 2.4 (0.9–6.9) 10.9 (3.5–33.8)	

Table 2.3.10. Studies on interaction of smoking and hepatitis B in the causation of cancer of the liver

Reference	Place, year	Study population	HBsAg categories	Smoking categories	Relative risk	Comments
Trichopoulos *et al*. (1987)	Athens, Greece, 1976–84	Cases: 194 incident hepatocellular carcinoma cases Controls: 456 hospital controls	HBsAg– subjects	Nonsmoker Former smoker 1–9 cigs/day 10–19 cigs/day 20–29 cigs/day ≥ 30 cigs/day	1.0 2.8 0.8 2.0 2.4 7.3	Logistic regression model; risk estimates adjusted for age, sex, and alcohol consumption [nonsmokers used as reference group for both HBsAg subgroups]
			HBsAg+ subjects	Nonsmoker Former smoker 1–9 cigs/day 10–19 cigs/day 20–29 cigs/day ≥ 30 cigs/day	1.0 1.3 1.2 2.2 1.2 2.0	
Chen *et al*. (1991)	China, Province of Taiwan, 1985–87	Cases: 200 incident cases (men) Controls: 200 population controls	HBsAg–, HBeAg–	Nonsmoker 1–10 cigs/day 11–20 cigs/day > 20 cigs/day	1.0 1.2 2.0 2.4	Stratified analysis [no formal test for interaction]
			HBsAg+, HBeAg–	Nonsmoker 1–10 cigs/day 11–20 cigs/day > 20 cigs/day	15.1 13.6 44.6 68.1	
			HBsAg+, HBeAg+	Nonsmoker 1–10 cigs/day 11–20 cigs/day > 20 cigs/day	27.8 107.0 206.9 197.6	

Table 2.3.11. Studies on interaction of human papillomavirus (HPV) and smoking in the causation of cancer of the cervix

Reference	Study type	Place, year	Study population	HPV exposure	Smoking categories	Relative risk (95% CI)	Comments
Basu *et al.* (1991)	Cross-sectional study	New York, USA	75 women referred to a colposcopy clinic for abnormal Pap smear			Cases vs non-cases (%)	Difference not statistically significant. Discrepancies between text and table for percentage of HPV-positive women among non-cases
					Smoker	53.5 *vs* 36.7	
					HPV-positive	66.7 *vs* 53.3	
Ylitalo *et al.* (1999)	Nested case–control (see Table 2.1.10.6)	Uppsala County, Sweden, 1965–95	Cohort: ~ 281 000 women Cases: 422 patients diagnosed with cervical carcinoma *in situ* Controls: 422 controls, matched on date of entry into cohort and birth year	HPV 16/18 DNA negative before diagnosis (n = 138)	Nonsmoker	1.0	Logistic regression models. Risk estimates adjusted for education, marital status, oral contraceptive use, age at sexual debut, number of sexual partners, age at menarche and parity. [No formal test for interaction]
					Former smoker	1.5 (0.7–3.4)	
					Current smoker	1.8 (0.9–3.6)	
					1–9 years of smoking	1.5 (0.7–3.4)	
					10–19 of smoking	1.7 (0.8–3.5)	
					≥ 20 of smoking	2.0 (0.7–5.9)	
					0.15–3.95 pack–years	1.4 (0.7–2.9)	
					4.00–7.95 pack–years	2.7 (1.2–6.4)	
					≥ 8.00 pack–years	1.6 (0.7–3.5)	
				HPV 16/18 DNA positive before diagnosis (n = 178)	Nonsmoker	1.0	
					Former smoker	2.1 (1.04–4.3)	
					Current smoker	2.3 (1.3–4.3)	
					1–9 years of smoking	2.3 (1.1–5.2)	
					10–19 years of smoking	2.5 (1.3–4.7)	
					≥ 20 years of smoking	1.8 (0.8–4.1)	
					0.15–3.95 pack–years	2.3 (1.1–4.8)	
					4.00–7.95 pack–years	3.4 (1.6–7.3)	
					≥ 8.00 pack–years	1.6 (0.8–3.2)	
Kjellberg *et al.* (2000)	Case–control	Northern Sweden, 1993–95	Cases: 137 women with high grade CIN Controls: 253 healthy population-controls, matched on age	HPV Ab–	Never-smoker	1.0	Risk estimates adjusted for age [although matched on age]. No evidence of interaction. [No numbers provided]
					Ever-smoker	5.6 (2.5–10.9)	
				HPV Ab+	Never-smoker	5.2 (2.5–10.9)	
					Ever-smoker	10.5 (5.0–22.4)	

Table 2.3.11 (contd)

Reference	Study type	Place, year	Study population	HPV exposure	Smoking categories	Relative risk (95% CI)	Comments
Hildesheim *et al.* (2001)	Cross-sectional	Costa Rica, 1993–94	Population: 989 HPV positive women Cases: 146 prevalent high-grade squamous intraepithelial lesions or cervical cancer Controls: women with or without low grade squamous intraepithelial lesions	All HPV positive	Never-smoker Former smoker Current smoker < 10 years smoking ≥ 10 years smoking 1–5 cigs/day ≥ 6 cigs/day	1.0 2.4 (1.2–5.1) 2.3 (1.3–4.3) 2.6 (1.2–5.3) 2.2 (1.2–4.2) 2.3 (1.3–3.9) 2.7 (1.1–6.7) *p* for trend = 0.0007	Logistic regression model. Risk estimates for overall analysis adjusted for age, HPV type, number of pregnancies and number of cigarettes/day. Risk estimates for high-risk analysis adjusted for age, number of pregnancies and number of cigarettes/day. No association was found between smoking habit of husband/live-in partner and high-grade squamous intraepithelial lesions/cancer among nonsmoking women. HPV testing for 44 different HPV types.
				High risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)	Never-smoker Former smoker Current smoker < 10 years smoking ≥ 10 years smoking 1–5 cigs/day ≥ 6 cigs/day	1.0 1.7 (0.8–4.0) 2.3 (1.2–4.3) 2.2 (1.0–4.8) 2.0 (1.0–3.8) 1.8 (0.99–3.3) 3.1 (2.2–7.9) *p* for trend = 0.003	

Table 2.3.12. Studies on the combined effect of tobacco smoking and silica exposure in the causation of lung cancer

Reference	Study design	Country, years of study	Source population	No. of cases and controls	Smoking categories (highest *vs* lowest exposure)	Silica exposure	Relative risk		Interaction[a]	Comments
							Non-smoker	Smoker		
Forastiere *et al.* (1986)	Retrospective case–control	Italy, 1968–84	Male residents in region with pottery industry	72 deaths, 319 controls	Cigarettes per day 0; 1–20; > 20	Ceramic workers without silicosis with silicosis	 1.5 0	 4.1 1.8	 ~ M (> M)	Deceased cases and controls; all silicotics were ceramic workers.
Mastrangelo *et al.* (1988)	Case–control	Italy, 1978–80	Workers in quarrying and tunnelling	309 cases, 309 controls	Nonsmoker Ever–smoker	No silicosis Silicosis	1.3 5.3	0.9 1.7	~ A ~ A	Unadjusted analysis
Hessel *et al.* (1990)	Case–control	South Africa, 1975–79	Miners, mainly in gold mines, with silicosis	231 deaths, 318 controls	Cigarettes per day 0; 1–10; 11–20; ≥ 21	Hilar gland silicosis Parenchymal silicosis	1.1 1.6	0.8 0.9	(< A) (< A)	Unmatched odds ratios
Siemiatycki *et al.* (1990)	Case–control	Canada, 1979–85	Male residents of Montreal, aged 35–70 years	479 cases, 875 controls	Pack–years 0; 1–< 30; 30–< 60; ≥ 60	Substantial	2.6	1.5	I	Adenocarcinoma excluded; silica exposure estimated from job titles; adjusted for age, socio-economic status, job history, education, marital status and asbestos exposure
Chiyotani *et al.* (1990)	Cohort	Japan, 1979–83	3335 patients with pneumoconiosis qualifying for workmen's compensation (58% silicotics)	60 deaths	Nonsmoker Former smoker Current smoker	Pneumoconiosis	1.8	6.1	(> M)	
Amandus & Costello (1991)	Cohort	USA, 1959–75	9912 metal miners; white males	132 deaths	Nonsmoker Former smoker Current smoker	Silicosis Silicosis in low radon mines	2.2 5.1	1.3 1.7	~ A (~ A)	Adjusted for age; 'interaction between silicosis and cigarette smoking habits not a statistically significant factor related to lung mortality'
Hnizdo & Sluis-Cremer (1991)	Cohort	South Africa, 1968–86	2132 white gold miners with silicosis, aged 45–54 years	77 deaths	Pack–years ≥ 26 *vs* ≤ 25	≥ 31 *vs* ≤ 30 dust particle–years	1.4	1.9		'Combined effect of dust and smoking is more than additive.'

Table 2.3.12 (contd)

Reference	Study design	Country, years of study	Source population	No. of cases and controls	Smoking categories (highest *vs* lowest exposure)	Silica exposure	Relative risk		Interaction[a]	Comments
							Non-smoker	Smoker		
Amandus *et al.* (1991)	Cohort	USA, 1940–83	760 silicotics among dusty trades workers	33 deaths	Never-smoker Ever-smoker	 Silicosis	SMR 1.7	SMR 3.4	 (> M)	Standardized mortality ratios using US male population as reference group
Chia *et al.* (1991)	Cohort	Singapore, 1970–84	159 granite workers with silicosis	9 cases	Nonsmoker Smoker	Silicosis	1.3	2.2	(> M)	
Hnizdo *et al.* (1997)	Nested case–control	South Africa, 1970–86	2260 white gold miners, aged 45–54 years	78 cases, 386 controls	Pack–years: < 10; 10–29; ≥ 30	Without silicosis With silicosis	1.0 4.1	11.7 48.9		'Strong multiplicative combined effect of smoking and the presence of silicosis on the risk of lung cancer'
Hughes *et al.* (2001)	Nested case–control	USA, 1940–84	2670 male industrial sand workers	123 deaths, 219 controls	Nonsmoker Ever-smoker					'No indication of an interaction effect of cigarette smoking and cumulative exposure'

Adapted from Saracci & Boffetta (1994)
[a] Numbers in parentheses are based on the assumption that the relative risk due to smoking is 10; A, additive; I, intermediate; M, multiplicative

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