5

Cancer Site by Site

5.1 Head and Neck Cancers

Summary

- Tobacco smoking, alone and in combination with alcohol, is the most important risk factor
- Tobacco chewing is also an important risk factor in some populations
- Infection of human papilloma virus is a recognised cause of some head and neck cancers
- Genes that metabolise alcohol appear to influence the risk of developing head and neck cancers

Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx and larynx. Each year there are approximately 400 000 cases of cancer of the oral cavity and pharynx, with 160 000 cancers of the larynx, resulting in approximately 300 000 deaths [2]. Regions with a high incidence include much of Southern Asia as well as parts of Central and Southern Europe.

The majority of head and neck cancers are squamous-cell carcinoma (SCC) in histology, and the main risk factors for these cancers are tobacco and alcohol use. Tobacco smoking is the most important risk factor for head and neck cancer, and the risk is higher for heavy smokers, long-term smokers and smokers of black tobacco or high-tar cigarettes. Cigar and pipe smoking also pose a risk, while stopping smoking is followed by a decrease in risk [3]. Smoking of bidis (small cigarettes common in parts of Asia) appears to have a higher risk for cancer of the hypopharynx and larynx than smoking of Western type cigarettes [4]. Consumption of alcoholic beverages also increases the risk of head and neck cancer. Relative to abstainers and very light drinkers, the risk in heavy drinkers is in the order of tenfold. This increased risk is unlikely to be related to alcohol consumption *per se*, but instead it may be caused by exposure to acetaldehyde, which is an intermediate metabolite of ethanol and is a known animal carcinogen [5]. Although the effect of alcohol and tobacco may vary slightly according to the different subsites, the combined effect of both exposures accounts for the majority of all head and neck cancers that occur globally. A recent pooled analysis from the INHANCE consortium based on over 10 000 cases and 15 000 controls, shows that approximately 70% of such cancers can be explained by these two exposures, ranging from 65% for oral cavity cancer (51% for women and 65% for men) to 86% for larynx cancer (79% for women and 86% for men). Furthermore, the proportion of those cancers caused by alcohol and tobacco was reduced with decreasing age, being just 32% for cancers diagnosed prior to age 45. Strong interaction between the two exposures was also apparent (Figure 5.1.1).

Other risk factors for these cancers are therefore clearly important. Established risk factors specifically for oral cavity cancer are betel quid and areca nut in India and Taiwan [6]. Several occupational substances or circumstances such as isopropanol manufacturing, inorganic acid mists containing sulfuric acid and mustard gas are suspected risk factors for laryngeal cancer [7]. Poor oral health and frequent use of mouthwash are also potential risk factors for oral cancer, although are unlikely to be relevant for other head and neck cancers [8].

Human papilloma virus (HPV) is a recognised cause of some head and neck cancers, with substantial evidence for a role of HPV16E6 from large case-control studies. The evidence comes primarily from several large epidemiological studies that have analysed associations of various HPV markers. HPV markers studied were (i) HPV DNA in biopsy tissues or oral cell scraping analysed by southern blotting or highly sensitive PCR methods, (ii) antibodies to HPV 16 capsids analysed by ELISA using HPV 16 major capsid protein L1-derived virus-like particles as antigens, and (iii) antibodies to HPV 16 E6 and E7 analysed by ELISA. HPV capsid antibodies are a cumulative marker of past and present HPV infection [9]. Young females with new genital HPV 16 infection demonstrated by HPV 16 DNA positivity will seroconvert to only about 60 % within 6 months. Titers of HPV capsid antibody titers usually are rather low but persist for many years. Mucosal HPV capsid antibodies are more prevalent in females than in males. Antibodies to the oncoproteins E6 and E7 of HPV 16 and 18 are markers of invasive cancer expressing these viral oncoproteins [10-12]. They are rare in the general population and among women with cervical cancer precursor lesions. In patients with invasive cervical cancer, prevalence of these antibodies increases with stage [10]. Antibodies to HPV 16 E6 and E7 also develop in patients with invasive HPV 16 DNA positive head and neck squamous-cell carcinoma [10], particularly in patients with evidence of HPV 16 E6 expression [13,14].

The largest study on the association of HPV and head and neck cancer, involving 1670 case patients (1415 with cancer of the oral cavity and 255 with cancer of the oropharynx) and 1732 control subjects, reported a prevalence of HPV DNA in 3.9% of specimens from the oral cavity and 18.3% of specimens from the oropharynx [15]. Furthermore, when cases were compared to controls, a strongly increased risk was observed for antibodies against HPV 16 E6 and E7 proteins, for both cancers of the oral cavity (OR=2.9, 95% CI 1.7–4.8) and oropharynx (OR=9.2, 95% CI 4.8–17.7). In a more recent US study comprising 204 head and neck cancer cases and 326 controls, a fivefold increased risk for HPV 16 E6/E7 antibodies was observed for oral cancer (OR=5.1, 95% CI 1.2–22.4), and a 70-fold increased risk was observed for cancer of the oro-pharynx (OR=72.8, 95%CI 16.0–330) [16]. In a systematic review of presence of HPV in DNA in head and neck cancers, HPV 16 accounted for practically all of the HPV infections of the oropharynx, whereas HPV 18 was also commonly observed in the oral cavity [17].

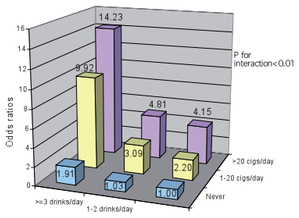
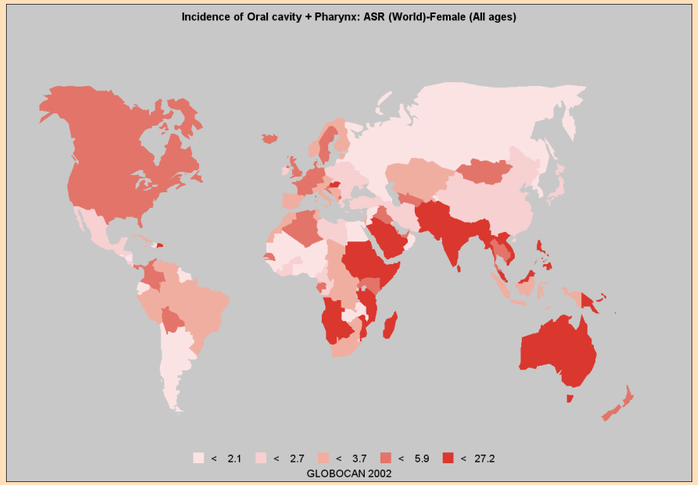


Fig. 5.1.1 *Interaction between tobacco and alcohol frequency on the risk of head and neck cancer*

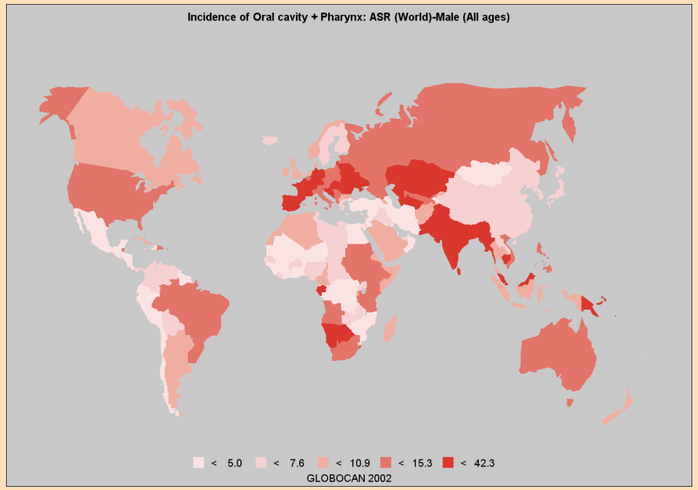
Important questions remain however regarding the role of other specific types of HPV, interaction with other risk factors, and the role of HPV in larynx cancer tumours. Furthermore, their role in determining response to treatment and survival from head and neck cancer is not well elucidated. Also, an effect between increased intake of fruits and vegetables and a reduced risk of head and neck cancers has been observed, although mostly in hospital-based case-control studies.

Treatment and survival

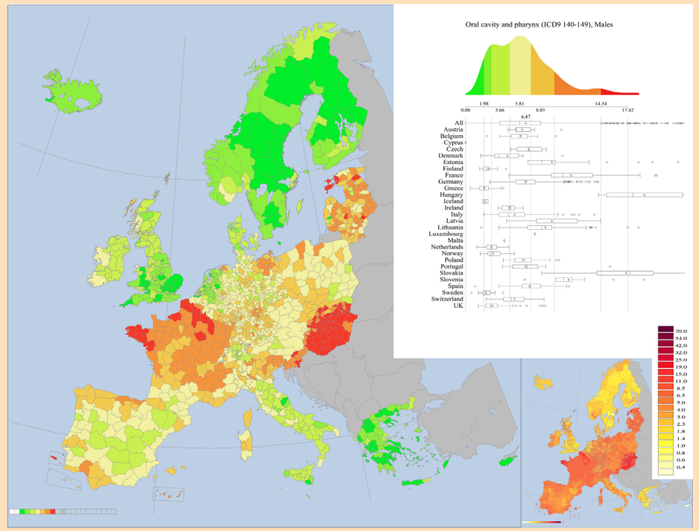
Primary treatment varies with the anatomic subsite and stage of disease. For most early cancers, surgical resection is the cornerstone of treatment [18]. However, for certain anatomic sites such as the tonsils, the base of the tongue, and the floor of the mouth, as well as for all locally advanced cancers, radiotherapy is used, either alone or combined with surgery. Occasionally, chemotherapy may be used in addition to radiotherapy. Following diagnosis of oral cavity and pharynx cancer, 5-year relative survival is close to 40% in the United States and in Europe, although it varies substantially among countries. Moreover, the prognosis is generally better for women and for malignancies of the oral cavity than for those arising in the hypopharynx. In Europe, 5-year relative survival rates remained virtually identical from 1983 to 1994, suggesting that no major progress has been made [19].



World Map 5.1.1



World Map 5.1.2



European Map 5.1.1 *The outstanding feature of this map depicting mortality from cancer of oral cavity and pharynx in the European Union in males is the higher levels of mortality in almost the whole of Hungary and Slovakia, in much of Slovenia, and in France with concentrations of excess in the north-west and north-east. There was also a belt of high rates extending across northern Germany and an aggregation of high rates in north-east Italy bordering Slovenia. Rates were generally low in the Nordic Countries, the United Kingdom and Ireland, much of Spain and Italy, and in Greece.*
The geographical distribution of areas of high cancer risk for oral cancer demonstrates that while the higher mortality rates in France end abruptly at the border with Belgium–the risk being around one half in Belgium (5.9 per 100 000) of that in France (11.3 per 100 000) - this phenomenon is not seen in the south, with rates in south-east France and in the north of Italy, and in southwest France and northern Spain being at much the same levels. This suggests that there were likely to have been comparable exposures in the south, whereas exposures and/or protective agents may have been different in the north.
Taking account of known risk factors, the high levels in males appear to be generally in regions where there is a prevalent habit in the population of drinking strong alcoholic beverages. Reduction of this, together with avoidance of cigarette smoking, would lead to a large reduction in risk [1].

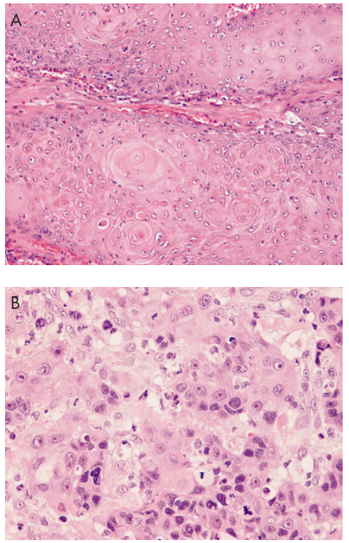


Fig. 5.1.2 *Squamous-cell carcinoma (SCC). A: Well differentiated SCC. B: Poorly differentiated SCC*

Genetic susceptibility to aerodigestive cancers

Genetic susceptibility studies for aerodigestive cancers have focused primarily on genes related to alcohol metabolism. A pooled analysis of 6 studies on the alcohol dehydrogenase 1C polymorphism comprising over 1300 cases and 1700 controls failed to identify any effect with the ADH1C variant genotype [20]. Subsequent analysis based on a collaboration of 3 large studies comprising over 3800 cases and 5000 controls has however provided extremely strong evidence for a protective effect for the ADH1B R48H variant (OR=0.54, 0.46–0.65; $p=10^{-12}$), and the ADH7 A92G variant (OR=0.68, 0.60–0.77; $p=10^{-9}$).

Furthermore, the effect of both variants was significantly modified by alcohol consumption. These results illustrate that interactions between environmental and genetic effects can be detected when (i) one has very large sample sizes, (ii) one has excellent lifestyle and environmental data, and (iii) one has identified genetic factors that have a real effect.

Larynx Cancer

It is estimated that between 25% and 30% of all cancers in developed countries are tobacco-related. For both sexes combined the proportion of cancers arising in the oesophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol is between 43% and 60%. Although the greatest hazard is caused by cigarette smoking, cigars can cause similar hazards if their smoke is inhaled and both cigar and pipe smoker cause comparable hazards of cancers of the oral cavity, pharynx, extrinsic larynx, and oesophagus.

Tobacco smoking has long been recognised as a major cause of cancer of the larynx and especially of the endolarynx [21,22].

Gandini et al. [23] conducted a systematic meta-analysis of observational studies on cigarette smoking and cancer from 1961 to 2003. The aim was to quantify the risk for 13 cancer sites recognised to be related to tobacco smoking by the International Agency for Research on Cancer, and to analyse the risk variation for each site in a systematic manner. Data were extracted from the 254 reports (177 case-control studies, 75 cohorts and 2 nested case-control studies) published in this period and included in the 2004 IARC Monograph on tobacco smoke and involuntary smoking [22]. The analyses were carried out on 216 studies with reported estimates for 'current' and/or 'former' smokers. Sensitivity analysis was performed, and the authors looked for publication and other types of bias. Lung (RR 8.96; 95% CI 6.73–12.11), laryngeal (RR 6.98; 95% CI 3.14–15.52) and pharyngeal (RR 6.76; 95% CI 2.86–15.98) cancers presented the highest relative risks for current smokers, followed by upper digestive tract (RR 3.57; 95% CI 2.63–4.84) and oral (RR 3.43; 95% CI 2.37–4.94) cancers. As expected, pooled relative risks for respiratory cancers were greater than the pooled estimates for other sites. The analysis of heterogeneity showed that study type, gender and adjustment for confounding factors significantly influence the risk estimates and the reliability of the studies.

Tuyns et al. [24] published results regarding tobacco and alcohol consumption from a large, multicentre, case–control study comprising 1147 male cases (cancer of the larynx and hypopharynx) and 3057 male controls. The relative risk associated with cigarette smoking was approximately 10 for all considered subsites of the larynx and hypopharynx. The risks for alcohol drinking varied by site, however, being higher for epilarynx and hypopharynx (OR = 4.3 for 80g/day or more) but lower at the same dose for endolarynx (OR = 2.1). Risk decreased within 10 years of quitting cigarette smoking, and smokers of blond tobacco were found to have about half the risk of smokers of black tobacco. The authors also reported that the risks associated with joint exposure to alcohol and tobacco were consistent with a multiplicative relative risk model [23].

The relationship between type of cigarettes smoked and the risk of cancer of the oral cavity and pharynx (excluding salivary gland and nasopharynx) was examined in a hospital-based case–control study involving 291 male cases and 1272 controls conducted in Pordenone Province and Greater Milan in Northern Italy (this is the same study base as above) [25]. As a basis for classification, the authors used tar-yield and the brand smoked for the longest time (<22mg, low to medium tar; ≥22mg, high tar). After adjustment for other risk factors, relative to non-smokers the risk among ever-smokers for oral and pharyngeal cancers were 8.5 (95% CI 3.7–19.4)) for low/medium and 16.4 (7.1–38.2) for high-tar cigarettes. For larynx cancer, the corresponding results were 4.8 (2.3–10.1) and 7.1 (3.2–15.6) relative to non-smokers. The authors concluded that these data provided further quantitative evidence of the importance of type of cigarette smoked on the risk of oral cancers as well as other cancers of the upper digestive and respiratory tract [25].

The incidence and mortality rates of laryngeal cancer in Poland and notably high and have been increasing for 25 years. Zatonski et al. [26] report a study among persons under the age of 65 in Lower Silesia, in southwest Poland, based on 249 newly-diagnosed cases and 965 controls. For smoking more than 30 cigarettes per day, the relative risk compared to non-smokers was 59.7 (95% CI 13–274) and the risk for consuming vodka regularly for 30 or more years was 10.4 (95% CI 4–27.2). Exposures to tobacco and alcohol showed a clear multiplicative effect in all categories of exposure. The risk of laryngeal cancer was shown to be reduced by quitting smoking or by having a history of intermittent smoking. Poor nutrition was identified as a strong independent risk factor in this study. It was estimated that smoking alone accounts for 95 per cent of all cases of laryngeal cancer in this population [26].

According to a large population-based case–control study in Southern Europe, about 90% of the current incidence of larynx cancer could be prevented by avoiding smoking and alcohol consumption, tobacco being responsible for the most of the risk [27,28]. A case–control study conducted in Poland estimated that smoking alone accounted for 95% of all cases of laryngeal cancer [26]. Similar conclusions have been drawn from an Italian study aimed at evaluating the impact of a reduction of cigarette smoking on mortality [29].

From a case–control study conducted in Liaoning province (China) in 1991 and 1992, smoking was the most important risk factor, with an OR of 16.8, and cigarette smoking in particular had an OR of 30.4 [30]. A different Chinese population-based case–control study, conducted in Shanghai between 1988 and 1990, confirmed that cigarette smoking was the main risk factor for laryngeal cancer accounting for 86% of the male and 54% of the female cases. The adjusted (for age and education) OR was 8.7 (95% CI 3.8–19.6) for ever versus never smoking. The risk increased with both the quantity and duration of smoking, with a 25-fold excess in the heaviest consumption categories; it declined following cessation [31].

The analysis of data from a case–control study conducted in Northern Italy between 1986 and 1992 showed a OR of 8.8 (95% CI 5.2–14.8) for heavy current smokers compared to never smokers and a OR of 3.3 (95% CI 1.9–5.5) for ex- or moderate smokers. Estimates of attributable risk implied that 77% of laryngeal cancers in men were due to smoking [31].

The risk of laryngeal cancer was shown to be reduced by smoking cessation [32]; having a history of intermittent smoking also seems to reduce the risk of laryngeal cancer compared with continued smoking, but this new finding, of considerable interest and potential importance with regard to possible mechanisms of laryngeal carcinogenesis, needs validation from further studies [26]. In a cohort of patients with laryngeal cancer, Hamzany et al. [33] observed that of 1443 patients treated for laryngeal carcinoma between 1960 and 2006, 55 (3.8%) were non-smokers: 40 (73%) had never smoked and 15 (27%) had stopped smoking 12 years or more before diagnosis.

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx and extrinsic larynx and of squamous-cell carcinoma of the oesophagus. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident. There is wide variability among European Union/European Economic Area countries in terms of per-capita average alcohol consumption and preferred type of alcoholic beverage.

Alcohol drinking

The relationship between increased laryngeal cancer risk and alcohol consumption has been consistently demonstrated by a variety of epidemiological studies [34,35]. A large population-based case–control study in Southern Europe found that reducing only alcohol consumption could prevent a quarter of the cases of laryngeal carcinoma [27].

The results from a case–control study conducted in Northern Italy were an OR of 1.5 (95% CI 1.0–2.2) for drinkers of 6 to 7 alcoholic drinks per day and an OR of 2.2 (95% CI 1.6–3.0) for drinkers of 8 or more drinks per day compared to teetotallers or moderate drinkers. Estimates of attributable risk implied that alcohol intake accounted for 25% of cases [36]. Other estimates showed ORs for men and women respectively of 2.0 and 2.6 for people in the highest intake category (42 or more drinks/week in women and 42-55 drinks/week in men) as compared to light drinkers [37].

A dose-dependent effect for alcohol has often been noted [38,39]. In a case-control study conducted in New York between 1985 and 1990, estimates of the risk for heavy drinkers (207 ml or more/daily) for supraglottic and glottic cancer were respectively 9.6 and 2.5. Interestingly, binge drinkers had higher ORs: 28.4 and 8.3 for supraglottic and glottic cancer respectively [38]. Similar results were obtained by another American case-control study (Seattle, Washington): for 7 to 13, 14 to 20, 21 to 41 and 42 or more drinks per week the OR were respectively 1.9 (95% CI 1.1–3.2), 2.1 (95% CI 1.0–4.4), 2.8 (95% CI 1.4–5.7) and 3.1 (95% CI 1.2–7.9) when compared to drinkers of fewer than 7 drinks per week [40].

Epidemiological studies provide definite evidence that alcohol drinking is an independent risk factor for laryngeal cancer. This risk increases with the amount of alcohol consumed: in a meta-analysis of 20 studies conducted in North America, Europe, Japan and Korea the multivariate relative risks were about 2 for 50g (approximately 4 drinks)/day and about 4 for 100g/day compared to nondrinkers, in the absence of evidence of a threshold. Genetic polymorphisms in the alcohol-metabolising enzyme aldehyde dehydrogenases have been found to be associated with upper aerodigestive tract cancer, including the larynx [41]. Further, the risk is increased with concomitant tobacco smoking, each agent approximately multiplying the effect of the other. In the absence of smoking, the relative and absolute risks are small for moderate alcohol consumption, but there is an increased risk for elevated alcohol consumption. After stopping drinking, some decrease in risk becomes apparent only in the long term. The supraglottis is more closely related to alcohol consumption, as compared to the glottis/subglottis. In various populations, the most commonly used alcoholic beverage appears to be the one most strongly associated with laryngeal cancer risk, suggesting that no meaningful difference exists for different types of alcoholic beverages.

The relationship between alcoholism and cancer of the larynx has been evaluated by a case–control study conducted in the United States [40]. The aim of the study was to determine if alcoholism (as measured by responses to the Michigan Alcoholism Screening Test (MAST)) was a risk factor for laryngeal cancer independently from alcohol consumption. They found an OR of 1.9 (95% CI 1.1–3.4) for a score of 5 or more compared with a score of 0, after having been adjusted for age, gender, average alcohol consumption and summary cigarette use. To investigate if there were a higher association for tissues that come into more direct contact with alcohol, they evaluated different multiple logistic regression models and obtained an OR of 1.9 (95% CI 1.0–3.7) for glottic and subglottic tumours and an OR of 2.3 (95% CI 0.9–5.5) for supraglottic tumours after having been adjusted for the same factors listed above. Possible explanations for the association between alcoholism and laryngeal cancer include the possibility that the MAST score may be serving as an additional measure of alcohol consumption, that is, measure of alcoholism improves the accuracy of assessment of alcohol consumption; that alcoholism is associated with a pattern of alcohol consumption (e.g. alcoholics may gulp drinks instead of sipping them, perhaps leading to a smaller amount of alcohol being aspirated) that increases the risk of laryngeal cancer; or that alcoholism may be a marker for host susceptibility to the carcinogenic effects of alcohol.

A different study, which examined the relationship between alcoholism and cancer risk in a population-based cohort of 9353 individuals who were discharged with a diagnosis of alcoholism between 1965 and 1983 found an excess risk for larynx cancer (standardised incidence ratio 3.3, 95% CI 1.7–6.0) [42].

Combined effects of tobacco smoking and alcohol drinking

Tobacco smoking [21,22] and alcohol consumption [34,35] are the major established risk factors for laryngeal cancer, as for other neoplasms of the upper aerodigestive tract. That the relationship between cigarette smoking and laryngeal cancer risk is causal is strongly suggested by the magnitude of the relative risk estimates derived from comparisons between smokers and non-smokers, by the positive trend in these estimates with increasing cigarette usage, by the relatively reduced risk incurred by groups who do not smoke, such as Seventh Day Adventists, by the decrease in risk among ex-smokers relative to those who continue to smoke and by the consistency of these findings in epidemiological studies of a variety of different designs [21,22,43]. There are, however, some quantitative differences in the association with other upper digestive tract cancers, since cancer of the larynx, and particularly the endolarynx, is less strongly associated with alcohol and more strongly with tobacco than cancer of the oral cavity or of the oesophagus [23]. This difference is biologically plausible since the endolarynx is not in direct contact with alcohol. There is still some debate on the nature of the biological and statistical interaction between alcohol and tobacco on risk of laryngeal cancer [34,35], although most investigations have concluded that the combined risk is multiplicative [26], or at least greater than additive [43]. This further indicates the importance of intervention on at least one factor for subjects exposed to both habits. The study from Poland estimated that cigarette smoking alone accounted for an estimated 95% of laryngeal cancer in that high risk area [26].

The separate effects of alcohol and tobacco on laryngeal cancer are quite strong. The risk of extrinsic laryngeal cancer is 2.5 times greater in heavy drinkers/non-smokers and over 9 times greater among current smokers/non-drinkers. Although alcohol drinking increases the risk of upper digestive and respiratory tract neoplasms even in the absence of smoking, alcohol drinking and tobacco smoking together greatly increase the risk of these cancers, each factor approximately multiplying the effect of the other. Compared with never-smokers and non-alcohol drinkers, the relative risk of these neoplasms is increased between 10- and 100-fold in people who drink and smoke heavily. If there were total abstinence from drinking and smoking, the risk of oral, pharyngeal, laryngeal and squamous cell oesophageal cancers in European countries would be extremely low.

Dietary factors and larynx cancer

Intake of fruit and vegetables may protect against head and neck cancer incidence, although few prospective studies have examined this association. In the USA, 490 802 participants of the NIH-AARP Diet and Health cohort were observed during 2 193 751 person-years of follow-up from 1995–2000 [44]. Of these, 787 participants were diagnosed with head and neck cancer. An inverse association was found between total fruit and vegetable intake and head and neck cancer risk (per serving/day/1000 calories, hazard ratio 0.94, 95% CI 0.89–0.99). In models mutually adjusted for fruit and vegetable intake, the association was stronger for vegetables (fifth vs. first quintile: 0.65, 0.50–0.85) than for fruits (fifth vs. first quintile: 0.87, 0.68–1.11). When further subclassified into botanical groups, those in the highest tertile of leguminosae (dried beans, string beans and peas, 0.80, 0.67–0.96), rosaceae (apples, peaches, nectarines, plums, pears and strawberries, 0.60, 0.49–0.73), solanaceae (peppers and tomatoes, 0.82, 0.69–0.98) and umbelliferae (carrots, 0.73, 0.60–0.89) had decreased risk of head and neck cancer, but no significant associations were seen for nine other botanical groups [44]. Results from this large prospective observational study are consistent with previous case–control studies [45] and support the hypothesis that total fruit and vegetable intake is associated with reduced risk of head and neck cancer.

Family history and genetic susceptibility

Tobacco smoking and consumption of alcoholic beverages are established causes of cancers of the upper aerodigestive tract (UADT), whereas reduced intake of vegetables and fruits are likely causes of UADT cancers (these include cancers of the oral cavity, pharynx (other than nasopharynx), larynx and oesophagus). The role of genetic predisposition and possible interactions of genetic with exogenous factors, however, have not been adequately studied. Moreover, the role of pattern of smoking and drinking, as well as the exact nature of the implicated dietary variables, has not been clarified.

Only a few epidemiologic studies have considered the relation between UADT risk and family history of head and neck cancer (HNC) and other cancers. Negri et al [45] pooled individual-level data across 12 case–control studies including 8967 UADT cases and 13 627 controls. A family history of HNC in first-degree relatives increased the risk of HNC (OR 1.7, 95% CI 1.2–2.3). The risk was higher when the affected relative was a sibling (OR 2.2, 95% CI 1.6–3.1) rather than a parent (OR 1.5, 95% CI 1.1–1.8) and for more distal HNC anatomic sites (hypopharynx and larynx). The risk was also higher in, or limited to, subjects exposed to tobacco. The OR rose to 7.2 (95% CI 5.5–9.5) among subjects with family history, who were alcohol and tobacco users. A weak but significant association (OR 1.1, 95% CI 1.0–1.2) emerged for family history of other tobacco-related neoplasms, particularly with laryngeal cancer (OR 1.3, 95% CI 1.1–1.5). No association was observed for family history of non-tobacco-related neoplasms and the risk of HNC (OR 1.0, 95% CI 0.9–1.1). Familial factors play a role in the etiology of HNC. A clear

message is that, regardless of family history of HNC, avoidance of tobacco and alcohol exposure may be the best way to avoid HNC [46].

In 2002 the IARC initiated the Alcohol-Related Cancers and Genetic susceptibility in Europe (ARCAGE) project, with the participation of 15 centres in 11 European countries. Information and biological data from a total of 2304 cases and 2227 controls have been collected and will be used in a series of analyses. A total of 166 single nucleotide polymorphisms of 76 genes are being studied for genetic associations with UADT cancers. About 80% of cases were males, and fewer than 20% of all cases occurred before the age of 50 years [47]. Overall, the most common subsite was larynx, followed by oral cavity, oropharynx, esophagus and hypopharynx. Close to 90% of UADT cancers were squamous-cell carcinomas. A clear preponderance of smokers and alcohol drinkers was observed among UADT cases compared with controls [47].

Hashibe et al. [48] investigated six alcohol dehydroxegenase (ADH) genetic variants in over 3800 aerodigestive cancer cases and 5200 controls from three individual studies. Gene variants rs1229984 (ADH1B) and rs1573496 (ADH7) were significantly protective against aerodigestive cancer in each individual study and overall (P<0.0001 in each case). These effects became more apparent with increasing alcohol consumption (P for trend=0.0002 and 0.065, respectively). Both gene effects were independent of each other, implying that multiple ADH genes may be involved in upper aerodigestive cancer etiology.

Using epidemiologic data and biological samples previously collected in three case-control studies from US and Chinese populations, Park et al. selected and genotyped one SNP from each of three previously determined regions within the 8q24 loci, rs1447295 (region 1), rs16901979 (region 2), and rs6983267 (region 3), and examined their association with several smoking-related cancers including cancer of the larynx [49]. A noteworthy association was observed between rs6983267 and upper aerodigestive tract cancers (adjusted OR 1.69; 95% CI 1.28–2.24), particularly in the oropharynx (adjusted OR 1.80; 95% CI 1.30–2.49) and larynx (adjusted OR 2.04; 95% CI 1.12–3.72). When the analysis was stratified by smoking status, an association was observed between rs16901979 and upper aerodigestive tract cancer among never-smokers. These results suggest that variants of the 8q24 chromosome may play an important role in smoking-related cancer development.

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5.2 Esophageal Cancer

Summary

- Over 450 000 cases and 380 000 deaths occur each year
- Squamous cell cancer predominates in low- and middle-income countries, and is typically associated with tobacco smoking and alcohol use
- Extremely high rates have been reported in Western and Central Asia (notably parts of China and Iran)
- Adenocarcinoma is increasingly important in high-income countries, and is related to obesity and chronic gastro-esophageal reflux

Cancer of the esophagus affects more than 450 000 people globally each year, and is the sixth most common cancer among men and ninth among women [2]. Survival is uniformly low, with 5-year survival rates usually less than 10%. In regions with established cancer registries that are included in the IARC *Cancer Incidence in Five Continents* series, populations with a high incidence are found among US black populations, as well as in South America, Asia, France and Africa (Table 5.2.1). Most notable are the extremely high rates for both men and women that are recorded in Cixian, China [3].

In those high-incidence registries that provide information on histological type, approximately 90% are squamous-cell carcinomas. This is in contrast to some lower-risk populations, such as Caucasian Americans, where adenocarcinomas now predominate. For example, SEER data from the same period indicate that among Caucasian Americans, who have an age-standardised incidence for esophageal cancer of 4.7/100 000 among men and 1.2/100 000 among women, 55% of cases are coded as adenocarcinoma as opposed to 45% squamous-cell carcinoma.

The main risk factors for squamous cell esophageal cancer in western countries are alcohol and tobacco consumption, which in individual studies have been found to account for 75–90% of the disease [4]. The risk of esophageal cancer increases rapidly with the amount of both tobacco and alcohol consumption, with no evidence of any threshold effect for either. Most studies show a dose-response relation with tobacco consumption, and decreases in risk are found after quitting smoking. Similarly, a dose-response relation is observed with increasing alcohol consumption.

Although alcohol and tobacco consumption are the primary lifestyle risk factors for oesophageal cancer in Western populations, dietary factors are also likely to be important. Fresh fruit and vegetable intake appears to have a strong protective effect [5], and although the relationship for particular types of fruits and vegetables is unclear, citrus fruits and green leafy vegetables appear to possess greater chemopreventative effects than other families of fruits and vegetables. Conversely, there is some evidence that frequent dietary consumption of salted meat and fish, as well as pickled vegetables may represent a risk factor.

Regarding the intake of hot beverages, consumption of hot mate, a herbal infusion consumed in parts of Southern Brazil, Argentina and Uruguay, appears to be strongly associated with development of esophageal cancer. Three case–control studies from Uruguay and Brazil have reported an increased risk among drinkers of mate, including a dose-response relationship [2,6,7]. An IARC monograph evaluation of mate consumption concluded that hot mate was *"probably carcinogenic to humans"* (Group 2A), although confounding from other lifestyle factors could not be excluded. Although mate is traditionally drunk very hot, any information on the temperature of mate consumption has been self-reported, and it is not possible to separate out a possible carcinogenic effect due to the temperature or the composition of the beverage.

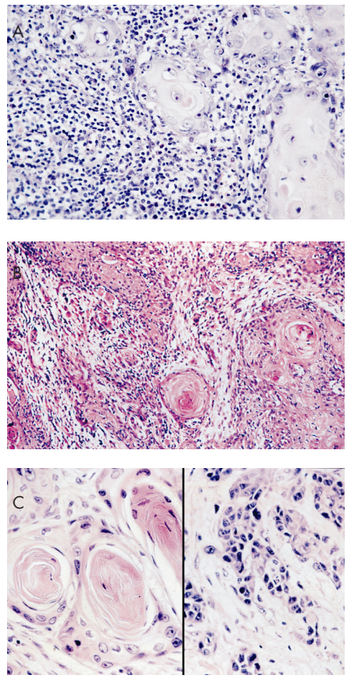


Fig. 5.2.1 *Squamous-cell carcinoma. A: Moderately differentiated. B: Well differentiated with prominent lymphoid infiltrate. C: Well differentiated areas (left) contrast with immature basal-type cells of a poorly differentiated carcinoma (right)*

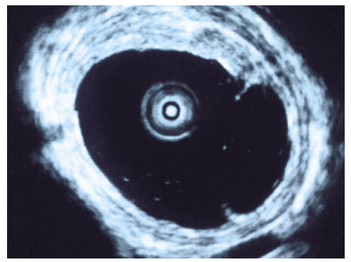
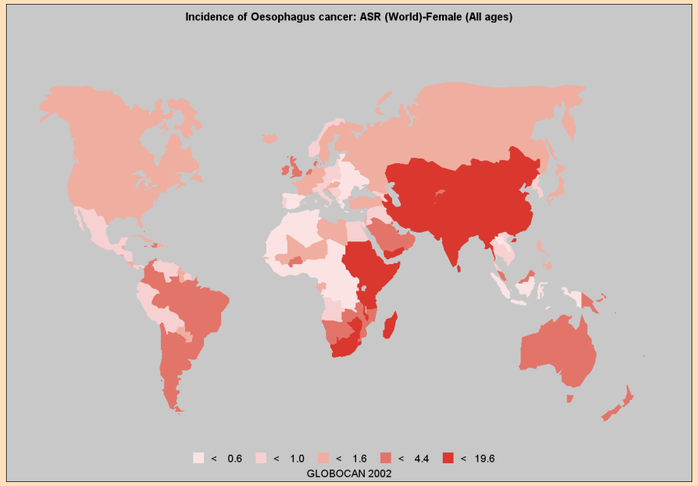


Fig. 5.2.2 *Catheter probe ultrasonograph of a squamous-cell carcinoma*

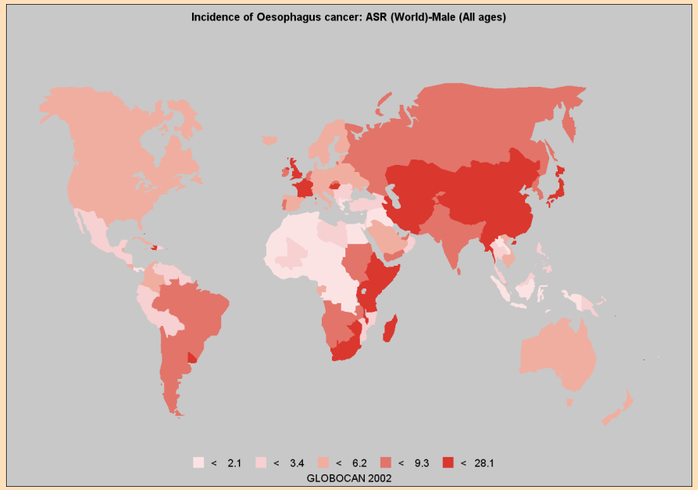
Hot tea consumption has also been suggested as a risk factor for esophageal cancer in Western populations. In a UK population-based case–control study on squamous cell cancer of the esophagus comprising 159 female case–control pairs, quantity of tea was identified as a risk factor for esophageal cancer along with a significant positive trend with temperature at which the tea was consumed (p=0.03) [8]. The increased risk for drinking tea at very hot temperatures was over threefold and, as the authors suggested, when coupled with smoking is likely to explain much of the increased incidence of esophageal cancer among UK women when compared to other European populations.

Other potential risk factors for squamous cell esophageal cancer include contamination of food products by fumonisin mycotoxins, which has been reported in studies from high-risk areas in China and Italy [9,10]. In the only prospective study of fumonisin exposure and esophageal cancer, which used sphingolipids as a biomarker of fumonison exposure in a high-risk population in Linxian, China, no relationship between fumonisis and esophageal cancer was observed [11]. Poor oral hygiene and tooth loss have also been reported to be associated with an increased risk of esophageal cancer, possibly related to alterations in oral bacterial flora and subsequent increases in the *in-vivo* production of carcinogens such as nitrosamines [12].

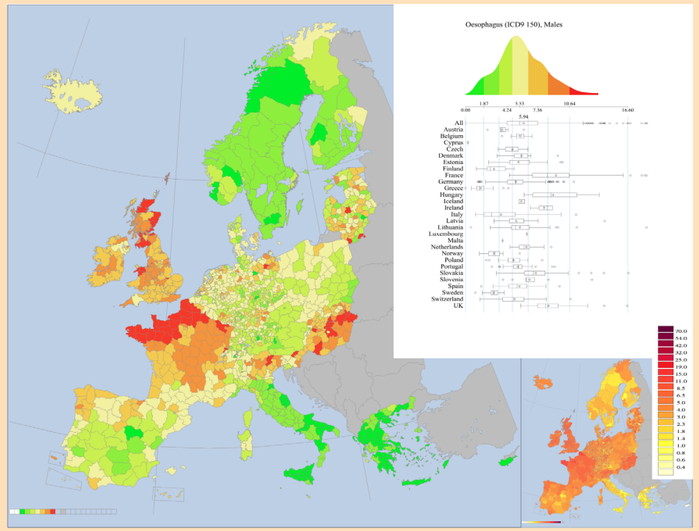
Regarding genetic susceptibility, esophageal cancer does not exhibit any strong familial component, and genetic studies of esophageal cancer have instead focused on genes such as cytochrome P 450 (CYP), gluthatione-S-tranferase (GST) and aldehyde dehydrogenase (ADH) 1C that metabolise suspected tobacco- and alcohol-derived carcinogens. No consistent findings have emerged, although most studies have been limited



World Map 5.2.1



World Map 5.2.2



European Map 5.2.1 *In males, the feature of the geographic pattern of esophageal cancer is the concentration of very high risk in northern France, extending up to the border with Belgium; there were also contiguous areas of above-average risk in the northeast of Italy, Slovenia and Hungary. Rates were also generally above average in the United Kingdom, particularly in parts of Scotland, and in Ireland.*
Lower rates were concentrated in Norway, Sweden and Finland, Greece and central and southern Italy. The geographical aldistribution was thus similar, but not identical, to that for oral cancer [Chapter 5.1] the main difference being above average mortality from esophageal cancer in the United Kingdom and Ireland [1].

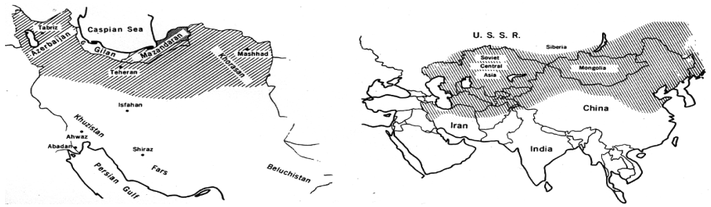


Fig. 5.2.3 *Iran and its position in the Central Asian Esophageal Cancer Belt*

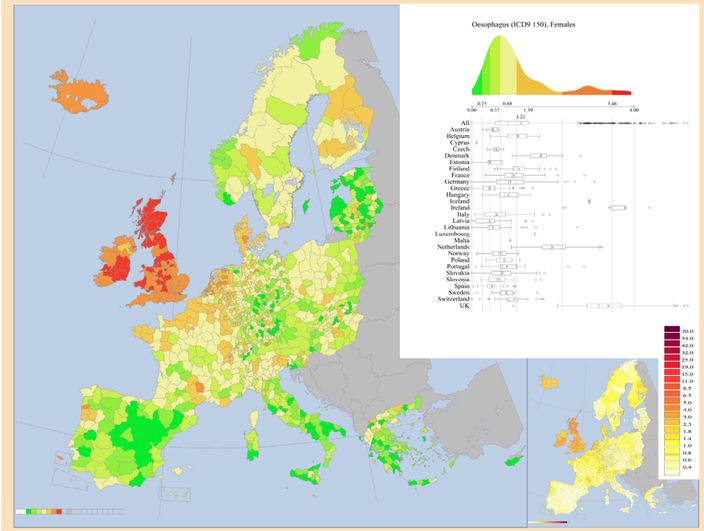
in size. Conversely, a strongly significant protective effect has been observed with ADHIB variants that encode for fast alcohol metabolism [13].

Increasing trends of esophageal adenocarcinoma have been reported, particularly in the USA and parts of Europe [14,15]. For example, incidence rates of esophageal adenocarcinoma in white males in the USA surpassed those of squamous cell cancer around 1990. The causes of this increasing trend include obesity, as well as an inverse association with *helicobactor* pylori [16,17].

Esophageal cancer in very high incidence regions

The geographical distribution of oesophageal cancer is characterised by very wide variations within relatively small areas. Although accurate cancer registry information is limited, very high rates (over 50/100 000) have been reported for both genders from northern Iran and the provinces of north central China, in certain areas of Kazakhstan and also among native Siberians [18,19]. These populations form a "Central Asian Esophageal Cancer Belt" (Figure 5.2.3), although whether these extremely high rates are due to a common risk factor is unclear. One possibility is that very high rates of esophageal cancer are linked to several factors including (i) a severely deficient in fruits and vegetables, (ii) a squamous injury from consumption of very hot beverages and (iii) intense carcinogen exposure from lifestyle factors including smoking or opium consumption. These hypotheses are however untested.

The earliest reports of the high incidence of cancer of the esophagus in northern parts of Iran go back to mid-1960s and early 1970s [20-24]. These reports emphasised the frequency of the disease in many young patients, a predominance of squamous cell cancers and a slightly higher female/male ratio. In order to investigate this finding in more detail a population based cancer registry was established in 1969 as a joint effort between Tehran University and the IARC, in the city of Babol,



European Map 5.2.2 *High rates of esophageal cancer among women were also apparent in the United Kingdom and Ireland. There was a belt of slightly above-average rates across northern France, Belgium, The Netherlands and Denmark, but no evidence of the excess risk in northeast Italy, Slovenia, Slovakia and Hungary that was seen in males [1].*
The geographical pattern observed in men can be related directly to the patterns of smoking and alcohol intake (in terms of ethanol) throughout Europe. It is much more difficult to ascribe the pattern of esophageal cancer observed in females to either these or other known risk factors. The similarity of the pattern in the ratios between the rates in men and women in each country with the corresponding pattern for oral cancer confirms that the risks arise from common etiological and/or cultural factors.

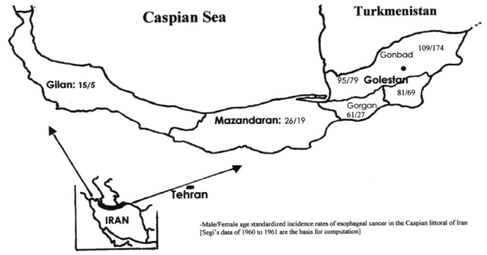


Fig. 5.2.4 *Age-standardised incidence rates /100 000 of esophageal cancer according to the data of the Caspian Littoral Cancer Registry, 1970*

Fig. 5.2.5 *A highly infiltrative adenocarcinoma in a Barrett oesophagus*

in Mazandaran province, on the eastern coast of the Caspian Littoral. This was subsequently extended to the western province of Gilan and the neighboring city of Ardabil in the southwest of the Caspian Sea in 1970 (Figure 5.2.4).

Initial results from this cancer registry emphasised the very high incidence of esophageal cancer in the eastern portion of Mazandaran province close to Turkmenistan (the Gonbad and Gorgan districts, now Golestan province), and particularly in the semi-desert plain settled mainly by people of Turkoman ethnicity, with incidence rates of 109/100 000 among men and 174/100 000 among women [21,22]. Sharp changes in the incidence of esophageal cancer were evident between regions only a few hundred kilometres apart. The incidence dropped to 17.2/100 000 for men and 5.5/100 000 for women in Gilan, 500

Registries			% by histological type - both sexes		
Africa	**Male**	**Female**	**SCC**	**Adeno**	**Other/unknown**
Zimbabwe, Harare	15.1	5.3	86.9	5.7	7.3
Uganda, Kyadondo	14.1	8.4	79.4	9.3	11.2
America, Central and South					
Brazil, Brasilia	13.1	3.9	67.1	15.7	17.2
Brazil, Sao Paolo	12.0	2.2	82.5	10.5	7.0
Brazil, Cuiaba	11.7	2.7	76.1	11.3	12.6
America, North					
USA, District of Columbia: Black	14.8	3.5	84.7	10.5	4.7
USA, South Carolina: Black	14.4	2.5	57.0	36.7	6.3
USA, Georgia: Black	11.1	3.1	89.3	7.0	3.7
Asia					
China, Jiashan	20.2	4.8	92.9	6.3	0.8
China, Zhongshan	16.5	1.9	73.5	3.0	23.6
Japan, Miyagi	15.4	2.2	91.3	3.0	5.8
Japan, Yamagata	13.0	1.6	90.1	5.6	4.3
Japan, Hiroshima	12.1	2.0	94.6	1.7	3.6
Europe					
France, Calvados	14.6	2.1	81.2	12.4	6.4
France, Somme	14.1	1.5	71.3	21.0	7.7
France, Manche	13.1	1.6	85.8	10.3	3.9
France, Loire-Atlantique	12.7	1.6	71.0	24.9	4.1
Scotland	11.7	4.7	42.6	51.2	6.2

Table 5.2.1 *Cancer registries with highest esophageal cancer rates, 1993-1997 – CI5 Vol IX*

kilometres to the west. Recent reports from the Ardibil cancer registry and from an esophageal cancer survey carried out in the eastern part of the Caspian littoral have confirmed these early findings [25,26].

Factor	Alteration
Tumour suppressor genes	
p53	60% mutation - high-grade intraepithelial neoplasia and carcinoma
APC	Late in intraepithelial neoplasia-carcinoma sequence
FHIT	Common, early abnormalities
CDKN2A (p16INK4A)	Hypermethylation common in intraepithelial neoplasia
Growth factor receptors	
CD95/APO/Fas	Shift to cytoplasm in carcinoma
EGFR	Expressed in 60% of carcinomas, gene amplification
c-erbB2	Late in dysplasia-carcinoma sequence, gene amplification
Cell adhesion	
E-cadherin	Loss of expression in intraepithelial and invasive carcinoma
Catenins	Similar loss of expression to E-cadherin
Proteases	
UPA	Prognostic factor in carcinoma
Proliferation	
Ki-67	Abnormal distribution in high-grade intraepithelial neoplasia
Membrane trafficking	
rab11	High expression in low-grade intraepithelial neoplasia

Table 5.2.2 *Genes and proteins involved in the development of adenocarcinoma from Barrett oesophagus*

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5.3 Stomach Cancer

Summary

- In most countries, a steady decline in gastric cancer mortality rates has been observed in the last few decades
- The bacterium *Helicobacter pylori*, which establishes long-term infection of the stomach, is a major risk factor for gastric cancer, increasing the incidence rate by a factor of 6. It is estimated to be responsible for 63% of all cases of non-cardia gastric cancer worldwide
- Genetic variation between strains of *Helicobacter* pylori may play an important role in gastric cancer risk
- Epidemiological studies suggest a diet rich in fresh fruits and vegetables is protective against gastric cancer. However, intervention trials that supplement the diet with anti-oxidant vitamins have not been successful in reducing gastric cancer risk.

According to the most recent available estimates, gastric cancer is the fourth most common cancer worldwide, with 934 000 cases per year [2]. Survival from gastric cancer is poor since patients are often diagnosed with advanced disease. In the USA, for example, five-year survival is 24% [3].

Gastric cancer incidence shows wide geographical variation. World Maps 5.3.1 and 5.3.2 shows a map of the incidence rates of gastric cancer in males, standardised to the world population. Incidence rates in females follow a similar pattern, but are about 50% lower. This sex ratio cannot be entirely attributed to differences in the prevalence of known risk factors between the sexes, and a protective role of female hormones has been hypothesized [4].

The high-risk areas are in Japan, China, Eastern Europe and certain countries in Latin America. Low-risk populations are seen among whites in North America, India, the Philippines, most countries in Africa, some western European countries and Australia. There is a 15–20-fold variation in risk between the highest- and the lowest-risk populations. Substantial variations in gastric cancer incidence may also be found within countries; a good example is Italy, where there is threefold variation in risk within the country, with male incidence rates ranging between 10 and 30 per 100 000 [5].

Gastric cancer incidence rates in both sexes have been declining worldwide for several decades. The precise reasons for this decline are unknown. Figure 5.3.1 illustrates the decline of gastric cancer mortality rates in men in Northern Europe from 1950 to 2005. In 1950, all countries illustrated in Figure 5.3.1 were high-risk countries for gastric cancer, with standardised mortality rates in men over 30 per 100 000. Now, all have mortality rates under 10 per 100 000, with the exception of the Baltic states Latvia, Lithuania and Estonia. Even in these countries, mortality rates in both men and women are in decline.

When cancers of the gastric cardia, the proximal part of the stomach, are analysed separately, incidence rates show a strong increase in some industrialised countries [6]. The distinct time trend shown by cardia cancer is an indication that it has a different etiology. There has been a concomitant rise in the incidence of adenocarcinoma of the oesophagus, which suggests that gastric cardia shares the same risk factors as cancers that arise in the lowest part of the oesophagus, namely obesity, gastro-oesophageal reflux and its occasional sequel, Barrett's oesophagus.

Gastric carcinogenesis is a long-term process, taking several decades. The progression from normal tissue to cancer has intermediate stages of chronic gastritis, gastric atrophy, intestinal metaplasia and dysplasia [7]. These precursor lesions, which may be asymptomatic, can be diagnosed by taking gastric biopsies. Observational studies and randomised trials have also studied these precursor lesions in relation to risk factors for gastric cancer.

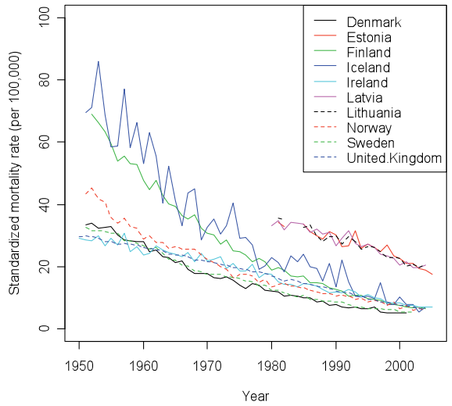


Fig. 5.3.1 *Mortality from gastric cancer in males in Northern Europe 1950–2005*

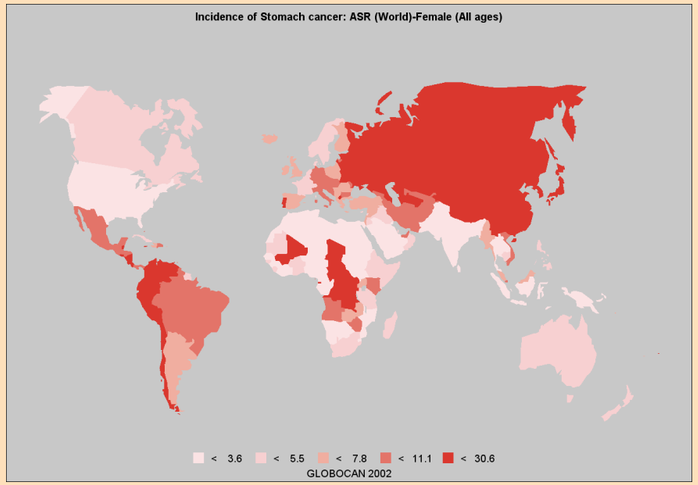
Risk factors for gastric cancer

Epidemiological evidence, mainly from case–control studies, suggests that a diet rich in fresh fruits and non-starchy vegetables is associated with a lower risk of gastric cancer. High salt intake has also been identified as a probable risk factor [8]. The hypothesis that fresh fruits and vegetables have a protective effect through the action of vitamins with anti-oxidant properties (e.g., vitamin C, beta-carotene and vitamin E) led to a number of intervention trials on gastric cancer or its precursor lesions using anti-oxidant vitamin supplementation [9].

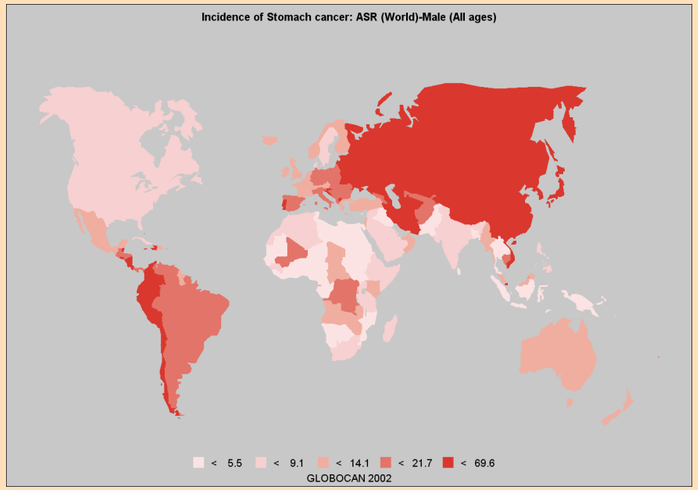
Helicobacter pylori (H. pylori) is a spiral gram-negative bacterium that colonises the stomach. It is one of the most common infections in humans with an estimated prevalence of 50% worldwide and 90% in developing countries. In high-prevalence populations, infection is rapidly acquired in childhood and persists throughout life. Prevalence of *H. pylori* infection is declining in many developed countries. It is believed that this is mainly a cohort effect, with the prevalence of infection declining in successive birth cohorts. Later acquisition of *H. pylori* may also contribute to low infection prevalence in children and young adults.

H. pylori was first isolated by Marshall and Warren (1984), who demonstrated its causal role in gastritis and peptic ulcer disease, and were awarded the 2005 Nobel prize for Medicine for their discovery. In 1994, an expert working group convened by IARC classified *H. pylori* as carcinogenic to humans [10] based on epidemiological evidence for its association with gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Since then, evidence has continued to accumulate for the causal role of *H. pylori* in gastric cancer.

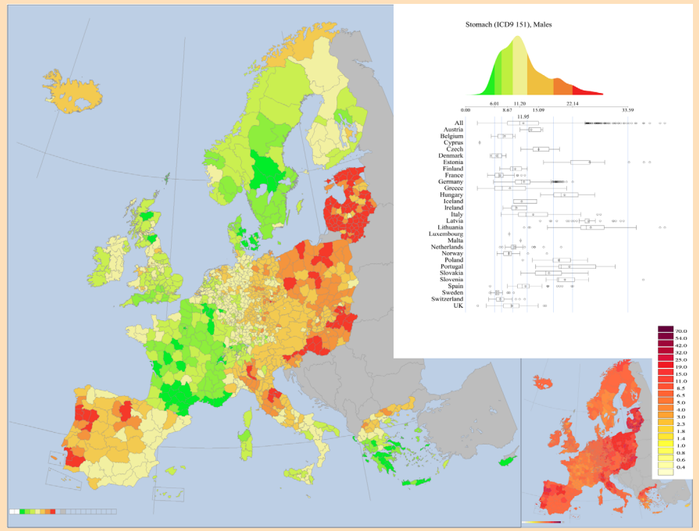
The strongest epidemiological evidence for the role of *H. pylori* in gastric cancer comes from a combined analysis of 10 prospective studies in which *H. pylori* antibodies were measured in stored blood samples, taken years before diagnosis of gastric cancer [11]. In this pooled



World Map 5.3.1

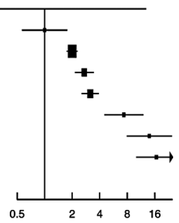


World Map 5.3.2



European Map 5.3.1 *There are very striking–and closely similar–geographic patterns for stomach cancer mortality in males and females. Moving broadly from southwest to northeast, there is a concentration of high rates in Portugal and much of the adjoining area of central and northern Spain. Rates were below average in the United Kingdom and Ireland, and in most of the mainland of western Europe; rates were also low in Scandinavia.*
Rates were above average in northern (but not southern) Greece, central and northern Italy, Austria, the east of Germany and the Czech Republic, and were highest across almost all of Slovenia, Slovakia, Hungary, Poland and the Baltic countries [1]

Diagnosis	cagA+ Hp+ /cagA- Hp+	OR[1] (95%CI)	FSE[2]	OR & 95% FCI[3]
Normal & superficial gastritis	16/48	1.00	0.291	
Chronic gastritis	346/532	2.00 (1.11-3.60)	0.071	
Chronic atrophic gastritis	124/144	2.71 (1.46-5.05)	0.123	
IM type I	162/166	3.16 (1.71-5.83)	0.111	
IM type II	53/24	7.35 (3.45-15.6)	0.250	
IM type III	61/15	14.0 (6.22-31.4)	0.291	
Dysplasia	90/18	16.7 (7.75-35.9)	0.260	



[1] *Odds ratio and 95% confidence interval adjusted for age and sex.*

[2] *Floating standard error on log scale.*

[3] *Odds ratio and 95% floating confidence interval adjusted for age and sex.*

Fig. 5.3.2 *The association between severity of precancerous lesions and H. pylori infection by cagA-genotype [16]*

analysis, *H. pylori* was not associated with gastric cardia cancer (relative risk=1.0, 95% CI 0.7–1.4). For non-cardia gastric cancers, however, the relative risk was 3.0 (95% CI 2.3–3.8). When analysis was restricted to blood samples taken more than 10 years before diagnosis, the relative risk was increased to 5.9 (95% CI 3.4–10.3).

The change in relative risk with time illustrates a hypothesis about the effect of progression to gastric cancer on *H. pylori* infection. The development of widespread gastric atrophy, a precursor lesion of gastric cancer, results in a reduction in bacterial load and consequent loss

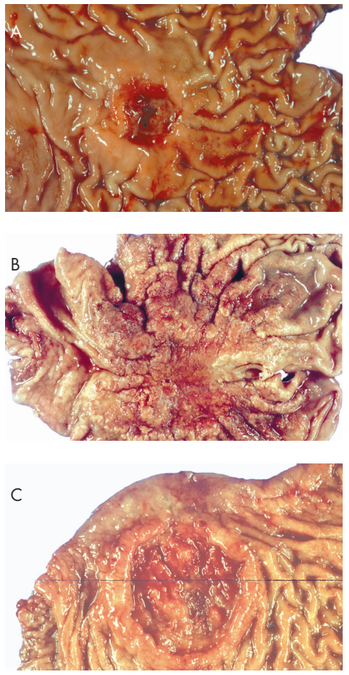
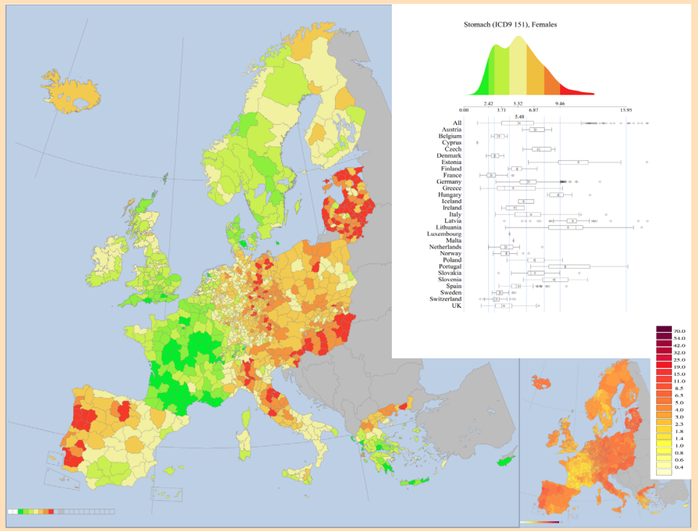


Fig. 5.2.3 *Advanced gastric carcinoma with varying degrees of infiltration*



European Map 5.3.2 *A clear message is the close similarity of the geographic patterns of stomach cancer observed in males and in females. This is present when considering the maps visually and is reinforced when statistical analyses are conducted [1]. There are traditional explanations put forward to explain some of the patterns apparent in the maps: the high rates in Portugal have been associated with the widespread practice of eating salted fish, and the high rates in Italy, Germany and Austria have been associated with cured meats. These hypotheses need to be re-assessed and tested as does the etiology underlying the regional variation in Greece.*
The important role of Helicobacter pylori in the etiology of stomach cancer provides an unusual opportunity for prevention via the development of an effective vaccine. Although the risk of stomach cancer is diminishing throughout Europe, pinpointing the risk factors responsible could help accelerate the decline of this form of cancer which has relatively poor survival (European average 22% in males and 26% in females at five years after diagnosis).

of antibody response. Therefore, measurements of *H. pylori* antibodies in gastric cancer cases are not considered reliable unless taken many years before diagnosis.

Based on the estimated relative risk of 5.9, the proportion of non-cardia gastric cancer attributable to *H. pylori* has been estimated to be 63% [12]. This aggregate measure of risk may conceal considerable variation between *H. pylori* strains. *H. pylori* is genetically highly diverse, and there is evidence that distinct genetic lineages of *H. pylori* differ in their pathogenicity. The most commonly studied pathogenicity genes are the cytotoxin-associated (*cagA*) gene and the vacuolating cytotoxin (*vacA*) gene. The *cagA* gene, which is not present in all strains, is considered to be a marker of a pathogenicity island of approximately 35 000 base pairs, encoding a type IV secretion system that transfers the CagA protein into the host cells [13]. Infection with *cagA*-positive strains increases the risk of atrophic gastritis and gastric cancer [14,15]. The *vacA* gene encodes a vacuolating cytotoxin that is excreted by *H. pylori* and damages epithelial cells. The *vacA* gene is present in all strains, but shows variation in *H. pylori* strains isolated from different populations worldwide. The *vacA* and *cagA* genotypes of *H. pylori* are strongly linked.

Figure 5.3.2 shows the results of a cross-sectional study on precancerous lesions of the stomach based on detection of *H. pylori* DNA from gastric biopsies [16]. Subjects in the study who were infected with *cagA*-positive *H. pylori* strains were at substantially increased risk of advanced precancerous lesions compared with uninfected subjects. Conversely, infection with *cagA*-negative *H. pylori* was not associated with any precursor lesion except chronic gastritis. These findings strongly implicate *cagA*-positive strains of *H. pylori* in gastric carcinogenesis.

Genetic susceptibility

The descriptive epidemiology of gastric cancer indicates that the risk is dominated by environmental causes. There may, however, still be a role for genetic factors. Individuals with blood group A have been known for decades to have an approximately 20% excess of gastric cancer compared with other blood groups. Germline mutations in a gene encoding the cell adhesion protein E-cadherin (CDH1) have also been found in familial diffuse gastric cancer [17].

One summary measure of the possible contribution of genetic risk factors to gastric cancer is the familial relative risk (FRR), the relative risk given gastric cancer in a first-degree relative. The FRR can be estimated from population-based studies that link cancer registries with a genealogical database. Three such studies have been conducted in Utah, USA [18], Sweden [19] and Iceland [20], giving FRR estimates of 2.09 (0.99–0.356), 1.31 (0.97–1.70), and 1.90 (1.74–2.05) respectively. Hence there is modest but consistent evidence for an increase in risk among relatives of gastric cancer cases. The impact of this familial aggregation in terms of attributable fraction is small however. In the Swedish study, the population attributable fraction of gastric cancer due to familial aggregation was estimated to be 0.45%. Moreover, the FRR is not

only a measure of the effect of shared genotype, but also includes the effect of shared environmental risk factors within the family. The studies in Sweden and Iceland found significantly elevated risk among spouses of gastric cancer patients.

Studies relating individual genes to gastric cancer risk have focused on candidate genes that may modulate the host response to infection with *H. pylori*. In particular, polymorphisms in interleukin-1B (IL-1B) and IL-1 receptor agonist (IL-1RN) genes have been extensively analysed, but results are not consistent between studies. Three independent meta-analyses have now been published, summarising the pooled results of studies on these polymorphisms, and all three reach slightly different conclusions [21-23]. This lack of agreement arises from the substantial heterogeneity between different studies conducted in different populations. A plausible explanation for this heterogeneity is that gastric cancer risk and susceptibility are determined by a combination of host genotype and virulent *H. pylori* strain genotype. Both factors must be measured to accurately quantify the risk.

Prevention of gastric cancer

The two major changes that could be made at a population level to reduce gastric cancer incidence are improvement in diet and reduction in the prevalence of *H. pylori*. These changes are already taking place in many populations, as a consequence of economic development, and may explain the decline observed in gastric cancer incidence. Active intervention in a population requires proof that the intervention is effective, and this can only come from randomised trials.

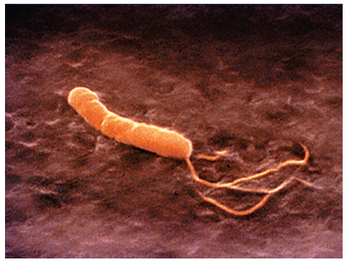


Fig. 5.3.4 *The Helicobacter pylori bacterium structure as revealed by scanning electron microscopy*

Several trials have been conducted using supplementation with selected vitamins as an intervention, and with gastric precancerous lesions or gastric cancer as an endpoint. The aim of vitamin supplementation in these trials was to simulate improved diet, assuming that the protective micronutrients in a healthy diet have been correctly identified. The results of these trials, however, have generally been disappointing, and it is unlikely that anti-oxidant vitamin supplementation is an effective tool for gastric cancer control [9]. Nevertheless, the negative results of randomised trials cannot be considered to contradict the epidemiological evidence for a protective effect of fresh fruits and vegetables, since the dose, duration and timing of anti-oxidant vitamin exposure in such trials are not directly comparable with a life-long healthy diet.

Several treatment regimens have been used to eradicate *H. pylori* infection, but triple therapy including bismuth salts, amoxicillin and clarithromycin is currently the regimen of choice. Randomised trials of anti-*H. pylori* treatment are reviewed by Correa [7], who concludes that curing *H. pylori* infection results in a modest retardation of the precancerous process, but does not prevent all cancers. The available trials of anti-*H. pylori* treatment are limited by the fact that they were conducted in adults in an advanced state of atrophy or intestinal metaplasia. It is possible that the impact on gastric cancer prevention may be magnified by eliminating *H. pylori* at an earlier stage of the precancerous process.

Conclusions

Geographical distribution and time trends suggest that the risk of gastric cancer is strongly determined by environmental factors. Etiological studies point to infection with *H. pylori* and poor diet as the main determinants of gastric cancer risk. Despite the long-term decline of gastric cancer incidence in many populations, there is considerable opportunity for active intervention to reduce the burden of gastric cancer, most notably the eradication of *H. pylori* in high-risk populations.

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5.4 Liver Cancer

Summary

> More than 80% of cases of hepatocellular carcinoma occur in Asia and Africa and irrespective of etiology, the incidence rate is more than twice as high in men as in women

> In Africa and Asia, hepatocellular carcinoma is most frequently caused by hepatitis B virus infection; concomitant dietary exposure to aflatoxins multiplies the risk. In Japan, this cancer is predominantly caused by hepatitis C virus infection

> In Western countries, liver cirrhosis due to chronic alcohol abuse is a major etiological factor. The spread of hepatitis C virus is a major challenge and is responsible for increasing rates of liver cancer in the USA and in parts of Europe

> Hepatocellular carcinoma is almost always lethal, survival from time of diagnosis often being less than six months; only 5–9% of patients survive five years or more

Hepatocellular carcinoma (HCC) arises from hepatocytes and accounts for about 80% of all primary cancers of the liver. Other tumour types include intrahepatic cholangiocarcinoma (tumours of that part of the bile duct epithelium located within the liver), hepatoblastoma (a malignant embryomal tumour of childhood) and angiosarcoma (arising from blood vessels) and are relatively rare compared to HCC. However, in some parts of the world such as eastern Thailand, cholangiocarcinoma occurs at a high rate as the result of infection of hepatic bile ducts by liver flukes (*Opistorchis viverrini*) due to the consumption of infected raw fish. The development of flukes in bile ducts induces a chronic inflammatory state that represents a major risk factor for the neoplastic transformation of bile duct epithelial cells.

Epidemiology

Liver cancer ranks third amongst the organ-specific causes of cancer-related deaths in men worldwide. Liver cancer accounts for approximately 6% of all new cancer cases diagnosed worldwide. Liver cancer is the fifth most common cancer among men worldwide, but is the eighth in women [2,3]. Globally, men are about three times as likely as women to be afflicted and the difference is higher in high-incidence than low-incidence areas. Liver cancer is a major health problem in low-resource countries, where more than 80% of the worldwide total occur (over 500 000 new annual cases). The highest incidence rates are recorded in China (55% of the world total), Japan, South East Asia and sub-Saharan Africa. In both high- and low-incidence areas, there is great variability in incidence among ethnic groups [4].

Age-specific rates of incidence show marked geographical variation. In the Gambia, age-specific rates peak in the 45–55 years age range, whereas in Europe and the USA, high risk is associated with older age.

Time trends in liver cancer are difficult to interpret due to changes in classification and variable inclusion of metastatic tumours. However, the incidence of hepatocellular carcinoma in Japan, the UK, Germany and the USA and several Nordic countries has demonstrated a sustained increasing trend over the past two decades and has become progressively associated with younger age groups [5]. Mortality rates have increased in several regions, including France. Some of these increases may be the result of improved detection, but the main causal factors are the spread of hepatitis C virus infection as well as the growing impact of non-alcoholic metabolic diseases.

Etiology

Hepatitis viral infections. Globally, the etiology of HCC is dominated by the interaction of viral and environmental risk factors. These factors and their overall impact are summarised in Table 5.4.1. The carcinogenic effect of chronic infection with hepatitis viruses B and C is well demonstrated by epidemiological and experimental evidence. Consistent epidemiological data have associated a significant risk of HCC with chronic HBV infection, which accordingly has been categorised as causing cancer in the context of IARC Monograph evaluations [6]. Worldwide, the proportion of HCC attributable to chronic hepatitis is about 54% for HBV and 31% for HCV. These figures should be considered as conservative estimates. Persistent, chronic HBV infection is usually defined by the release into the bloodstream of the surface antigen HBsAg for a period of at least 6 months post infection. There is evidence that HBV can also persist in an occult form, with no release of HBsAg but persistence of viral DNA. These occult infections may represent the terminal phase in the natural course of HBV persistent infection and they should be taken into account in estimates of the risk of HCC attributable to HBV. Furthermore, co-infections with HBV and HCV may occur, with a cumulative effect on the risk of HCC that varies from additive to multiplicative. Thus, overall, the burden of liver cancer attributable to hepatitis viral infections is likely to be close to 90%.

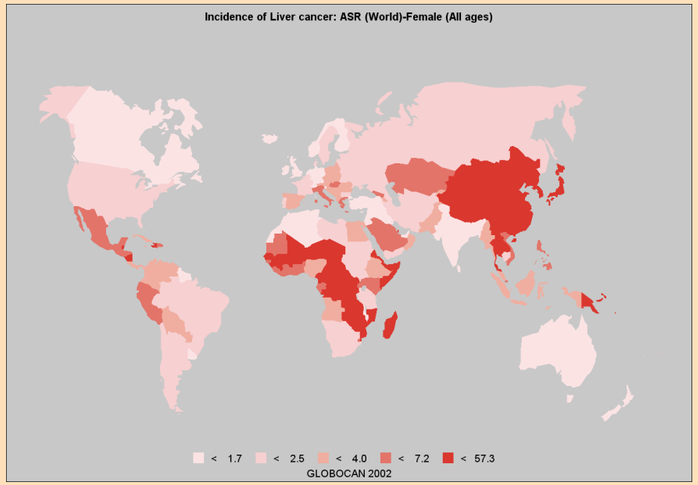
It should be noted that the impact of hepatitis virus infections shows substantial geographic variation, in both the population prevalence of persistent infection and the specific genetic characteristic of the viruses involved. In many low-resource tropical countries, chronic HBV carriage is high in the general population (10–15%), and it can be estimated that over two thirds of liver cancer cases in low-resource countries are attributable to this virus [7]. HBV is particularly implicated in hepatocellular carcinoma in Africa and Asia, and HCV in Japan and the USA. However, the relationship between chronic carrier prevalence and incidence of HCC is a complex one, and striking discrepancies exist in some populations and geographic areas. Inuits (Canada, Greenland) and Maoris (New Zealand) have among the highest population rates of HBV carriage in the world but they show relatively modest incidences of HCC. HBV exists in 8 distinct genotypes (defined by groups of viruses that have 8% or more differences in their DNA sequence, Figure 5.4.1), which differ by their infectivity, transmission mechanisms, pathogenicity, rate at which they persist, and risk of chronic liver disease and HCC. For example, Genotype F, which is found among the native population of Alaska, carries a risk of HCC several fold higher than most other genotypes.

There are an estimated 400 million HBV chronic carriers worldwide. Of those carriers, at least 50% will remain asymptomatic with progressive disappearance of HBsAg. Of the remainder, many will develop chronic liver disease of variable severity. A common, severe condition is liver cirrhosis. In western countries, about 70–90% of hepatocellular carcinomas develop in patients with macronodular cirrhosis. In eastern Asia and West Africa, the proportion of patients with pre-existing liver cirrhosis at the time of HCC diagnosis appears to be much lower, perhaps in the range of 25–50%. However, there is a lack of detailed prospective studies on precursor liver conditions in these areas. Therefore, cirrhosis is not an obligatory pre-cancer step to HCC.

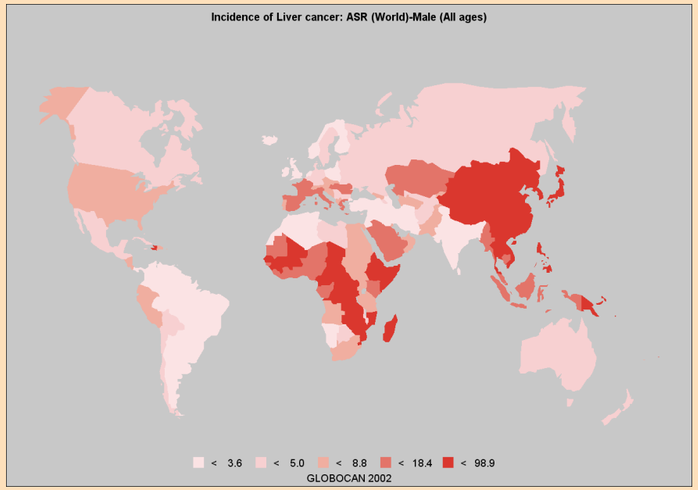
Significant differences related to the population rate of chronic carriage and the viral genotype also exist for HCV. In several countries, for example in Egypt, there is evidence that the extremely high population prevalence of chronic carriage (21%) results from the dissemination of the virus through the use of inadequately sterilised needles during medical interventions such as mass vaccination programmes.

Dietary and environmental carcinogenesis

In low-resource tropical countries, dietary exposure to aflatoxins, a class of mycotoxins produced by moulds of the genus Aspergillus, is a significant risk factor that operates synergistically with both HBV and HCV chronic infection. Aflatoxins contaminate many traditional crops such as groundnuts (peanuts), grains or



World Map 5.4.1



World Map 5.4.2

maize. Furthermore they develop under poorly ventilated storage conditions in hot and humid climates. Aflatoxin B1 (produced by Aspergillus flavus) is a significant contaminant of staples throughout sub-Saharan Africa and Southeast Asia, as well as in many parts of Latin America. The toxin is metabolised in the liver to produce an epoxide that covalently binds on the N7 position of Guanines, in particular at the third base of codon 249 in TP53. Processing of this adduct leads to the formation of promutagenic DNA lesions which, if not repaired, lead to the formation of stable mutations during transcription or replication (R249S, AGG to AGT, arginine to serine). Subjects with several "at-risk' polymorphisms in genes encoding aflatoxin metabolising and detoxifying enzymes, as well enzymes involved in DNA adduct repair, have a significantly higher risk of HCC in combination with aflatoxin exposure. The reasons why the R249S occurs almost exclusively in a context of joint exposure to HBV and aflatoxin B1 are unknown. Presence of HBV may play a role in site-specific DNA damage by aflatoxin or in affecting the efficiency of repair at that defined position. Alternatively, the R249S mutant may have special functional properties that cause efficient hepatocyte transformation.

In high-resource countries, the main known risk factors are smoking and, significantly, chronic alcohol abuse [8]. Alcohol is primarily responsible for metabolic liver injury that leads to the development of liver cirrhosis, which is a common precursor of HCC. Iron overload caused by untreated haemochromatosis or by excess exposure to iron in some African populations may provoke in some patient series a risk of death of as much as 45% from hepatocellular carcinoma [9]. Hepatic iron overload in these conditions often results in fibrosis and cirrhosis, suggesting that free iron-induced chronic necroinflammatory hepatic disease plays a role in hepatocarcinogenesis.

Metabolic syndrome. Non-alcoholic fatty liver disease (NAFLD) is a rapidly increasing metabolic syndrome that is a risk factor for HCC, and may be considered a precursor disease [10]. This syndrome is characterised by lipid accumulation within hepatocytes leading to hepatic steatosis, non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. In the USA, the estimated prevalence of NAFLD in the general population ranges from 3–24%, with highest estimates in the 6–14% range. NAFLD is extremely common among patients undergoing bariatric surgery, ranging from 84–96%. NAFLD is strongly associated with caloric overconsumption, physical inactivity, hypertension, obesity, insulin resistance including diabetes and with other features of the metabolic syndrome, such as high serum triglyceride and low HDL levels. The metabolic syndrome appears to be more common in men, and increases with increasing age and after menopause. An AST/ALT ratio greater than 1 in the serum may also indicate more severe disease. Other metabolic disorders that may carry an increased risk of hepatocellular carcinoma or other liver cancers include tyrosinaemia, alpha-1-trypsin deficiency, hypercitrullinaemia, porphyria cutanea tarda and glycogen storage disease.

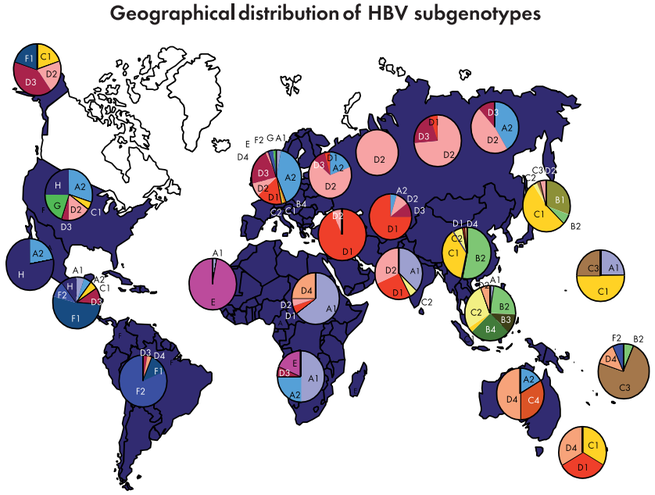


Fig. 5.4.1 *Geographical distribution of HBV subgenotypes*
Figure provided by Heléne Norder - Swedish Institute for Infectious Disease Control

Pathology and genetics

Hepatocellular carcinoma is a malignant epithelial tumour derived from hepatocytes, and thus resembles normal liver both structurally and cytologically. Small early-stage hepatocellular carcinomas (<2 cm) are generally well-differentiated histologically and arranged in a thin trabecular pattern without a capsule (Figure 5.4.2) [9]. Tumour cells grow in cords of variable thickness that are separated by sinusoid-like blood spaces. Hepatocellular carcinoma is believed to progress from adenomatous hyperplasia (or dysplastic nodules) through atypical hyperplasia to early hepatocellular carcinoma. Trabeculae become thicker with de-differentiation. Larger cancer nodules may consist of more than two types of tissue of different histological grade [11]. Invasion into the blood vessels, especially the portal vein, is a characteristic of hepatocellular carcinoma. The malignant cells produce alpha-fetoprotein which may be detected in the serum of many patients.

Genetic change in hepatocellular carcinoma may be directly related to relevant environmental factors. In areas with high exposure to aflatoxin B1, mutation of the third nucleotide in codon 249 of TP53 is frequent, compatible with miscoding due to the binding of aflatoxin (adduct formation) to relevant nucleotides in DNA. There is evidence that mutation of p53 is an early event in hepatocellular carcinomas in high-incidence areas. In high-resource countries, TP53 mutations occur at many different positions in the coding sequence and are thought to represent late events. Recent studies on biomarkers of HCC have identified broad molecular categories of cancers, based on genetic changes and viral infection status [11]. The first category contains tumours that are genetically unstable, often contain TP53 mutations, mutations in AXIN1 and multiple loss of alleles at different loci. These tumours are often associated with persistent HBV infection. The second category includes tumours that are genetically more stable, contain mutations in CNNB1 encoding beta-catenin, and often develop in the absence of HBV infection. Whether these two broad categories correspond to cancers with different biological and clinical characteristics remains to be demonstrated.

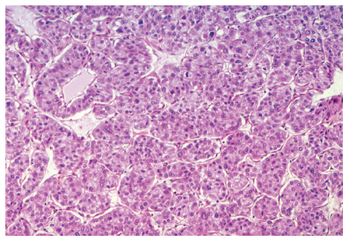
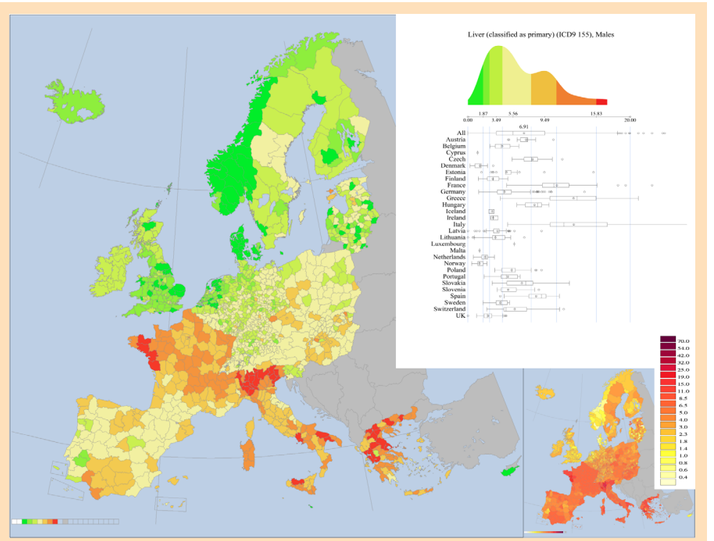


Fig. 5.4.2 *Histological appearance of hepatocellular carcinoma: a well-differentiated, trabecular carcinoma containing numerous sinusoid-like capillary vessels*



European Map 5.4.2 *In men, higher-than-average rates were found in most of France, Italy and Greece and in southern Spain. In women, the higher rates were also found in most of Italy and Greece and in Spain—but not in France; there were also higher rates in the neighbouring countries of Hungary, Slovakia, the Czech Republic and Poland in central Europe, and in parts of Sweden but not elsewhere in Scandinavia. In both sexes, the lowest rates were to be found in the United Kingdom, Ireland, Belgium, The Netherlands, Denmark, Finland and Norway.*
The patterns apparent in the maps are compatible with an alcohol and hepatitis etiology in males, with high rates in France (alcohol) and Greece, Italy and (southern) Spain (hepatitis). In females, where alcohol consumption levels are much lower, the geographic pattern is compatible with a hepatitis etiology. Hepatitis B, and particularly hepatitis C, should be regarded as public health priorities in southern Europe. The difficulties in separating the diagnosis of metastases from primary liver cancer in many countries must, however, be borne in mind [1].

The contribution of hepatitis viruses to the mechanisms of carcinogenesis is still a matter of debate. With HBV, at least three overlapping mechanisms may be involved. First, persistent HBV infection induces oxidative stress damage as well as endoplasmic reticulum stress due to accumulation of HBsAg in the reticulum. These stresses cause widespread cell destruction and stimulate compensatory cell proliferation, resulting in a deregulated, inflammatory context which is one of the hallmarks of cirrhosis. In this modified environment, transformed cells would have survival advantage due to their capacity to proliferate and to escape apoptosis, and may thus be selected to form rapidly expanding lesions. Second, HBV DNA integrates into the genome of the host cell and may act as an insertional mutagen to activate or repress the transcription of genes in the vicinity of the integration point. There is however no consensus integration region in the genome of hepatocytes. Third, the virus encodes several proteins that have a significant impact on the host cell's signalling pathways. HBx, the protein encoded by the X gene of the viral genome, is a multi-factorial protein that acts as a transcriptional regulator, interferes with several signalling pathways and may promote degradation of several intracellular proteins. These biochemical effects may contribute to tumour initiation or to the maintenance of the transformed phenotype.

HBV virus persistence contributes to a chronic inflammatory state that may predispose to cancer. There is also evidence that viral antigens may interfere with the pathways of apoptosis in hepatocytes, thus providing a survival advantage. In the case of HCV, the mechanisms involved are much less well understood.

The role of NAFLD as a precursor disease may also be linked to overproduction of reactive oxygen species overload and chronic inflammation resulting from the intracellular accumulation of lipids as well as from mitochondrial leakage during hyperactive oxygen-dependent energy metabolism.

Intrahepatic cholangiocarcinoma comprises cells resembling those of bile ducts, which is the site parasitized by liver flukes [12] . Most intrahepatic cholangiocarcinomas are adenocarcinomas showing tubular and/or papillary structures with a variable fibrous stroma. Mutations of the KRAS and TP53 genes are the most common genetic abnormalities identified.

Major Etiologic Factors	Incidence Data	Mortality Data
Hepatitis B infection (>50%) Hepatitis C infection (>25%) Alcohol consumption Aflatoxin B1 Tobacco smoking Obesity/diabetes/fatty liver/ Iron overload	551 000 cases/year worldwide 5th most common cancer 83% of all cases in developing countries 54% of the total cases in China	529 000 deaths/year worldwide 3rd most frequent cause of cancer death 8.8% of total cancer deaths

Table 5.4.1. *Liver cancer: Etiologic factors, incidence and mortality*
From Kirk, Bah and Montesano [7].

T = primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into subserosa or into non-
	peritonealised pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures and/or
	perforates visceral peritoneum
N = regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
M = distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 5.4.2 *TNM classification of cancer of the colon and rectum*

Detection

Screening for HCC in those patients at highest risk for progression has the potential to significantly reduce morbidity and mortality [13]. Elevated AFP levels are an aid to diagnosis but this biomarker lacks specificity for application in a screening context. Other plasma biomarkers have been proposed but none of them has been fully validated in prospective studies.

Recent observations indicate that free DNA originating from tumour cells is detectable in the plasma of liver cancer patients at an early stage. Detection of relevant genetic changes in the plasma (such as TP53 mutation at codon 249 in the inhabitants of high incidence areas and aberrant methylation of CDKN2A in most parts of the world) may soon become useful aids in screening tests for hepatocellular carcinoma. In a series of patients from the Gambia, the combination of high mutant TP53 plasma DNA levels (over 10 000 DNA copies per ml) with HBV chronic infection carries a risk of HCC increased by over 65-fold as compared to low TP53 plasma DNA levels [14]. The availability of simple, genetic or proteomic plasma-based tests would be an important contribution to screening programmes.

Clinical manifestations

Common symptoms of hepatocellular carcinoma are abdominal pain, weight loss, fatigue, abdominal swelling and anorexia. Most patients, particularly in sub-Saharan Africa, present with hepatomegaly; other common signs are ascites and jaundice. Hepatocellular carcinoma that infiltrates a cirrhotic liver often compromises the already impaired hepatic function and thus causes death before becoming very large, as is the case in most patients in Japan and the USA. Intrahepatic cholangiocarcinoma is characterised by general malaise, mild abdominal pain and weight loss, and by jaundice and cholangitis at later stages. The majority of cases can be diagnosed by computed tomography (CT) (Figure 5.4.3) and ultrasonography. A definitive diagnosis may depend on histological analysis via fine needle biopsy. Endoscopic retrograde, transhepatic or magnetic resonance cholangiography can identify the level of biliary obstruction in the case of intrahepatic cholangiocarcinoma.

Management

The treatment of primary and malignant liver tumours depends on the extent of the disease and the underlying liver function [15]. The most frequently used staging system is that in which the patient is evaluated according to the adverse criteria of ascites, serum albumin and bilirubin concentration and tumour size. The TNM system is less useful as it does not take into account underlying liver disease. Liver cancer follows a rapid, progressive course: only about 8% of patients survive at least five years in the USA, and the percentage is much lower in low-resource countries. In the absence of extrahepatic disease, resection with negative pathologic margins is the mainstay of treatment for malignant liver neoplasms. In patients in whom a small liver remnant is anticipated, portal vein embolisation is used to increase the size of the future liver remnant [16]. The fact that most hepatocellular carcinomas occur in a cirrhotic liver excludes many patients from consideration for surgical resection, due to the risk of liver failure. Other techniques used alone or as an adjuvant to resection include radiofrequency ablation and cryoablation. Liver transplantation is currently used as a curative therapeutic approach in such patients. In Europe and in the USA, the use of this procedure has declined due to a number of factors, including the frequency of death from tumour recurrence, especially in the transplanted liver, and organ shortages. This procedure is however becoming widespread in the management of liver cancer in China and in several other countries of Southeast Asia. In some countries, there is a justified fear that the rapidly expanding demand of transplantable organs may fuel uncontrolled commerce in organs.

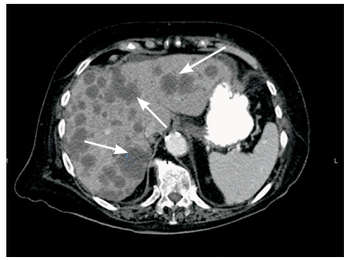


Fig. 5.4.3 *CT image of a multifocal hepatocellular carcinoma (arrows)*

Hepatocellular carcinoma is largely radiotherapy resistant [11]. Non-surgical treatments include hepatic artery infusion of drugs or thrombotic agents (via implanted infusion port or pump), chemoembolisation and percutaneous alcohol or acetic acid injection, although side-effects are many and benefit to the unresectable patient is doubtful [17,18]. Recent results suggest that a chemotherapy regimen combining cisplatin, doxorubicin, interferon and 5-fluorouracil may elicit a response, although previously no agent, either singly or in combination, has been found to improve survival. Hormone therapy is also disappointing, although results with octreotide are more hopeful than with tamoxifen. Metastatic hepatocellular cancer commonly spreads to the lungs and bones. Response to chemotherapy and local regional therapy is poor [18,19]. The liver is also a frequent site of metastases from cancers at other sites, of which the most common is colorectal cancer.

Prevention

The poor prognosis and lack of effective therapies for hepatocellular cancer indicate that the development of prevention programmes is of critical importance. Since the early 1980s, safe and affordable HBV vaccines have been available. Their introduction in mass vaccination programmes has demonstrated that these vaccines are efficient for reducing the rate of HBV infection and, significantly, of acquisition of carrier status. In Taiwan, where infection occurs mostly in adolescents and liver cancer in young adults, a sharp and significant drop in the incidence of HCC has been observed in young, vaccinated adults in the years following the introduction of the vaccine [20]. However, due to the long-term impact of chronic carriage, a full evaluation of long-term vaccine protection is not yet available. In high incidence areas, several randomised or semi-randomised trials are currently in progress to evaluate the protective efficacy of newborn HBV vaccination against persistent infection, chronic liver disease and, ultimately, cancer. Two population-based trials were started in the mid-1980s and will reach their evaluation phase around 2015, when the target population will be around 40 years of age. The largest trial, in The Gambia, West Africa, is a joint endeavour of IARC, the Medical Research Council of the UK and the government of the Republic of The Gambia. The trial was developed in the period of introduction of HBV vaccine in the Expanded Programme of Immunization in The Gambia, from 1986 to 1990 [21]. During that period, 125 000 newborns were recruited, half of whom received HBV vaccine before 1 year of age in addition to other Expanded Programme of Immunisation (EPI) vaccines. Since 1990, all newborns have been vaccinated, and the two arms of the 1986–1990 cohort are being followed-up for the evaluation of vaccine efficacy against infection and carriage, as well as for the assessment of liver cancer incidence through a National Cancer Registry. Recent cross-sectional studies within the vaccination cohort showed sustained, excellent protection of adolescents against chronic carriage. This trial provides a model for introduction of HBV vaccine in other African countries. Current projections support the view that complete coverage of the continent with the current, low-cost vaccine could reduce HCC incidence by over 60% within the next 50 years.

The lack of an equivalent vaccine-based preventive strategy is a major challenge in the control of HCV infection. Current prevention

measures focus on the absolute requirement for using disposable or adequately sterilised material in medical and public health interventions in low-resource countries and on the screening of blood and organ donors for the risk of HCV infection.

There is evidence that regulation against the distribution of aflatoxin-contaminated foodstuffs effectively decreases levels of aflatoxin exposure in the population [22] Such measures remain very difficult to implement in low-resource countries, where aflatoxin-contaminated crops represent an important part of the rural income as well as a major component of the diet that cannot be easily replaced by other foodstuffs. In such a context, it is however possible to implement relatively simple, commonsense measures to triage contaminated crops, and store them in conditions that will limit the proliferation of the moulds. A pilot, community-based intervention in Guinea has shown that such measures could significantly reduce individual exposure to aflatoxin, as measured by the levels of aflatoxin biomarkers in blood and urine.

Other risk factors are amenable to prevention, such as alcohol drinking, tobacco smoking or exposure to excess environmental iron. One of the biggest challenges in high-resource countries is to develop public health policies that will be effective in curbing the increase in the incidence of NAFLD.

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5.5 Pancreas Cancer

Summary

- Pancreatic cancer is the 13th most common cancer worldwide, with over 232 000 new cases diagnosed each year. In general, the highest incidence rates occur in more developed countries
- About 20% of pancreatic cancer is attributable to tobacco smoking
- Familial clustering of pancreatic cancer and pancreatic cancer related to rare genetic syndromes, including hereditary pancreatitis, occurs in 5–10% of cases of pancreas cancer
- No population-based screening or early diagnostic testing procedures are currently available, although there are efforts underway to address these deficiencies
- The five-year survival rate is <5%, the lowest survival rate of the major cancers
- Mutations in *KRAS, TP53, p16/CDKN2A,* and *SMAD/DPC4* are implicated in over 50% of pancreatic tumours. Ductal pancreatic adenocarcinomas appear to progress from pancreatic intraepithelial neoplasia, PanIN, to pancreatic adenocarcinoma. Stromal elements and a strong desmoplastic response appear to play a role in the growth and aggressiveness of pancreas tumours
- Treatment and management for pancreas cancer patients have seen few recent improvements. Management for most patients still focuses on palliation. Surgical resection is still performed in fewer than 15% of all cases. Combined modalities involving both standard and new treatments may improve the management and survival of pancreas cancer in the coming years

Pancreas cancer is one of the most aggressive human tumours. At diagnosis, fewer than 10% of cases present with disease locally confined to the pancreas. The majority of pancreas tumours (95%) occur in the exocrine portion of the pancreas with the remainder occurring in the endocrine portion or arising from the islets of Langerhans. Most pancreatic tumours of the exocrine pancreas are classified as ductal adenocarcinomas. Tumours of the body or tail of the pancreas occur with a 30-40% frequency, while the remainder occur in the head of the pancreas. About 80% of pancreas tumours occurring in the body or tail are more advanced (stage IV), while about 33% of those in the head are diagnosed at stage IV. Consequently, survival and prognosis vary by the initial site of the tumour within the pancreas.

Epidemiology

Pancreas cancer is the 13th most common cancer worldwide, with over 232 000 new cases occurring each year. The overall 5-year survival rate for pancreas cancer is the lowest of all the major cancers at 3% to 5% (Figure 5.5.1). In the minority of pancreas cancer patients for whom surgery is an option, the 5-year survival rate is between 10 and 15%. In the USA, pancreas cancer is now the fourth leading cause of cancer death for men and women, and in the year 2008, it is estimated that there will be 37 680 new cases of pancreas cancer and 34 290 deaths [2]. Reasons for the poor survival in pancreas cancer include the typically insidious and aggressive nature of these tumours, late diagnosis, low rates of resection, and lack of effective therapies.

Pancreas cancer incidence and mortality rates vary around the world. Incidence and mortality are generally higher in the Americas, Europe, Australia and Japan. More specifically, worldwide rates are highest for African American men, New Zealand Maoris (particularly women), Korean Americans, female native Hawaiians, and the male population in Kazakhstan. Worldwide incidence and mortality rates are lowest in India, Africa (although quality data are generally lacking), Southeast Asia, and parts of the Middle East. Rates in Latin America are generally intermediate between the higher rates in North America and the lower rates in India [3].

Etiology

Advancing age is one of the strongest and most consistent predictors of pancreas cancer risk. Pancreas cancer is very rare under the age of 30 years, with the majority of cases occurring after the age of 65 years. Incidence rates are about 25–50% higher in men than in women until later in life, when incidence rates become nearly equivalent (Figure 5.5.2). These observations, along with data from animal studies, suggest that hormonal factors could play a role in the development of pancreas cancer. So far, the epidemiological studies that have addressed reproductive factors and hormone use in relation to pancreas cancer have yielded inconclusive results.

The most important (and avoidable) environmental risk factor for pancreas cancer is tobacco smoking. Most studies to evaluate smoking and pancreas cancer report relative risks around

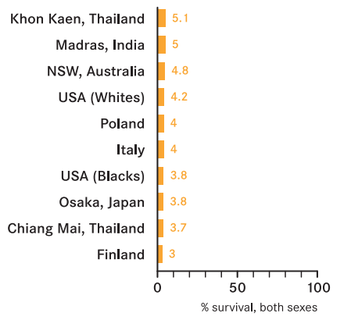
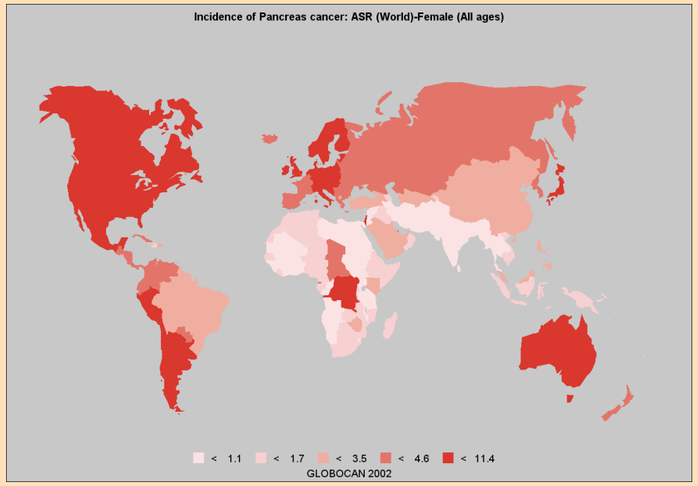


Fig. 5.5.1 *Five-year relative survival rates for both sexes combined by region [USA (blacks), USA (whites); India (Madras/Chennai), Finland, Italy, Poland, Thailand, Australia, Japan]*

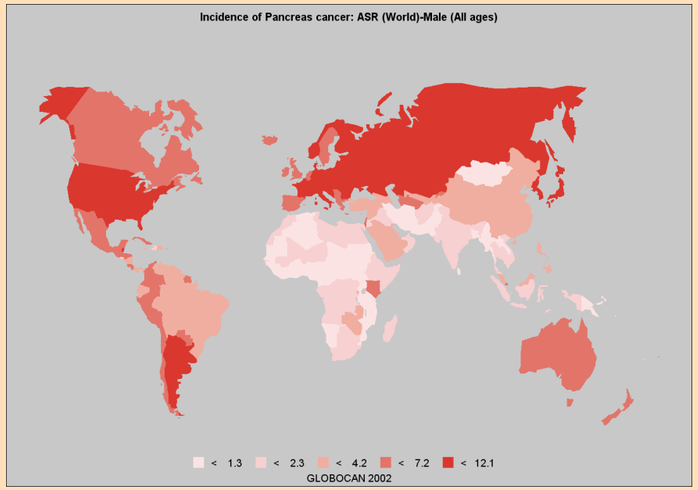
two-fold [3]. It is estimated that 20–29% of all pancreas cancers are attributable to smoking [4,5]. Despite the overwhelming evidence that smoking is a cause of pancreas cancer, the biological mechanism underlying pancreatic carcinogenesis remains elusive. Quitting smoking can reduce the risk of pancreas cancer by up to 50% after two years of not smoking, and after about 10 years of not smoking may decrease risks to those seen in never-smokers [4].

Various dietary factors have been associated with increased and decreased risks for pancreas cancer. Diets high in red meats and fat and high in calories appear to increase the risk of pancreas cancer, while diets high in fruits, vegetables and fibre appear to decrease risk. Further, the method of cooking, in particular methods that increase heterocyclic amines in cooked meats such as high temperature broiling, grilling and barbequing, may also increase the risk of pancreas cancer [6]. Moderate consumption of coffee and alcohol do not appear to increase risk; however, very heavy alcohol drinking and alcohol bingeing may increase risk. Obesity appears to be related to a higher risk for pancreas cancer [7]. Higher levels of physical activity, possibly related to higher energy expenditure, appear to be associated with a decreased risk for pancreas cancer [8].

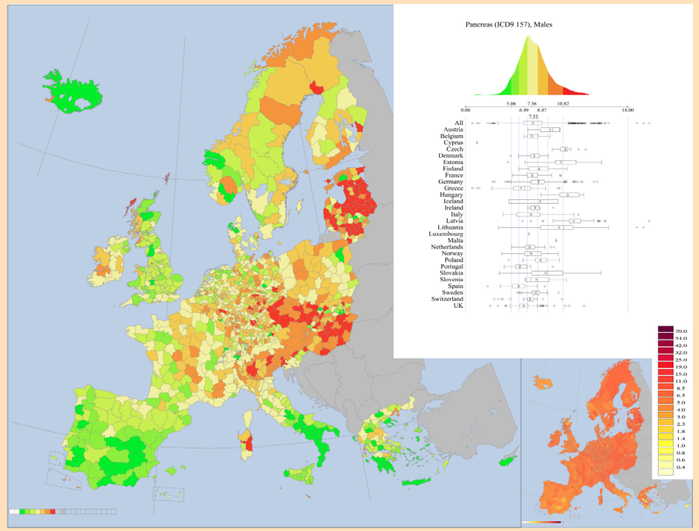
Long standing diabetes is associated with about a two-fold increased risk for pancreas cancer. Chronic inflammatory pancreatitis, in particular hereditary pancreatitis, although rare, is associated with a high risk (greater than 10-fold and higher) for developing pancreas cancer. The biological mechanisms underlying the increased risks for pancreas cancer associated with diabetes and pancreatitis are currently unknown. A recent analysis of pre-diagnostic plasma C-peptide showed a positive association with subsequent risk of pancreas cancer, suggesting that underlying insulin resistance and hyperinsulinemia may play a role in pancreatic carcinogenesis [9]. The relation between a history of allergies and pancreas cancer risk has been evaluated in a number of studies. A



World Map 5.5.1



World Map 5.5.2



European Map 5.5.1 *In men, there were several distinct aggregations of regions with high rates of pancreas cancer. One extended over northern Sweden and Norway; a second covered all three Baltic Countries; and a third extended from northern Italy into eastern Austria, the Czech Republic, Slovakia and Hungary. There is marked contrast between the high rates in the north of Italy and the very low rates in the south of the country; and there were low rates in Portugal, Spain and most of Greece and the United Kingdom [1].*

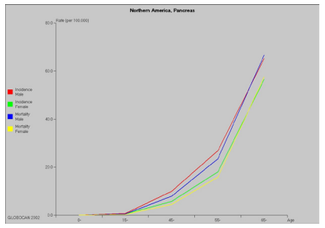


Fig. 5.5.2 *Age-specific incidence and mortality of pancreas cancer in men and women (in North America). The small differences between incidence and mortality reflect the poor prognosis for this disease. Men are somewhat more frequently affected than women*

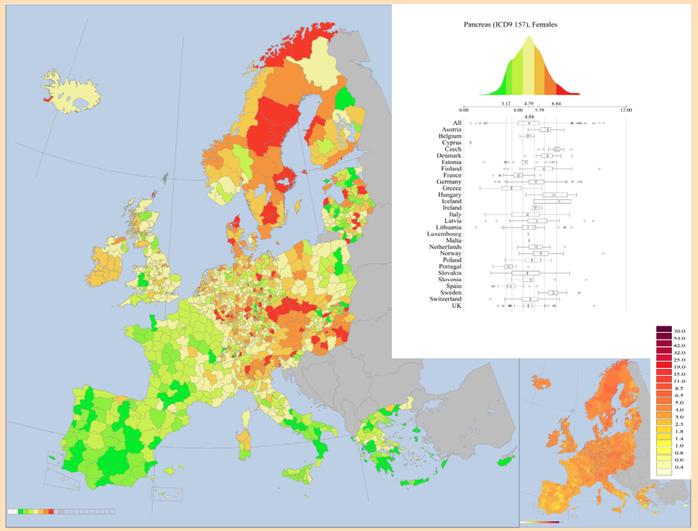
recent review and meta-analysis suggested that having a history of allergies, in particular those related to atopy, is associated with a lower risk of pancreas cancer [10]. There is some evidence that *H pylori* infection may contribute to pancreas cancer incidence, but studies to date have involved too few cases to adequately address this topic. The use of aspirin has been inconsistently associated with pancreas cancer, with some studies showing inverse associations and others showing little or no association. To date, the possibility that aspirin and other non-steroidal anti-inflammatory drugs lower pancreas cancer risk is inconclusive.

Many studies have evaluated occupations and workplace exposures in relation to risk of pancreas cancer. In general, there does not appear to be any single occupation or workplace exposure that explains much of the disease. The few consistent occupations that have been associated with pancreas cancer have been those associated with exposure to chlorinated hydrocarbons, pesticides, solvents, metals, polycyclic aromatic hydrocarbons and nitrosamines, and some occupations involved in the pulp and paper industry.

Detection

There is currently no early diagnostic test or population-based screening procedure for pancreas cancer detection and screening. Patients usually report symptoms that lead to a physical examination and several tests on urine, blood, and stool. Laboratory tests which may indicate the presence of pancreas cancer include elevated bilirubin levels and increased levels of liver enzymes. Based on the physical examination and laboratory tests, the physician may request imaging studies of the pancreas, the best being multiphase spiral or helical computerised tomography (CT), although transabdominal or endoscopic ultrasonography (EU) and magnetic resonance imaging (MRI) may also be used. Endoscopic retrograde cholangiopancreatography (ERCP) has risks associated with the procedure (pancreatitis, perforation and bleeding) and is now largely reserved for therapeutic purposes for stent placement to relieve obstruction.

If an imaging study identifies a possible mass or tumour in the pancreas, a biopsy may be taken to determine definitively the presence of pancreas cancer and to provide staging information. There are two ways that a biopsy may be performed to diagnose pancreas cancer (or to determine resectability), including EU-guided fine-needle aspiration and brush biopsy performed in conjunction with ERCP. Pancreas cancer may also be diagnosed (or resectability determined) with biopsy material taken during surgery on the pancreas such as laparoscopy and laparotomy.



European Map 5.5.2 *In women, the broad pattern was similar, but there were some noticeable differences, with high rates over most of the Nordic Countries, particularly Sweden, and in Austria, the Czech Republic and Hungary, but only average rates in the three Baltic Countries. As in males, there were low rates throughout Spain, Portugal, southern Italy and much of Greece [1].*

Pathology and genetics

There is growing evidence that the molecular pathogenesis of pancreas cancer progresses from early stage neoplasia, or PanIN, to malignant ductal pancreatic cancer (Figure 5.5.3). The first stage of neoplasia, flat hyperplasia, involves the columnarisation of the ductal epithelium. This may then advance to papillary hyperplasia, the presence of crowded mucosa with a folded structure, which may possess varying degrees of cellular and nuclear abnormalities. True carcinoma of the pancreas is characterised by invasion of the ductal walls of the lumen and a strong desmoplastic (inflammatory) response. The molecular pathways and genes involved in pancreas cancer progression are being actively pursued by the scientific community [11].

Hereditary conditions. From 5 to 10% of pancreas cancer cases exhibit some degree of familial clustering. There are a number of hereditary syndromes that have been associated with an increased lifetime risk of pancreas cancer (Table 5.5.1). Over 20 genes have been implicated in the molecular pathogenesis of pancreas cancer (Table 5.5.2). Somatic alterations involving four genes have been implicated in over 50% of pancreas tumours, including *KRAS* oncogene (>90%) and *p16/CDKN2A* (>40%), *TP53* (>50%) and *DPC4/SMAD4* (>35%) tumour suppressor genes [12] (Table 5.5.2). The genetic progression of pancreas cancer from normal epithelium to invasive carcinoma is generally associated with the accumulation of genetic alterations starting with *KRAS* mutations and telomere shortening followed by *p16/CDKN2A* loss and finally mutations in *TP53*, *DPC4/SMAD4*, and *BRCA2* (Figure 5.5.3) [11]. Other genes known to be involved in pancreas cancer development, albeit less frequently than the genes listed above, include *BRCA1*, *MKK4*, *PRSS1*, *LKB1/STK11*, *MSH2*, *MLH1*, *FANC-C* and *FANC-G*. Germ-line mutations in *BRCA2* represent the most common inherited predisposition to pancreas cancer described so far. In one study, 7% of sporadic cases of pancreas cancer (those with no apparent family history of pancreatic cancer) were found to harbour inherited mutations in *BRCA2* [13]. In addition to the above-mentioned genetic alterations, a number of growth factors are over-expressed in pancreas tumours, including EGF, TGF-alpha, TGF-beta, alphaFGF, and their receptors [12,14].

Molecular epidemiology

The discipline of molecular epidemiology is a relatively new field of study. Despite this, there are a small but increasing number of published reports addressing common, inherited genetic variation and environmental exposures such as tobacco smoking in relation to the risk of sporadic pancreas cancer. Early evidence suggests that DNA repair and carcinogen metabolism gene variation, in combination with heavy smoking, may help to define susceptible subgroups at greater risk for pancreas cancer [15,16]. Additional studies and pooled analyses involving thousands of cases may help to define combinations of genes and exposures that increase the risk of developing pancreas cancer. Such information may lead to improved screening and detection as well as treatment and management of sporadic forms of pancreas cancer.

Management

Pancreas cancer is often referred to as a "silent" disease because the tumour can grow for years before there are any notable signs or symptoms. Typical symptoms of pancreas cancer include jaundice, generalised itching, pain in the abdomen or back, nausea, loss of appetite, unexplained weight loss and general weakness. These symptoms are often ignored by many

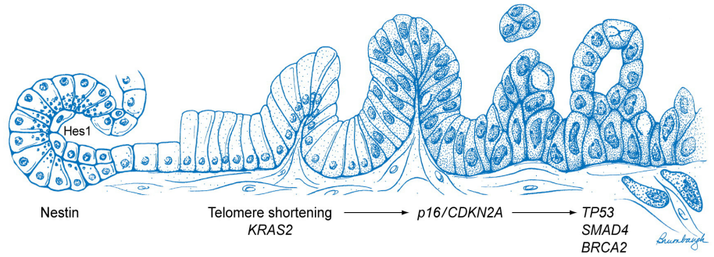


Fig. 5.5.3 *Genetic progression model of pancreatic adenocarcinoma (Pancreatic Cancer. Ann. Rev. of Pathol. Mech. Dis. Vol.3:157-188, 2008)*

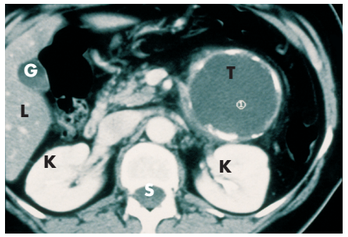


Fig. 5.5.4 *A CT image of a mucinous cystic neoplasm in the pancreas. The thick wall shows focal calcification. T = tumour, K = kidney, L = liver, S = spinal cord, G = gallbladder*

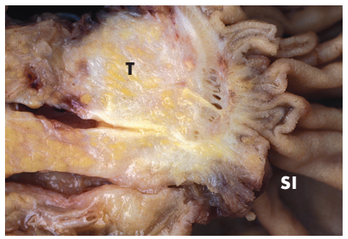


Fig. 5.5.5 *Surgical specimen of a pancreatic ductal adenocarcinoma (T) in the head of the pancreas. SI = small intestine*

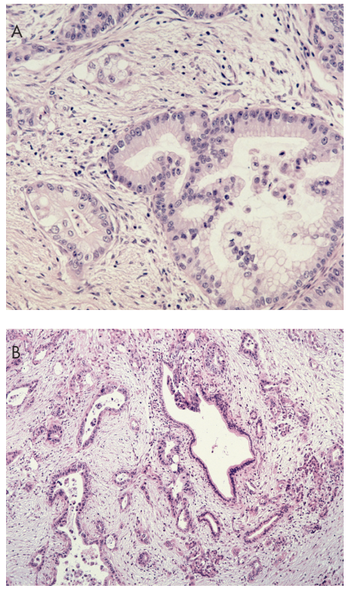


Fig. 5.5.6 *Ductal adenocarcinoma. A: Well differentiated tumour with desmoplasia and irregular gland formation. B: Well differentiated neoplasm involving a normal duct (right part).*

patients early on and can be mistakenly attributed to other general health problems. Tumours in the head of the pancreas are more likely to cause jaundice, whereas advanced tumours and tumours in the body of the pancreas are more likely to cause pain.

Surgery remains the best chance for a cure, but only a minority of patients receive any form of surgery (less than 15% of cases, usually tumours in the head of the pancreas). Pancreaticoduodenectomy (the "Whipple procedure") involves resection of the entire duodenum with a short section of the jejunum, the pancreatic head, and the gallbladder, excision of the common bile duct, and distal gastrectomy followed by reconstruction. Unfortunately, complications are common, morbidity is high and patient recovery is slow. The outcome in specialist centres is considerably better [17]. In total pancreatectomy, the entire pancreas as well as the duodenum, common bile duct, gallbladder, spleen and local lymph nodes are removed. The serum biomarker CA19-9 is elevated in pancreatic cancer and can be used to monitor curative resection. Symptoms and obstruction in non-resectable tumours can also be relieved by bypass surgery. In terms of chemotherapy, single-agent gemcitabine is still the current standard of treatment for most pancreas cancer. Combinations of radiation plus 5-flourouracil or gemcitabine are in use to control local spread. A number of clinical investigations of combined therapies and multimodality approaches are currently underway in the USA and other countries [18,19]. Progress has been very slow and at times disappointing, but it is hoped that with continued understanding of the molecular pathogenesis of pancreas cancer along with clinical trials of new therapeutic approaches [11] the outlook for pancreas cancer patients will improve in the coming years.

Hereditary condition	Gene (chromosome)	Lifetime risk of pancreas cancer
Hereditary pancreatitis	*PRSS1* (7q35)	25–40%
Familial atypical multiple mole melanoma (FAMMM)	*p16/CDKN2A* (9p21)	10–17%
Familial breast cancer	*BRCA2* (13q12) *BRCA1* (17q21)	5% 1%
Fanconi anaemia syndrome (young-age-onset pancreatic cancer)	*FANCC* (9q22) *FANCG* (9p13)	Unknown
Ataxia telangiectasia (heterozygotes)	*ATM, ATB*, others (11q22-q23)	Unknown
Peutz-Jeghers syndrome	*STK11/LKB1* (19p13)	30-60%
Hereditary non-polyposis colorectal cancer (HNPCC)	*MSH2* (2p15) *MLH1* (3p25) *PMS2* (7p1) *MSH6* (2p16)	<5%
Cystic fibrosis (heterozygotes)	*CFTR* (7q31)	Unknown; rare
Familial pancreatic cancer (3 or more first-degree relatives with pancreatic cancer)	Unknown	16%

Table 5.5.1 *Table of hereditary syndromes with lifetime risk of pancreatic cancer*

Gene	Chromosome	Mechanism of alteration	% of cancers
Oncogenes			
KRAS2	12p	Point mutation	>90
CMYC	8q	Amplification	20-30
MYB, AKT2, AIB1, EGFR	6q, 19q, 20q, 7p	Amplification	10-20
ERBB2 (Her/2-neu)	17q	Overexpression	70
BRAF	7q	Point mutation	Rare
Tumour suppressor genes			
P16/CDKN2A	9p	Homozygous deletion Loss of heterozygosity and intragenic mutation Promoter hypermethylation	40 40 15
TP53	17p	Loss of heterozygosity and intragenic mutation	50-75
DPC4/SMAD4	18q	Homozygous deletion Loss of heterozygosity and intragenic mutation	35 20
BRCA2	13q	Inherited mutation and Loss of heterozygosity	5-10
LKB1/STK11	19p	Loss of heterozygosity and intragenic mutation Homozygous deletion	5-10
ACVR1B	12q	Homozygous deletion	5-10
TGFBR1, TGFBR2	9q, 3p	Homozygous deletion	5
BRCA1	17p	Inherited mutation	<5
MKK4	17p	Homozygous deletion, Loss of heterozygosity and intragenic mutation	<5
RNASEL	1q	Inherited mutation	1-3
DNA mismatch repair			
MSH2, MLH1	2p, 3p	Inherited mutation Methylation?	<5

Table 5.5.2 *Genes modified in pancreas cancer*

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WEBSITES

NCI Pancreatic Cancer Homepage:

http://www.cancer.gov/cancer_information/cancer_type/pancreatic

The John Hopkins Medical Institution, Pancreatic Cancer Homepage:

http://www.path.jhu.edu/pancreas/

CANCER INSTITUTE PROFILE: Oncology Institute of Southern Switzerland (IOSI)

The Oncology Institute of Southern Switzerland (IOSI) is a multisite oncology institute that comprises all the facilities related to cancer treatment at different public hospitals. Among them, the Ospedale San Giovanni in Bellinzona harbours the most important assets: the radiotherapy centre, the PET-scan, the haematology division and the inpatient ward for palliative treatment, as well as 30 beds for chemo-radiotherapy and for aggressive chemotherapy treatment, including autologous bone marrow transplantation.

The institute sees 2500 new patients a year, representing a comprehensive care centre that also includes a cancer register, a central library and facilities for clinical and translational research. Three of Europe's major cancer research structures have their operational offices at IOSI: IELSG (International Extranodal Lymphoma Study Group), IBCSG (International Breast Cancer Study Group), and SENDO-SAKK (coordinating Phase I trials).

website: www.iosi.ch

Oncology Institute of Southern Switzerland
Ospedale San Giovanni
CH-6500 Bellinzona, Switzerland

CANCER INSTITUTE PROFILE: National Colorectal Cancer Roundtable

The (USA) National Colorectal Cancer Roundtable, cofounded by the American Cancer Society and the US Centers for Disease Control and Prevention, is a national coalition of public, private and voluntary organisations, and invited individual experts dedicated to reducing the incidence of and mortality from colorectal cancer through coordinated leadership, strategic planning and advocacy. The Roundtable works as a catalyst to stimulate key member organisations to act earlier, act more effectively, and act collaboratively in the area of colorectal cancer.

The Roundtable taps into the expertise of its members to create tools, conduct studies, develop consensus and support projects that can advance the community's overall work in this area. Many of these projects, such as the creation of the Blue Star symbol, the development of a colorectal cancer Clinician's Guide and Toolbox, and the development of a study to measure how increasing screening rates impacts downstream costs, fill a key need among collaborating partners. Such initiatives create a multiplier effect in the community's work against this disease.

website: www.nccrt.org

5.6 Gallbladder Cancer

Summary

> Gallbladder cancer incidence is higher in women than in men in most areas of the world. The highest incidence areas are Chile, India and some other countries of Latin America, Asia and central Europe

> Incidence and mortality have been declining in most areas of the world over the last few decades, mainly due to the increasing frequency of cholecystectomy

> Gallbladder anomalies and cholelithiasis are the major risk factor for GC

> Other risk factors are obesity and selected aspects of diet, linked to gallstones

The biliary tract consists of an interconnected system of intra- and extrahepatic ducts that transport bile secreted from the liver to the digestive tract. The gallbladder, lying just under the liver, is an important organ of the biliary system, receiving, storing and then releasing the bile through bile ducts into the duodenum to help in the digestion of fat. Gallbladder cancer (GC) is the most common type of cancer of the biliary tract [2]. GC is a relatively rare neoplasm, and despite being a non-sex-related cancer, is more frequent among women than among men in most populations. Detection of GC is difficult because symptoms and signs of GC are not specific and often appear late in the clinical course of the disease. For this reason, diagnosis is generally made when the cancer is already in advanced stages, and prognosis for survival is less than 5 years in 90% of cases [3].

Descriptive epidemiology

Gallbladder cancer incidence is characterised by worldwide variation (Figure 5.6.1), being low in several European countries and the USA, relatively high in selected central European countries, and very high in some countries of Latin America and Asia. GC has been shown to be the most common cause of cancer death among women in some areas of Chile[4].

According to incidence rates recorded by cancer registries in the mid-1990s, the highest incidence rate worldwide occurs in women from Delhi, India (21.5/100 000), followed by South Karachi, Pakistan (13.8/100 000) and Quito, Ecuador (12.9/100 000). Cancer registries reporting high GC incidence rates were in East Asia (Korea and Japan), Eastern Europe (including Slovakia, Poland and the Czech Republic) and South America (Colombia). In Western Europe, elevated incidence rates were shown in Granada, Spain. Although systematically lower than in women, high incidence rates among men (ranging between 4.4 and 8.0/100 000) were found in some areas of Asia and Eastern Europe [4]. Most registries from Northern Europe indicate low incidence rates (below 3/100 000 women and 1.5/100 000 men), with the partial exception of Sweden.

The female to male (F/M) incidence ratio of GC incidence rates varied greatly; it was >5 in several high-risk areas (e.g. Pakistan, India, Colombia and Spain) as well as in a few selected low-risk areas (e.g. Denmark), but was typically between 2 and 3 in the majority of countries. F/M ratio was close to 1 in Korea, Japan and some parts of China [4].

Incidence rates of GC in various ethnic groups from selected cancer registries in the USA confirmed the worldwide pattern (Figure 5.6.2), as GC was substantially more frequent among Hispanic than non-Hispanic white women, and remarkably elevated among Korean and Chinese men. Very high incidence was also among Native Americans in New Mexico. Also the F/M ratio was high among Hispanic whites, and close to 1 among Koreans, Filipinos, Japanese and Chinese [4].

Risk factors

The number of epidemiological which studies published on risk factors for GC has been limited because of 1) the rarity of GC in countries where most medical research is funded and performed, 2) the difficulties of histological identification of GC, 3) the lack of relevant animal models and tumour cell lines for GC, and 4) the lack of comprehensive national or international registries for information on GC cases [2]. Risk factors for GC include genetic predisposition, geographic variation and ethnicity, female gender, chronic inflammation, congenital abnormalities, low socio-economic status, low frequency of cholecystectomy for gallbladder diseases and exposure to certain chemicals.

Selected major risk factors for GC are reported in Table 5.6.1. History of gallstones and cholecystitis are considered the major risk factors for GC. Several cohort and case–control studies found strong associations between history of benign gallbladder diseases (mainly gallstones) and GC risk. Relative risks (RRs) from case-control studies varied greatly, and this variation probably results from differences in study design and methods and definitions used to collect information on gallstones. The summary RR for history of gallstones was 4.9 [95% CI 3.3–7.4], and was 2.2 (95% CI 1.2–4.2) among cohort studies and 7.1 (95% CI 4.5–11.2) among case–control studies [4].

Cholesterol and mixed gallstones (containing >50% of cholesterol) account for 80% of all gallstones, and pigment stones (composed largely of calcium bilirubinate) account for the remaining fraction. The aetiology of cholesterol gallstones is thought to involve the interaction of genetic factors (e.g. modification of MDR3 and CYP7A1 genes, and numerous lithogenic genes) and several environmental factors (age, female gender, obesity, multiple pregnancies, family history of gallstones and low levels of physical activity) [2].

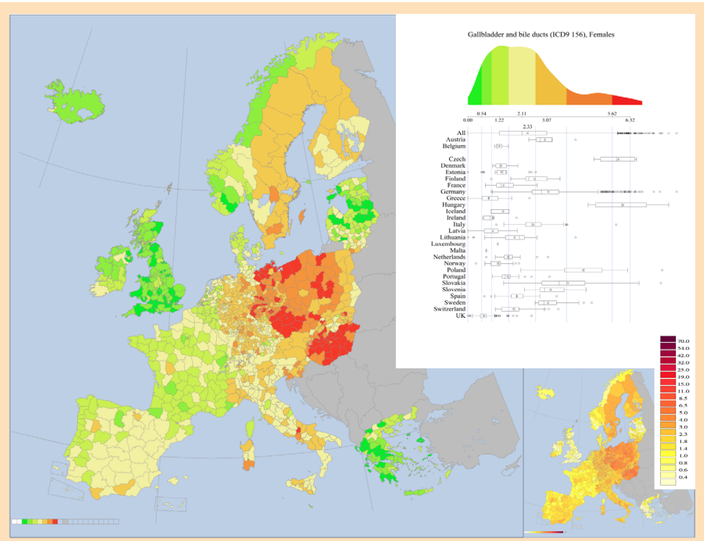
The worldwide distribution of gallstone prevalence shows a strong geographic and ethnic variation, and a positive correlation with the incidence rates of GC. High gallstone prevalence (≥50%) among women was found among American Indians in the USA, and among Mapuche Indians in Chile, both populations presenting very high GC incidence rates. Other areas with high or intermediate prevalence of gallstones were identified in South America, and in Eastern and Western Europe. Very little is known about some regions of the world, such as India, where a high incidence of symptomatic gallstones has been observed, but results from ultrasound-based studies are not available. Low-risk areas for gallstones (i.e. where prevalence is <10% among women) included African countries, but also Thailand, China, Korea and Japan which reported high GC incidence rates [4].

Only a small proportion (1–3%) of patients with gallstones develop GC; thus other risk factors are thought to play a role [5].

Obesity and overweight are major risk factors for gallstones, and large cohort studies show that the association of GC with obesity is one of the strongest seen for any cancer site (Table 5.6.2). Compared with individuals of 'normal weight', the summary RR of GC for those who were overweight was 1.2 (95% CI 1.0–1.3) and for those who were obese the OR was 1.7 (95% CI 1.5–1.9). The association with obesity was stronger for women than for men [4,6]. The influence of obesity, however, like the influence of belonging to certain ethnic groups, seemed to be at least in part mediated by an increased predisposition to develop gallstones.

The overall increased frequency of GC in women suggests a possible role for hormonal factors, especially in the formation of cholesterol gallstones. High parity and high number of pregnancies, again recognised risk factors for gallstones, have been related to increased GC risk. Among parous women, older age at first birth or pregnancy has been associated with reduced risk of GC. Oral contraceptive use was not materially related to GC risk; neither were duration of use and time since first and last use. Inconsistent results were obtained for the association of GC risk with menopausal status and HRT use. Thus, the precise role of female hormones remains unresolved, but it is unlikely that they play a major role [4,7].

Chronic infection of the gallbladder may contribute to the onset of GC, *per se* or via gallstone formation. Most available evidence implicates *(S.)-typhi* and *paratyphi* and *Helicobacter* species [5]. Eleven epidemiological studies concerning the relation between *Salmonella (S.) typhi* and *paratyphi* and GC have been published. The summary RR for typhoid infection was 4.8 (95% CI 1.4–17.3), and rose to 10.2 (95% CI 2.0–50.9) after exclusion of studies based on self-reported diagnosis of infection. The summary RR for case-control studies was 2.6 (95% CI 1.1–6.1), which rose to 5.2 (95% CI 2.1–12.7) after exclusion of studies based on self-reported diagnosis of infection [4]. All epidemiological studies on *S. typhi* and *paratyphi* and GC based on biological markers, such as serum Vi antigen or the presence of the bacteria in bile specimens, found a significant positive association between *S. typhi* and *paratyphi*



European Map 5.6.1 *The distribution of gallbladder and bile duct cancer mortality in women in Europe was quite unlike that for any other form of malignant disease, with generally lower than average rates in the west of Europe, including Iceland, Norway, the United Kingdom and Ireland, Denmark, The Netherlands, Belgium, France, Spain and Portugal. Rates were above average in a band across most of the centre of Europe, extending from Italy in the south through Germany to Sweden in the north. The high rates also extended eastwards into eastern Austria, the Czech Republic, Hungary and parts of Slovakia in both males and females, and into Poland for females [1].*

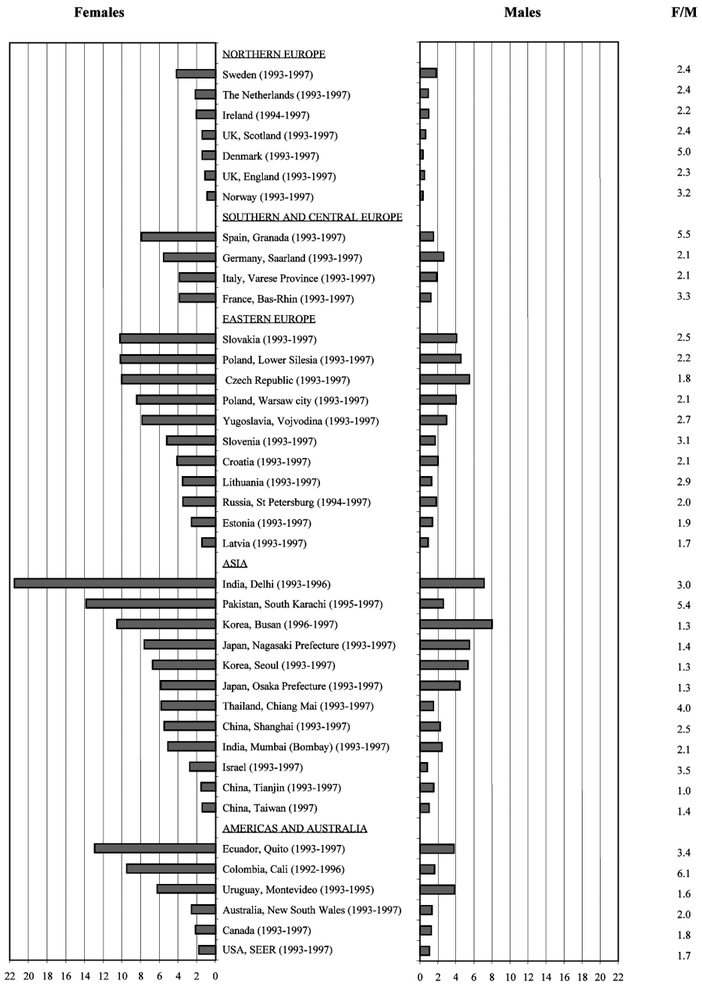


Fig. 5.6.1 *Age-standardised incidence rates* per 100 000 (world population) and female/male ratio for gallbladder cancer in 40 selected areas*
**Truncated for individuals aged 35–74*

carrier status and GC risk. Also *Helicobacter bilis* and *pylori* have been identified in bile specimens and associated with risk of biliary tract cancer (RR 4.3; 95% CI 2.1–8.8) [4].

Most studies of infection and GC to date have had limited power (no more than 15 exposed cases), have lacked well-matched controls (with or without gallstones), and have been hampered by a lack of standardised and non-invasive methods for the detection of these infectious agents.

With respect to dietary factors, in the multinational collaborative study from the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) Programme of the International Agency for Research on Cancer (IARC), which included 169 cases and 1515 controls [8], the strongest direct associations with GC risk were for total carbohydrate intake (RR 11.3 for the highest quartile versus the lowest quartile) and total energy intake (RR 2.0), with inverse associations for dietary intake of fibre, vitamin B6, E and C (RRs ranging from 0.4–0.5). However, apart from obesity, there is no nutritional or dietary factor consistently related to GC risk.

Conclusions and perspectives

It has been proposed that there are two main pathways to GC [2]. The predominant pathway involves gallstones and resultant cholecystitis, and affects women to a greater extent than men. The other pathway involves an anomalous pancreatobiliary duct junction (APBDJ), a congenital malformation of the biliary tract that is more prevalent in Japan, Korea, and possibly China than in Western countries. With APBDJ, the pancreatic and common bile ducts join together before reaching the duodenal wall, allowing reflux of secretions of the exocrine pancreas into the gallbladder. APBDJ appears to be associated with papillary carcinoma of the gallbladder, which is less invasive and fatal than other carcinomas of the gallbladder [2].

Author, Year (Country)		RR (95% CI)	Adjustment
History of benign gallbladder diseases[1]			
Cohort studies[2]			
Maringhini, 1987 [Ann Intern Med 107: 30-35] (USA)		2.8 (0.9-6.6)	Age and sex
	Men	8.3 (1.0-30.0)[3]	Age and sex
	Women	2.0 (0.4-5.7)[3]	Age and sex
Chow, 1999 [Br J Cancer 79: 640-644] (Denmark)		3.6 (2.6-4.9)	Age and sex
Yagyu, 2004 [Cancer Sci 95: 674-678] (Japan)	Men	1.2 (0.3-4.7)	Age
	Women	1.1 (0.4-2.9)	Age
Case-control studies[4]			
Lowenfels, 1985 [J Natl Cancer Inst 75: 77-80] (USA)	Non-Indians	4.4 (2.6-7.3)	Age, sex, centre, alcohol, smoking, education and response status
	Indians	20.9 (8.1-54.0)	Age, sex, centre, alcohol, smoking, education and response status
Nervi, 1988 [Int J Cancer 41: 657-660] (Chile)		7.0 (5.9-8.3)	Age, sex, country
WHO, 1989[5] [Int J Epidemiol 18: 309-314]		2.3 (1.2-4.4)	None reported
Kato, 1989 (Japan) [Jpn J Cancer Res 80: 932-938]		34.4 (4.51-266.0)	None reported
Zatonski, 1997[6] [J Natl Cancer Inst 89: 1132-1138]		4.4 (2.6-7.5)	Age and sex
Okamoto, 1999 (Japan) [Am J Gastroenterol 94: 446-450]		10.8 (4.1-28.4)[7]	
Khan, 1999 (USA) [Am J Gastroenterol 94: 149-152]		26.6 (7.0-101.4)	Sex, age, ethnicity, smoking and socioeconomic status
	Women	28.9 (4.7-173.0)[3]	Age, ethnicity, socioeconomic status, hysterectomy, menopause, parity, diabetes and smoking
Family history of benign gallbladder diseases			
Case-control studies[8]			
Kato, 1989 (Japan) [Jpn J Cancer Res 80: 932-938]		3.0 (1.3-6.5)	None reported
Strom, 1995 (Bolivia, Mexico) [Cancer 76: 1747-1756]		3.6 (1.3-11.4)	Age, sex and hospital
Family history of gallbladder cancer[9]			
Cohort studies[10]			
Goldgar, 1994 (USA) [J Natl Cancer Inst 86: 1600-1608]	First-degree relatives	2.1 (0.2-6.1)	Age at diagnosis
Hemminki, 2003 (Sweden) [Gut 52: 592-596]	Parents	5.1 (2.4-9.3)	Age, sex, region, period and socioeconomic status
	Offspring	4.1 (2.0-7.6)[3]	Age, sex, region, period and socioeconomic status
Case-control studies			
Fernandez, 1994 (Italy) [Cancer Epidemiol Biomarkers Prev 3: 209-212]	First degree relatives	13.9 (1.2-163.9)	Age, sex, residence and education

Table 5.6.1 *Relative risks (RR) with corresponding 95% confidence intervals (CI) of gallbladder cancer for the history of selected diseases*
[1] Summary RR for all studies was 4.9 (95% CI: 3.3–7.4) and heterogeneity test between studies was χ_6^2 = 57.361, p < 0.001. [2] Summary RR for cohort studies was 2.2 (95% CI: 1.2–4.2) and heterogeneity test between studies was χ_3^2 = 6.918, p 5 0.075. [3] Not included in the summary estimates.[4]Summary RR for case-control studies was 7.1 (95% CI: 4.5–11.2) and heterogeneity test between studies was χ_2^2 = 28.540, p < 0.001. [5]Chile, China, Colombia, Israel, Kenya, Mexico.[6]Australia, Canada, Netherlands, Poland.[7]Estimated from available data.[8]Summary RR for case-control studies was 3.2 (95% CI: 1.7–6.1) and heterogeneity test between studies was χ_1^2 = 0.007, p = 0.791.[9]Summary RR for all studies was 4.8 (95% CI: 2.6–8.9) and heterogeneity test between studies was χ_2^2 = 1.647, p 5 0.439. [10]Summary RR for cohort studies was 4.5 (95% CI: 2.4–8.5) and heterogeneity test between studies was χ_2^2 = 0.895, p = 0.344.
Taken from Randi et al, 2006

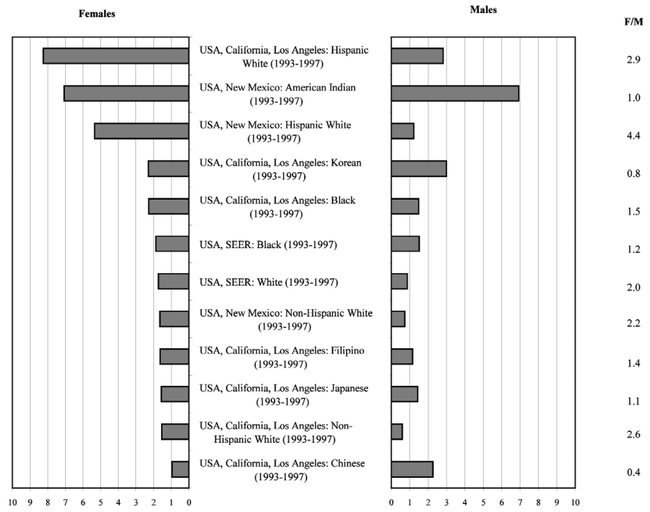


Fig. 5.6.2 *Age-standardised incidence rates* per 100 000 (world standard population) and female-to-male (F/M) ratio for gallbladder cancer in selected ethnic groups of the USA*
**Truncated for individuals aged 35–74.*

Gallbladder cancer is a highly lethal and aggressive disease with a poor prognosis, but radical surgery can be curative when appropriate clinical assessments are performed preoperatively. Behavioural interventions meant to prevent overweight and obesity are difficult to implement, but have the added benefit of preventing diabetes mellitus, cardiovascular diseases and some cancers in addition to GC. If the etiologic roles of *S. typhi* and *paratyphi*, *Helicobacter* species or other agents were better demonstrated, the benefits of prevention and treatment of these infections could be substantial. Diagnosis of gallstones and removal of the gallbladder represent the keystone to GC prevention in the majority of the populations at high risk.

Fig. 5.6.3 *Gallbladder carcinoma with a white, irregular cut surface next to a large gall stone*

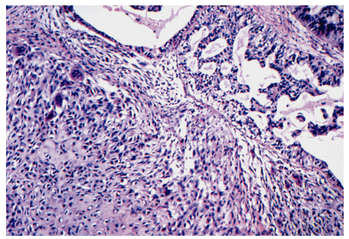


Fig. 5.6.4 *Carcinosarcoma of gallbladder. The tumour shows malignant glandular elements and a sarcomatous component with osteoid formation*

Author, Year (Country)	Reference category	Highest category		RR (95% CI)	Adjustment
Cohort studies					
Moller, 1994 [Eur J Cancer 30A: 344-350] (Denmark)	Non obese	Obese	Men	0.5 (0.1-1.8)	None reported
	Non obese	Obese	Women	1.4 (0.9-2.1)	None reported
Wolk et al, 2001 [Cancer Causes Control 12; 13-21] (Sweden)	Non obese	Obese	Men	0.9 (0.1-3.4)	Age and calendar year
	Non obese	Obese	Women	1.7 (1.1-2.5)	Age and calendar year
Calle et al, 2003 [N Engl J Med 348: 1625-1638] (US)	18.5-24.9	30.0-34.9	Men	1.8 (1.1-2.9)	Age, race, education and many (8) lifestyle variables
	18.5-24.9	30.0-34.9	Women	2.1 (1.6-2.9)	Age, race, education and many (8) lifestyle variables
Samanic et al, 2004 [Cancer Causes Control 17: 901-909] (US)	Non obese	Obese	White men	1.7 (1.1-2.6)	Age and calendar year
	Non obese	Obese	Black men	0.9 (0.2-3.9)	Age and calendar year
Kuriyama et al, 2005 [Int J Cancer 113: 148-157] (Japan)	18.5-24.9	25.0-27.4	Men	0.5 (0.1-3.9)	Age and many (11) lifestyle and reproductive variables
	18.5-24.9	≥30	Women	4.5 (1.4-14.2)	Age and many (11) lifestyle and reproductive variables
Oh et al, 2005 [J Clin Oncol 23: 4742-4754] (Korea)	18.5-22.9	≥27	Men	1.3 (0.7-2.2)	Age, area of residence, smoking, physical activity, alcohol
England et al, 2006 [Cancer Causes and control 16: 987-996] (Norway)	18.5-24.9	>30	Men	1.4 (1.0-1.9)	Age and birth cohort
	18.5-24.9	>30	Women	1.9 (1.6-2.2)	Age and birth cohort
Samanic et al, 2006 [Cancer causes and control 17: 901-909] (Sweden)	18.5-24.9	>30	Men	1.4 (0.7-2.7)	Age and smoking
Case-control studies					
Moerman, 1994 [Int J Cancer 57: 146-153] (Netherlands)	<27	≥27	Women	1.4 (0.7-2.6)*	Subjects frequently matched for age and sex
Strom, 1995 [Cancer 76: 1747-1756] (Bolivia, Mexico)	<24	>28	BMI average	1.6 (0.4-6.1)	Age and sex
	<25	>29	BMI maximum	2.6 (0.5-18.6)	Age and sex
Zatonski, 1997 [J Natl Cancer Inst 89: 1132-1138] (†)	I quartile	IV quartile	Men	1.0 (0.3-2.8)	Age, centre, alcohol, smoking, education and response status
	I quartile	IV quartile	Women	2.1 (1.2-3.8)	Age, centre, alcohol, smoking, education and response status
Serra, 2002 (Chile)	< 24.9	> 30		0.9 (0.4-1.8)	Age, sex, gallstone disease

Table 5.6.2 *Relative risks (RR) with corresponding 95% confidence intervals (CI) of gallbladder cancer for highest vs lowest category of body mass index (BMI)*
**Estimated from available data 1Australia, Canada, Netherlands, Poland*
Updated from Randi et al, 2006

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CANCER INSTITUTE PROFILE:
The University of Texas M. D. Anderson Cancer Center

The University of Texas M. D. Anderson Cancer Center was created by the Texas Legislature in 1941 and named one of the first three Comprehensive cancer centres by the National Cancer Act of 1971. It was ranked in 2007 by *U.S. News & World Report* as the top American hospital for cancer care. M. D. Anderson, which receives more research grants from the US National Cancer Institute than any other institution, spent in excess of US $465 million on research last year. Almost 84 000 patients were served in Houston-based facilities that include 512 inpatient beds and ambulatory units where more than 922 000 outpatient visits and treatments were provided. A record 12 000 patients participated in therapeutic clinical trials in 2007. M. D. Anderson awards bachelor's degrees in seven allied health disciplines and jointly confers master's and Ph.D. degrees in biomedical sciences. It also operates a two-unit Science Park in central Texas, has affiliations with caregivers as far away as Madrid, Spain, and has sister institution agreements in Asia, Europe, and Central and South America.

Website: www.mdanderson.org

5.7 Colorectal Cancer

Summary

> Colon and rectal cancers account for approximately 9.4% of total worldwide cancer cases, equivalent to about 1 million new cases, with a similar number of cases in men and women for colon cancer and a male predominance for rectal cancer

> Worldwide, there is at least a 25-fold variation in occurrence of colorectal cancer, with high incidence rates in affluent societies (accounting for 65% of all new cases)

> Differences in diet and lifestyle, particularly alcohol intake and physical inactivity, are believed to account for a large proportion of this variation

> Familial clustering has a genetic basis, usually through familial adenomatosis polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC)

> Randomised trials have demonstrated the efficacy of faecal occult blood testing in reducing mortality from colorectal cancer. Trials of sigmoidoscopy are approaching completion. Colonoscopy is the most reliable means for early detection and prevention of colorectal cancer by removal of adenomatous polyps

> Improved treatment has resulted in a five-year survival rate of about 50%, although this rate varies considerably worldwide based on available treatment options and between developed and developing areas

Incidence of colorectal cancer ranks fourth in men (after lung, prostate and stomach) and third in women, after breast and cervix uteri, with over 1 million new cases occurring every year worldwide [1]. The majority of cancers occurring in the colon and rectum are adenocarcinomas, which account for more than 90% of all large bowel tumours.

Colorectal cancer incidence shows wide geographical variation, with higher rates observed in New Zealand, Australia, North America, Europe and more recently Japan, and lower rates reported in Asia and Africa. Overall, similar patterns are observed in the two sexes, although colon and rectal cancer rates are 20% and up to 50% higher, respectively, in men than women. Incidence rates of colorectal cancer are increasing in countries where overall risk was formerly low (especially in Japan, but also elsewhere in Asia), while in high-risk countries, rates are either gradually increasing, stabilising (Northern and Western Europe) or declining with time (North America) [1].

Five-year survival estimates (in men) have been reported to be 65% in North America and 54% in Western Europe, 34% in Eastern Europe, and 30% in India. Globally, mortality is approximately one half that of incidence (about 529 000 deaths in 2002 in men and women combined). In terms of prevalence, colorectal cancer is the second most common cancer worldwide next to breast cancer [1]. The ratio of colon to rectal cancer incidence is about 2:1 or more, with higher values in North America and Australia/New Zealand, whereas in lower-risk countries the incidence is similar between the two anatomical sites. Overall, higher colon to rectal cancer ratios are observed in women.

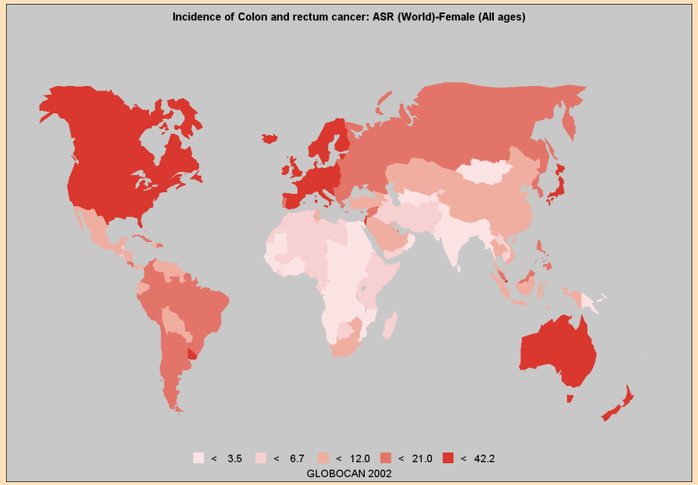
Colorectal cancer incidence presents a large economic burden worldwide, indicating a high benefit-cost ratio for research investment and the development of appropriate prevention and screening strategies.

Etiology and prevention

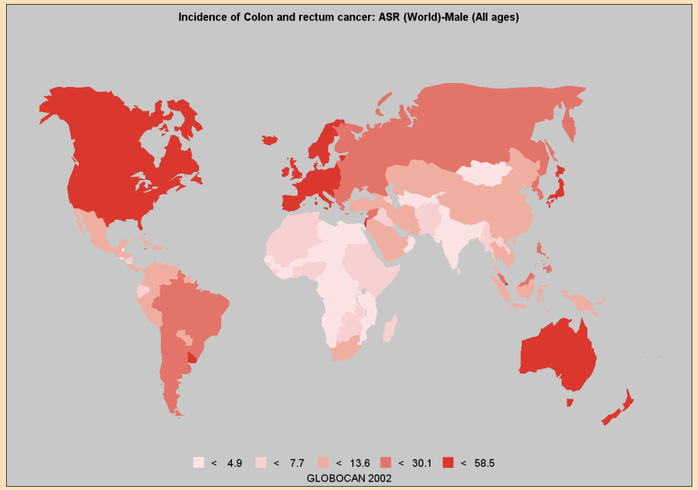
Initially, colorectal cancer was thought to arise primarily via a multistep process highlighted by changes in cell proliferation patterns with loss of growth control leading to sequential development of pre-malignant lesions (adenoma-carcinoma sequence) and involving several genetic changes (Figure 5.7.1). However, the underlying genetics and molecular mechanisms of colorectal cancer development are being continually refined. Recent studies of the genomes of a small series of colorectal tumours suggest that although a large number of genes are mutated, only a small proportion are responsible for driving tumour progression and growth [4]. It has been suggested that most colorectal tumours develop via three somewhat distinct pathways (suppressor, mutator and methylator), each of which appears to be associated with various genetic changes [5]. Some recent evidence is also suggestive of different etiologies for cancers based on their anatomical location in the colorectum [6]. The majority (~75%) of colorectal cancers are sporadic, arising from somatic mutations and clonal evolution at the tumour site. The remainder of cases are comprised of hereditary syndromes (familial adenomatous polyposis [FAP; 1%] and hereditary nonpolyposis colorectal cancer [HNPCC; 4–7%]), family/personal history of the disease or adenomatous polyps (15–20%), or other high-risk conditions (inflammatory bowel diseases, previous diagnoses for cancers of the ovary, endometrium, breast, bile duct, pancreas, stomach; 1%). HNPCC cancers do not usually develop via the adenoma-carcinoma sequence and are highlighted by mutations in mismatch repair genes and microsatellite instability. Genetic predisposition and age are the main non-modifiable risk factors for this disease.

Evidence from migrant studies has shown that populations moving from low- to high-risk areas rapidly reach the higher level of risk of the adopted country, indicating that lifestyle and dietary factors likely play an important role in colorectal cancer aetiology. Indeed, of all common cancers, a dietary influence on colorectal cancer risk is the most plausible because the colorectal mucosa is in direct and constant contact with food components and is also exposed to diet-induced metabolic and physiologic changes. However, the complexities of various dietary patterns, macro/micro-nutrient composition of foods, multiple potential interactions between nutrients, hormonal effects, gene-diet interactions and methodological issues make the study of the diet-colorectal cancer connection inherently difficult. Nonetheless, numerous dietary risk factors have been identified from experimental platforms as well as retrospective and prospective epidemiological studies. The weight of the existing evidence suggests that higher intake of total energy [7], red/processed meats [8,9] and alcohol [10] are all associated with increased risk of colorectal cancer whereas higher intake of fruits and vegetables may only moderately reduce the risk [11,12]. A colorectal cancer preventive role of dietary or cereal fibre is debatable [13], despite recent findings suggesting a negative association with high intakes [14]. Higher intake of calcium and Vitamin D has been reported to be colorectal cancer protective, but except for modest findings for calcium supplementation in some intervention studies of adenoma recurrence [15,16], evidence is still lacking for any firm conclusions. Much further research is required to elucidate the role of other compounds, foods, food components or their derivatives that may have effects that are colorectal cancer protective (folate, antioxidants, vitamins C/E, magnesium, selenium, phytochemicals, phytoestrogens, butyrate, resistant starches, tea/coffee, fish, whole grains, low glycemic index foods) or promotive (insulin, dietary carcinogens, secondary bile acids, iron, heterocyclic amines, refined sugars, high glycemic index foods). In addition, there are many complex interactions between environmental, dietary and genetic factors that may well modify colorectal cancer risk.

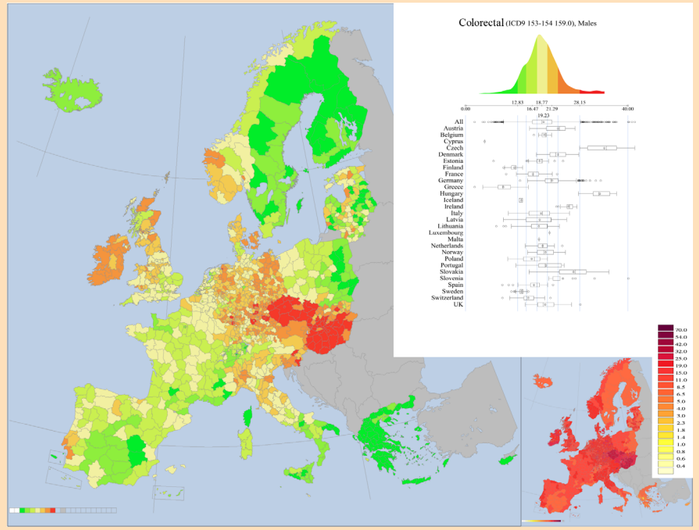
Among lifestyle factors, obesity has been suggested to be associated with an increased risk of colorectal cancer, although effects may vary by anatomical site and gender [17,18]. Physical inactivity has also been associated with an increased risk, although primarily for colon and less clearly for rectal cancer[20,21]. Thus, regular physical activity and avoidance of calorie over-consumption may represent two of the most effective ways of preventing this



World Map 5.7.1



World Map 5.7.2



European Map 5.7.1 *It is apparent from the maps that the pattern of geographical distribution in both men and women is substantially the same, with a broad band of high rates running east-west across the middle of Europe. Higher-than-average rates were found in Ireland and the northern parts of the United Kingdom, Denmark, southern parts of Norway, Germany and eastern Austria. Rates were also above average in parts of northern Italy and southern Portugal–more markedly in males than in females.*

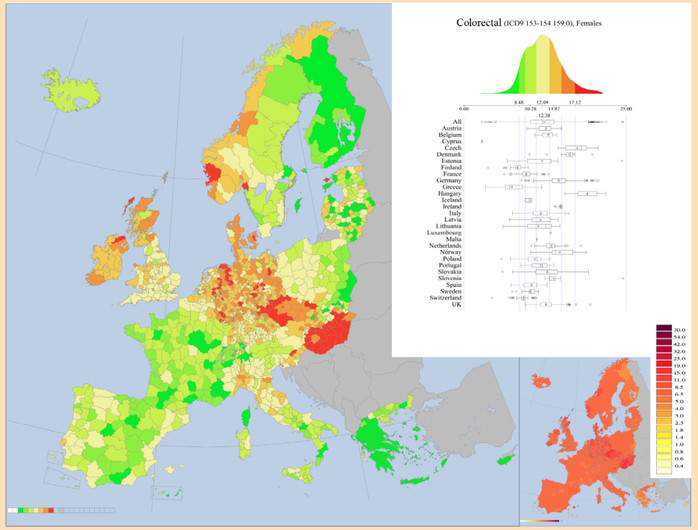
disease. Cigarette smoking is another major modifiable lifestyle factor that recent studies suggest is involved in the colorectal carcinogenesis process [22], although an induction period of four decades has been suggested [23].

Evidence from observational studies indicates that long term use of non-steroidal anti-inflammatory drugs (NSAIDS), particularly aspirin, may reduce the risk of colorectal cancer [24-27]. Although randomised controlled trials on the risk of colorectal adenoma indicate that these medications may have anti-cancer effects [28-32], results from trials actually focusing on colorectal cancer risk have been inconsistent. Trials providing lower-dose aspirin failed to show a protective effect [33-35], while those providing higher doses show a protection against colorectal cancer after at least 5 years of treatment, with a latency period of about 10 years [24]. Nevertheless, recommendations to general populations on NSAID or aspirin use for cancer prevention are premature given that use of these medications is accompanied by many side effects and may increase the risk of other serious medical conditions, necessitating close medical supervision. Thus, their use as chemopreventive agents may only be practical in those at very high risk of developing colorectal cancer (e.g. FAP patients). In women, use of hormone replacement therapy (HRT) has been associated with a reduced risk of colorectal cancer but also with concomitant increases in the risk of breast cancer, and possibly coronary heart disease and thromboembolic events, making its use in any colorectal cancer prevention strategy impractical. Removal of adenomatous polyps has also been found to reduce disease risk, but in practice it is only applicable to those undergoing invasive screening.

As with many cancers, early detection of precancerous lesions and rapid, effective treatment of early colorectal tumours appear to be key points of screening and treatment strategies, not only for those at high risk of the disease, but also for general populations at large. Nonetheless, the primarily sporadic nature of the disease indicates that a reduction in colorectal cancer incidence worldwide can best be achieved by effective primary prevention and changes in modifiable risk factors.

Conclusions

The worldwide variations in colorectal cancer risk suggest a large contribution of dietary and lifestyle factors to the etiology of the disease. Most colorectal cancers are sporadic adenocarcinomas arising via a multistep process that involves identifiable pre-cancerous lesions. Although it is understood that regular screening and removal of adenomatous polyps are effective prevention strategies, they are expensive and necessitate close medical supervision. The most important lifestyle changes for disease prevention appear to be weight reduction, physical activity and smoking cessation. The weight of the current literature suggests that a diet low in alcohol, red/processed meats, and refined carbohydrates, and higher in fruits, vegetables, whole grains and dietary fibre may assist in colorectal cancer prevention. Although NSAIDS and HRT have been shown to decrease colorectal cancer risk, their association with increased risk of other disease states makes their use as chemopreventive agents impractical, except in those at very high risk. Future research should focus on elucidating the role of complex gene-diet interactions, and identifying protective dietary and lifestyle patterns.



European Map 5.7.2 *The highest rates in men and women were in the Czech Republic, Slovakia, Slovenia and Hungary. Low rates were found in Finland, Sweden and Poland, and in much of southern Europe: Greece and southern Italy, France, Switzerland and Spain [Boyle and Smans, 2008].*

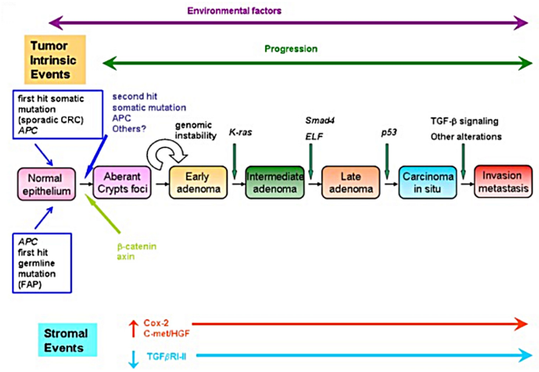


Fig. 5.7.1 *A schematic diagram of pathways that control colorectal tumourigenesis. Adapted from Misbra et al; Oncogene (2005) 24, 5775-5789*

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CANCER INSTITUTE PROFILE: Children's Cancer Research Institute (CCRI)

The Children's Cancer Research Institute (CCRI), in Vienna, Austria, conducts specialised research into the causes and improved treatment of malignant childhood diseases. It is supported by the St. Anna Kinderkrebsforschung, which was founded as a charity-based non-profit association in 1986 by a parents' initiative. The CCRI is closely associated with the St. Anna Kinderspital, the major children's hospital in Austria, which has a strong focus on oncology. The CCRI currently houses 9 research groups and a documentation department. Major areas of research comprise the study of functional consequences of genetic aberrations in childhood cancer, engineering of the immune system to fight the tumour and to improve haematopoietic stem cell transplantation, improved diagnosis and individualisation of therapy. In addition, the CCRI supports a number of clinical trials in paediatric cancer patients. The CCRI is involved in several European research projects and closely collaborates with the major paediatric research and treatment centres in Europe and the USA to advance scientific knowledge and improve outcomes in children with cancer.

website: www.ccri.at

5.8 Nasopharyngeal Carcinoma

Summary

> Nasopharyngeal carcinoma (NPC) is a significant health problem in southern and eastern Asia

> Preserved foods and EBV are key exposure factors involved in NPC etiology

> Genetic susceptibility is certainly a risk factor, but which genes are involved remains unclear

Nasopharyngeal carcinoma (NPC) is a malignant tumour arising in the epithelial lining of the nasopharynx. NPC presents most commonly among people of 40-55 years of age, but presentation in adolescence has also been observed. There is a gender bias, NPC being approximately 2-3 times more common in males than females. Treatment of this malignancy usually involves radiotherapy, either alone or in conjunction with chemotherapy, with a 5-year survival rate of approximately 60-65% and a slightly better prognosis in women than men [1]. WHO criteria classifies NPC into general histological subtypes: keratinizing squamous-cell carcinoma (WHO-I) and non-keratinising squamous-cell carcinoma. Non-keratinising squamous-cell carcinoma was previously subdivided into differentiated (WHO-II) and non-differentiated forms (WHO-III) but it has more recently suggested to be merged into a single broader category to account for overlap between the two [2]. A quite rare form, basaloid squamous-cell carcinoma, is also recognized [2]. Keratinizing squamous-cell carcinoma histology tends to be more common in Caucasian (non-endemic) populations [2], while non-keratinising squamous-cell carcinoma tends to be more prominent in Asian (endemic) populations [3].

Etiology

NPC incidence has an extremely heterogeneous geographical and ethnic distribution which is currently not explained. In high-resource nations NPC is generally a rare malignancy (incidence 3 <1/100 000/year). By contrast, relatively high rates are recorded across Asia where age-standardised incidence rates reach 20/100 000 among men [2,5-8] (Figure 5.8.1). Regions of Southern China contain the most clearly described high-risk areas, although similar high rates are reported across most of Southeast Asia. Moderately high rates have also been reported in Northern Africa and among natives of the Arctic region [4,7]. The Malaysian region of Sarawak has one of the highest incidences of NPC, where age-standardised rates of NPC were 13.5 and 6.5 among men and women, respectively. Rates among Chinese and Malays in Sarawak were similar to rates observed in these ethnic groups in Singapore. However, the Malaysian Bidayuh ethnic subgroup population appeared to have an exceptionally high incidence, reaching 31.5/100 000 and 11.8/100 000 among men and women respectively. These incidence levels represent the highest reported rates in any population, being approximately 50% higher than in Hong Kong (summarised in Figure 5.8.1), which has the next highest reported incidence rate [4]. The reason for this high risk in this particular ethnic subset is unclear, and other studies from other regions show relatively little difference between ethnic subgroups [8].

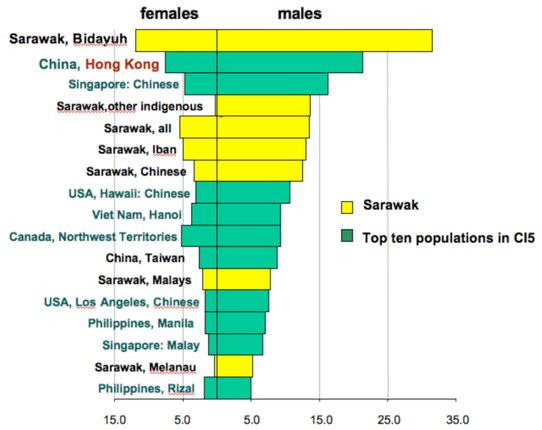


Fig. 5.8.1 *Age-standardised incidence rates of NPC across various populations in number of new cases per 100 000 population per year.[4]*

NPC risk exposures

Epstein-Barr Virus (EBV). From research dating to the 1960s, EBV has been consistently implicated in NPC susceptibility [9]. Titres of EBV antibodies have been found to be higher in NPC cases compared to control individuals [1,5]. The full-length EBV genome is found in the nuclei of almost all malignant NPC cells. The tight correlation between EBV and NPC has meant that there have been efforts to use EBV, or indicators of EBV-related activation, as early NPC detection tools [8,10]. The carcinogenic mechanisms underlying EBV infection and NPC susceptibility remain unclear. Infection with EBV is relatively ubiquitous in most populations, yet NPC incidence has an extremely heterogeneous geographical and ethnic distribution. It is therefore unlikely that EBV infection itself is a single cause of NPC. An underlying etiological model may be that some EBV strains may escape immune surveillance, with genetic susceptibility and other environmental factors playing an important role in this process.

Preserved foods. The consumption of foods preserved using high amounts of salt or other preservatives has also been consistently linked with NPC risk [6]. Epidemiological studies have consistently noted that consumption of fish

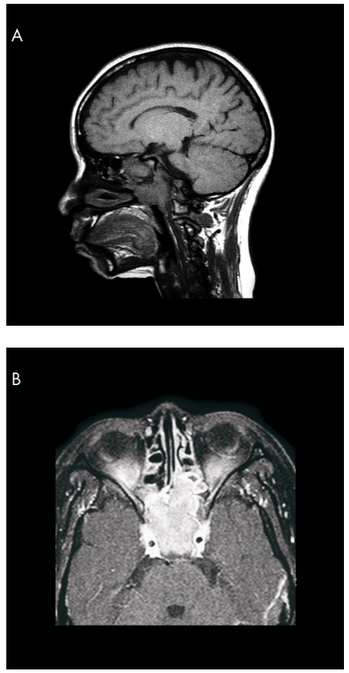
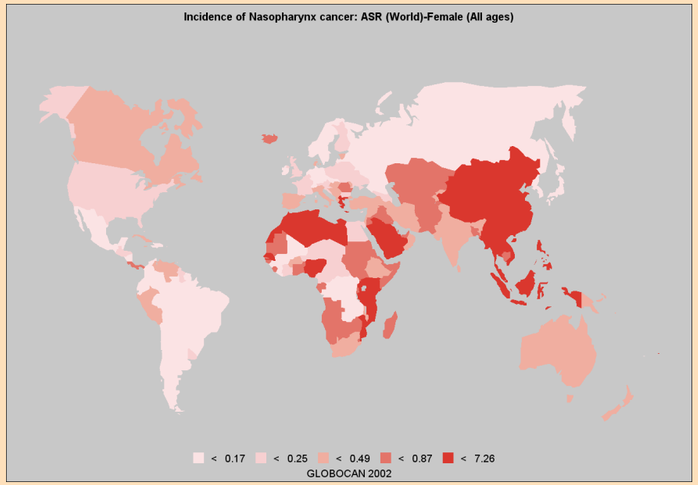
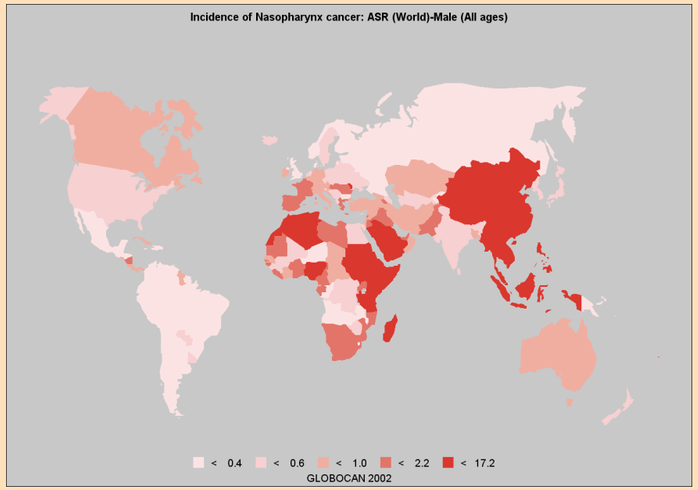


Fig. 5.8.2 *A and B: Magnetic resonance imaging of nasopharyngeal carcinoma*



World Map 5.8.1



World Map 5.8.2

preserved using high levels of salt conferred a 2-3-fold increase in NPC risk. This risk appears to be most apparent when such foods are consumed at early ages [1]. Although the evidence is somewhat less consistent, similar risks have been associated with other preservation processes [11]. The majority of the high-risk regions appear to use such preservation practices, notably in Southern China and South East-Asia (salted fish), and similarly in other at-risk populations such as North Africa (*quaddid*, rancid butter). Early-age exposure may have particular relevance to these populations as use of such foodstuffs as weaning foods is relatively common in many of the high-risk NPC populations.

The evidence that high-salt preservation techniques are implicated in NPC is also supported by experiments in animal models, with diets high in salted fish leading to occurrence of NPC in rats [12,13]. The carcinogenic mechanism is thought to be related to the food preservation process not being completely efficient, thus leading to a partial putrefaction of the food material. This partial putrefaction results in high levels of N-nitrosamines (N-nitrodimethlyamine (NDMA), N-nitropyrrolidine (NPYR) and N-nitrosopiperidine (NPIP)), which have been postulated to be carcinogens [14].

Tobacco, alcohol and other exposures. There is sufficient evidence to suggest that tobacco exposure increases risk of NPC, [15] with most studies reporting a 2-6 fold increase in risk for those exposed. Whether consumption of alcohol is involved in NPC risk is less clear [9], with some studies suggesting an increased risk, but most studies finding no association. Although again their role has not yet been clearly elucidated, occupations that result in exposure to chemicals and solvents, smoke fumes or wood dust have been suggested to play a role in NPC risk, particularly in Causasian populations [8].

Genetic susceptibility to NPC

Genetics appear to play an important role in susceptibility to NPC. Familial clustering appears common among NPC patients, with >5% of NPC cases reported to have a similarly affected first-degree relative [16]. The familial relative risk has been estimated to be in the region of 8-10 fold, [17] indicating that NPC has one of the most important genetic relative risks of all types of cancer [18]. Conclusions from migrant studies are also consistent with genetic risk, with second-and third-generation migrants from endemic regions maintaining an increased risk of developing NPC in low-risk areas [1].

Genes implicated in NPC susceptibility. The identity of the genes involved in susceptibility to NPC is far from clear. The most consistent line of evidence for genetic risk factors for NPC is the HLA Class I region, with increased risks being observed for both HLA-A and B variants in a number of studies [19,20]. Involvement of the HLA region and immunological response would also be consistent with the involvement of EBV in NPC susceptibility.

Family-based linkage analysis has also provided evidence of two other susceptibility loci. A family study based on 20 multicase families from Guangzhou, southern China has also been conducted, [21] showing LOD scores of up to 3.67 for the region 4p15.1-q12, suggesting the potential for a major susceptibility locus in this region. A subsequent study was based on 18 multiple-case families from Hunan Province, southern China, including 46 affected and 96 unaffected individuals, who were genotyped for 5 polymorphic markers in the region 4p15-q12, as well as for 8 markers on chromosome 3q and 7 markers on the short arm of chromosome 9q [22]. In contrast to the initial study by Feng et al. [21], no evidence for linkage was identified for polymorphic markers on chromosome 4. An NPC susceptibility locus was identified on 3p21 with a maximum LOD score of 4.18.

While some NPC susceptibility genes have been suggested under the linkage peaks on chromosomes 3, 4 and 6 [23-25], there have been no conclusive candidates, and considerable effort in this area is clearly required. Additional candidate genes deduced from the proposed function of the gene (e.g. *NAT2* or *CYP2A6*) have been examined, but again without conclusive evidence [8].

Conclusions

In the high-prevalence regions such as Southeast Asia and southern China, NPC makes a considerable contribution to the overall burden of cancer morbidity and mortality. Exposure to EBV and consumption of partially putrefied foods appear to play key roles in NPC development, but each of these alone does not appear predominant in causing NPC susceptibility. How these factors interact with other unknown NPC risk factors (in particular genetic factors) remains unclear. Recent technological advances in genetic research, in combination with large, well-designed epidemiological studies, offer the possibility of elucidating the factors that lead to this multifactorial disease.

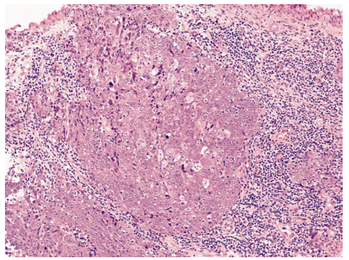


Fig. 5.8.3 *Nasopharyngeal nonkeratinizing carcinoma. Tumour islands are obvious in the lymphoid stroma*

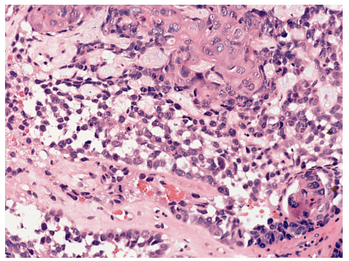


Fig. 5.8.4 *Basaloid squamous-cell carcinoma of the nasopharynx. The basaloid tumour cells show a festooning growth pattern, and are interspersed by tumour cells with squamous differentiation*

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5.9 Kaposi Sarcoma

Summary

> Kaposi sarcoma is an AIDS-defining malignancy, and it has become one of the commonest cancers in both men and women in Sub-Saharan Africa

> Kaposi's sarcoma-associated herpesvirus (KSHV), the eighth human herpesvirus to be identified (also called HHV-8) is the causative agent of Kaposi's sarcoma

> Different subtypes of KSHV are related to geographical localisation, ethnicity and prevalence of HIV

> The widespread use of combined antiretroviral treatment has led to a marked decrease in the incidence of KS in the developed world whereas it remains extremely common among AIDS patients in Sub-Saharan Africa

Kaposi sarcoma (KS) is a tumour that develops from lymphatic endothelial cells. The clinical hallmarks of KS are red-purple nodular lesions on skin or visceral surfaces associated with prominent angiogenesis [1].

KS is classified in four different clinico-epidemiological forms: a) classic KS, usually affecting elderly men from the Mediterranean region; b) endemic KS, found mainly in Equatorial Africa; c) iatrogenic KS, found in patients submitted to immunosuppressive therapy and d) epidemic KS, affecting patients with Acquired Immunodeficiency Syndrome (AIDS-KS) [2]. Kaposi's sarcoma-associated herpesvirus (KSHV) is now recognised to be the cause of all forms of KS. KSHV is also the causative agent of primary effusion lymphoma (PEL) and HIV-associated multicentric Castleman's disease, a B-cell lymphoproliferative disorder [1].

Epidemiology of Kaposi sarcoma

Kaposi sarcoma (KS) was first described in 1872 by Moritz Kaposi, a Hungarian dermatologist, who reported five elderly men of Mediterranean origin with indolent multi-focal vascular tumours designated "idiopathic multiple pigmented sarcoma of the skin" (classic KS). Subsequently, a form affecting the skin of the lower limbs of young men was described in the 1920s in Sub-Saharan Africa (endemic KS). KS remained a rare cancer for many years until the 1980s, when an increase in the incidence of an aggressive form of KS was associated with the advent of AIDS (epidemic KS). The observation that homosexual and bisexual men were at higher risk of KS than any other HIV transmission group triggered suspicions that specific sexual practices would increase the risk of KS, leading to the search and discovery of Kaposi's sarcoma-associated herpesvirus (KSHV), the infectious agent causative of KS.

The worldwide epidemiology of KS has changed dramatically since the advent of AIDS. Before the spread of HIV (years 1968–1970), KS represented approximately 7% of all cancers registered in males in Sub-Saharan Africa, whereas in the years 1989–1991, KS accounted for 50% of the total number of cancers affecting males [2]. All of the highest-risk areas for KS are in Sub-Saharan Africa (Figure 5.9.1). Elsewhere, KS incidence rates are lowest in England (ASR of 0.014) and highest in Sardinia, Italy (ASR of 1.6 per 100 000) in both men and women [2].

In the early phase of the HIV epidemic, KS was the cancer type most frequently diagnosed among AIDS patients. Since the introduction of highly active antiretroviral therapy (HAART) for HIV in the developed world, the incidence of KS has declined sharply, with incidence rates coming second to non-Hodgkin lymphomas between years 1996–2002 [3]. However, it has become the commonest cancer diagnosed in the general male population in some areas of Sub-Saharan Africa (ASR of 30 per 100 000 in Central Africa), whereas among women it is now surpassed only by cervical cancer [4].

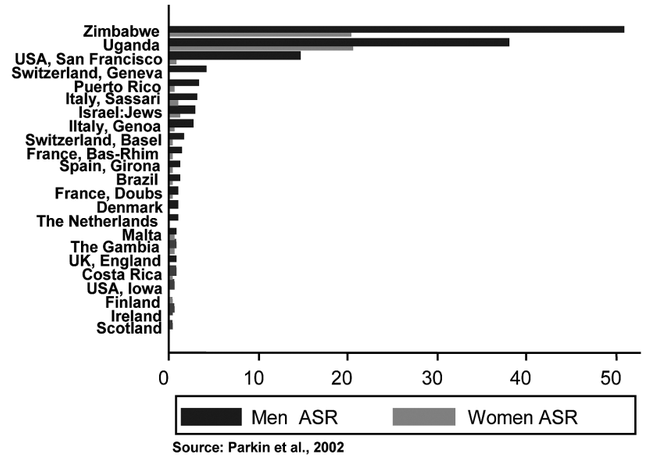


Fig. 5.9.1 *Kaposi sarcoma age-standardised (world) incidence (ASR) per 100.000 among males in selected countries*

Epidemiological studies have shown that the risk of KS is a thousandfold greater in patients with AIDS than in the general population and men are at higher risk of developing KS than women. Male to female ratios of 2–3:1 are found in classic KS [2]. In epidemic KS, the KS incidence was much higher in men (ASR of 8.0 per 100 000) than women (ASR of 0.09 per 100 000) in the USA during years 1979-1998 [5], whereas in Africa, the male to female ratio has declined from 10:1 in the pre-AIDS era to 3:1 after the spread of HIV [2]. The risk of KS is significantly higher in homosexual and bisexual men than among other HIV transmission groups, and women who report having had sex with bisexual men are 4 times more likely to have KS in comparison with women reporting sexual partners from other HIV transmission groups [6].

The age distribution of KS has been changed by the AIDS epidemic. While classic KS used to be diagnosed mainly in elderly men, the incidence of the associated KS is now highest in the late thirties [2]. No strong risk factors other than age, gender and immunosupression have been so far identified in HIV-seronegative populations in various case–control studies.

AIDS-defining KS is strongly associated with a decrease in CD4+ T-cell count and is seldom seen with CD4+ T-cell count above 300/µl. Immune deficiency is also associated with the development of KS in solid-organ transplant recipients (iatrogenic KS). People living with HIV however, have shown a much greater risk of developing KS than iatrogenically immunosuppressed patients, probably on account of differences in KSHV prevalences [7]. Indeed, the incidence of KS among iatrogenically immunosuppressed patients is higher in geographic areas where the prevalence of KSHV infection is also high, such as in the Mediterranean basin, e.g. Italy [8] than in Northern Europe or the United States. Unexplained low incidences of KS are reported in a few populations where the prevalence of KSHV infection is notably high, such as among Brazilian Amerindians [9]. Such discrepancies between the prevalence of KSHV and KS incidence point to either severe underreporting of KS in some countries or unknown protector factors in the development of KS [9].

Etiology of Kaposi sarcoma

As early as 1972, herpesvirus-like particles were first identified in cell lines prepared from endemic KS tumour tissue, suggesting that a herpesvirus could play a role in the pathogenesis of KS [1].

It was not until 1993 when "herpesvirus-like" DNA sequences were identified in 25/26 (92.7%) AIDS-KS biopsies by using advanced techniques of molecular biology for DNA amplification. The sequences found were homologues to the gammaherpesvirus herpesvirus saimiri and Epstein-Barr virus. After comparisons of viral genomes, Kaposi sarcoma-associated herpesvirus (KSHV), the first human gamma-2 herpesvirus to be identified, was classified as belonging to the Rhadinovirus genus, sub-family gammaherpesvirus [10]. The authors that discovered the virus named it Kaposi sarcoma-associated herpesvirus (KSHV), but the designation human herpesvirus eight (HHV-8) is also used.

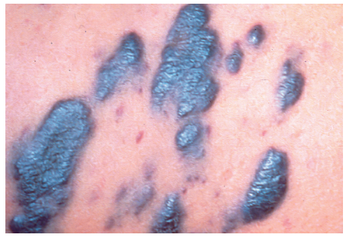
Subsequently, several studies described the presence of KSHV DNA in tumour tissue biopsies of classic, endemic, iatrogenic and epidemic types of KS [10].

Diagnostic tests to detect infection with Kaposi sarcoma-associated herpesvirus (KSHV)

Polymerase Chain Reaction (PCR). KSHV/DNA can be detected by PCR in tumour tissue samples obtained from the large majority of patients with classic, endemic, iatrogenic or epidemic KS (AIDS-KS). Less frequently, KSHV DNA can be amplified from blood cells obtained from patients with any type of KS, with successful detection in up to 50% in some cases series [2].

KSHV DNA detection from blood of general populations is difficult. The virus is more often detected in blood donors using second-round PCR or quantitative real-time PCR, with prevalence of detection ranging between 0% in USA to 20% in Sub-Saharan Africa [2] among blood donors.

Serological diagnosis. As with any other herpesvirus, KSHV genome encodes for viral proteins involved in latent and lytic viral life cycles. Serological assays using KSHV latent and lytic cycle-associated viral antigens have been developed to detect KSHV infection [11]. The viral antigen expressed during the latent phase of infection is termed latency-associated nuclear antigen (LANA). Immunofluorescence-based assays (IFA) can identify nuclear (IFA-LANA) or cytoplasmic (IFA-lytic assay) punctuate staining under the fluorescence microscope [12]. Since the identification of a handful of KSHV antigens that are able to initiate antibody response, serological assays have been produced using these antigens, with IFA or enzyme-linked immunosorb-



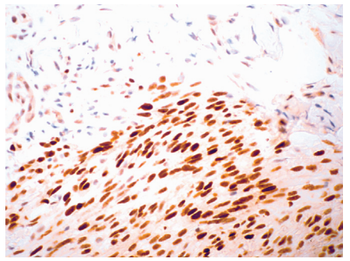


Fig. 5.9.2 *Kaposi sarcoma of the skin in a patient with AIDS. The biopsy (below) reveals the presence of human herpes virus 8 (HHV-8) in tumour cell nuclei, demonstrated by immunohistochemistry (brown colour). Affected individuals are uniformly co-infected with HIV and HHV-8*

ent (ELISA) based-assays being the most widely used diagnostic tests to detect KSHV infection.

A gold standard serological assay for KSHV infection does not yet exist; therefore some discrepancies between studies may be attributable to the use of different testing methods [2].

Epidemiology of Kaposi's sarcoma-associated Herpevirus (KSHV) infection

KSHV serosurveys have shown that the seroprevalence of KSHV infection amongst HIV-seronegative populations varies geographically, being as high as 50% in Uganda and only 0.2–5% in Asia, USA and United Kingdom (Table 5.9.1). Risk factors associated with KSHV seropositivity have not been clearly defined in the general population (Table 5.9.1). The strong association with anal intercourse among men who have sex with men suggested that KSHV would be a sexually transmitted agent, but sexual transmission has not been consistently confirmed among heterosexuals. Sexual behaviour has been associated with KSHV infection among men (OR=2.8; 95% CI 1.3–5.7) but not women in the USA [13]. Consistent increases in KSHV seroprevalence with increasing age have only been found in areas where infection with KSHV is endemic such as Sub-Saharan Africa. The risk of KSHV infection is also higher among children living with a sibling infected with KSHV in French Guiana (OR=3.8 95% CI 1.1–16.5), indicating that the KSHV transmission can occur horizontally, probably through saliva. Vertical transmission of KSHV has not been demonstrated in HIV-seronegative populations, but reactivation of KSHV during pregnancy in HIV-infected women suggests the possibility of vertical transmission in this population [14].

Molecular epidemiology

KSHV is an ancient virus that probably started spreading 100 000 years through human migrations between continents. Molecular studies based on a genetically variable genomic region of KSHV DNA (namely, ORF K1), have identified 5 main subtypes of KSHV (designated A, B, C, D and E) that are not associated with severity of disease, but have preferential geographical distributions [15]. Thus, subtypes A and C are found in Europe, the USA and Asia; strains B and A5 are found mainly in Africa and French Guyana. Subtype D, first reported in Taiwan and in some Pacific islands, has also been described in Australia, while the most recently reported subtype E has been found among South American Amerindian populations from the Amazon and French Guyana [9]. In addition to clustering by geographical localisation, KSHV strains have also been associated with ethnic background, with KSHV subtypes B and variant A5 being detected mainly in people of African descent and subtypes A and C, being usually found in Caucasian populations. The rarer subtypes D and E have only being described in Amerindians and Indigenous people from the Pacific Islands [9,15].

Management of Kaposi sarcoma

No cure exists for KS and the treatment is mostly palliative. In AIDS patients, the control of HIV replication and the consequent increase in CD4+ T-cell counts lead to marked regression of KS mucocutaneous lesions following initiation of HAART.

The use of HAART alone is an option for treatment of KS among HIV-infected patients [16]. The dissemination to internal organs and the obstruction of lymphatic systems are rare in AIDS patients receiving HAART, but the severest clinical pictures are often seen in Sub-Saharan Africa, where HAART is not available and life expectancy following the diagnosis of KS is less than one year.

Gatrointestinal and pulmonary symptoms warrant endoscopic examination to search for visceral KS lesions. Like AIDS patients, organ-transplanted recipients also experience improvement of their KS lesions after the cessation of the immune suppressive treatment.

The clinical presentation of classic KS is less severe, and local treatment can often be employed to treat the characteristic indolent lesions.

The use of systemic cancer chemotherapy is indicated when mucocutaneous lesions are disseminated or visceral organs are affected. Chemotherapy agents used in the management of KS include adryamycin, bleomycin, vinblastine, vincristine, doxorrubicin and etoposide. The use of liposomal anthracyclines and taxanes are considered the best option for disseminated KS. Other options include radiotherapy, cryotherapy and intra-lesional chemotherapy for local treatment of isolated cutaneous lesions for cosmetic and palliative reasons [16].

Region/Country	Population (N)	KSHV infection (% positive)*	Risk factors associated with KSHV seropositivity
Latin America			
Jamaica	Blood donors (n=1,010)	2.7%	Older age > 26 (Ptrend=0.001) [17]
French Guiana	Rural community	13.2%	Age > 39 y (Ptrend<0.001), KSHV infected sibling (OR=3.84 [95% CI: 1.6-9.5) [18]
Brazil, Sao Paulo	Blood donors (N=400)	4%	Female gender (OR=3.86 [95% CI: 1.1-16.6]) [19]
North America			
USA (San Francisco)	Blood donors (N=122)	0	Not analysed [20]
USA	General population (n=13,894)	1.6% 1.5%	Hepatitis B (OR=3.1 [95% CI: 1.6-5.8]) Sexual behaviour for men (OR=2.3 [95% CI: 1.4-3.8]) [13]
Europe			
Italy North			Not analysed [21]
Po valley	B. donors (N=139)	13%	
Milan & Trieste	B. donors (N=265)	3%	
Italy South			
Calabria	B. donors (N=38)	4%	
Sicily	Bl. donors (N=60)	20%	
United Kingdom	Blood donors (N=174)	5%	Not analysed [22]
Asia			
India	N=108	4.0%	Not analysed [23]
Thailand	N=75	4.0%	
Malaysia	N=159	4.4%	
Sri Lanka	N=80	3.8%	
Africa			
Tanzania	Blood donors (N=174)	2.9% 22%	Not analysed Not analysed [24]
Uganda (Kampala)	HIV-seronegative cancer patients from a case-control study (N=607)	50%	Older age (Ptrend<0.001), Ever married (OR=2.1 [95% CI: 1.1-4.1]) [25]
South Africa	HIV-seronegative cancer patients (N=2,191)	39%	Older age among men (OR=2.1 [95% CI: 1.2-3.8]) Older age among women (OR=3.8 [95% CI: 1.6-9.3]) [26]

Table 5.9.1 *Worldwide seroprevalence of KSHV infection in cross-sectional studies of HIV-seronegative individuals. N, number of HIV-seronegative individuals tested for KSHV; OR, odds ratio; CI, confidence interval; *Serological asssays detect anti-KSHV antibodies either to lytic of LANA KSHV antigens.*

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CANCER INSTITUTE PROFILE: The Ocean Road Cancer Institute (ORCI)

The Ocean Road Cancer Institute (ORCI) in Dar es Salaam was established as the National Cancer Institute for Tanzania by an Act of Parliament in 1996. It is the only specialised cancer centre in the country that offers cancer treatment, training, research, surveillance and cancer prevention. Since its establishment, ORCI was designated as the National Coordinator for Cancer Control in Tanzania and given a mandate to formulate and ensure the development of cancer control actions in Tanzania. During its 10 years of existence, the ORCI has been a leader in terms of cancer control in Tanzania, implementing actions in strategic areas such as cancer prevention, early detection, cancer treatment, human resources development, research, surveillance, information and palliative care through the referral system of the Ministry of Health of Tanzania.

Currently ORCI has 160 beds and 200 staff members including 5 senior professionals with Academic status with the Muhimbili University of Health and Allied Sciences. As a renowned tertiary care centre, it accepts 3000 inpatients and 10 000 outpatients each year from all over Tanzania and neighbouring countries such as Malawi, Zambia and the Democratic Republic of Congo.

In 2006, following the endorsement of recommendations from the IAEA Programme of Action for Cancer Therapy (PACT) for strengthening cancer control capabilities by the government of Tanzania, the ORCI formed a secretariat for a Steering Committee appointed by the Minister of Health. The main tasks of the steering committee are to focus on formulating and strengthening each component of national cancer control system and develop action plans for the National Cancer Control programme.

5.10 Lung Cancer

Summary

- Lung cancer is the most common cause of cancer death worldwide
- Survival is poor and no effective screening is available
- In most populations, tobacco smoking accounts for 80% or more lung cancers
- Other causes of lung cancer include occupational (e.g. asbestos, heavy metals) and environmental exposures (e.g. secondhand smoke, radon decay products)
- Genetic susceptibility factors that might interact with tobacco smoking have been identified
- Tobacco control is the main tool in the fight against lung cancer

Lung cancer was a rare disease until the beginning of the twentieth century. Since then, its occurrence has increased rapidly; this neoplasm has become the most frequent malignant neoplasm among men in most countries and represents the most important cause of cancer death worldwide. It accounts for an estimated 960 000 new cases and 850 000 deaths each year among men, and 390 000 cases and 330 000 deaths among women. Survival from lung cancer is poor (5–10% at five years).

The geographical and temporal patterns of lung cancer incidence are to a large extent determined by consumption of tobacco. An increase in tobacco consumption is paralleled some 20–30 years later by an increase in the incidence of lung cancer; similarly, a decrease in consumption is followed by a decrease in incidence.

The highest incidence rates in men (>70/100 000) are recorded among blacks from the United States and in some Central and Eastern-European countries [2,3]. Rates are declining among US white men and among men in the United Kingdom and Northern Europe. The lowest incidence rates are reported from Africa and Southern Asia.

Rates in women are high in the USA, Canada, Denmark and the UK, and low in countries such as Japan and Spain, in which the prevalence of smoking in women has increased only recently. The lowest rates (<3 cases per 100 000 people) are recorded in Africa and India. China is a notable exception, with relatively high rates recorded among women (e.g. 37/100 000 in Tianjin during 1993–1997; [2], despite a low prevalence of smoking.

The main histological types of lung cancer are squamous-cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma. Over the last few decades, the proportion of squamous-cell carcinomas, which used to be the predominant type, has decreased and an increase of adenocarcinomas has taken place in both genders. This is probably due to changes in the composition of tobacco products and in smoking behaviour (e.g. use of filtered cigarettes, lower tar content, reduced inhalation). Despite some minor differences, the main risk factors for lung cancer are associated with all histological types.

A carcinogenic effect of tobacco smoke on the lung was demonstrated in the 1950s and has been recognised by public health and regulatory authorities since the mid-1960s [4]. The risk of lung cancer among smokers relative to the risk among never-smokers is of the order of tenfold or more. This overall risk reflects the contribution of the different aspects of tobacco smoking: average consumption, duration of smoking, time since quitting, age at start, type of tobacco product and inhalation pattern, with duration being the dominant factor. As compared to continuous smokers, the excess risk decreases in ex-smokers after quitting, but a small excess risk is likely to persist in long-term quitters throughout life. In the United Kingdom, the cumulative risk of lung cancer of a continuous smoker is 16%, and it is reduced to 10%, 6%, 3% and 2% among those who stopped at age 60, 50, 40 and 30, respectively. Smokers of black (air-cured) tobacco cigarettes are at higher risk of lung cancer than smokers of blond (flue-cured) tobacco cigarettes. A causal association with lung cancer has also been shown for consumption of cigars, cigarillos, pipes, bidis, water pipes and other smoking tobacco products [4], but not for use of smokeless tobacco products [5].

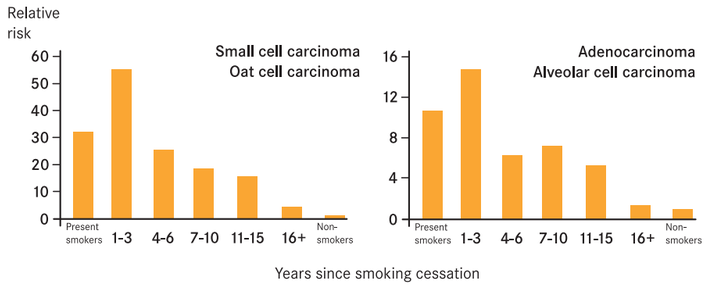


Fig. 5.10.1 *The relative risk of lung cancer is markedly lower five years after quitting, and decreases further with time (by comparison with those who continue to smoke)*

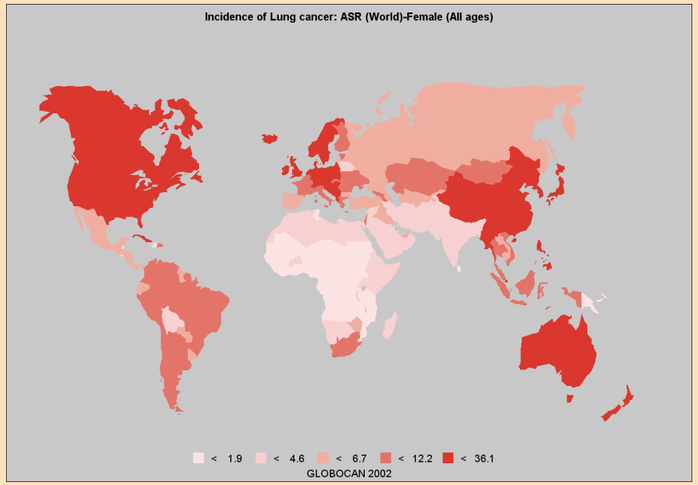
An association has been shown in many studies between exposure to involuntary smoking and lung cancer risk in non-smokers. The magnitude of the excess risk among non-smokers exposed to involuntary smoking is of the order of 20% [6].

There is limited evidence that a diet rich in vegetables and fruits exerts a protective effect against lung cancer [7]. In particular, a protective effect has been suggested for intake of cruciferous vegetables, possibly because of their high content in isothiocyanates [8]. Despite the many studies of intake of other foods, such as cereals, pulses, meat, eggs, milk and dairy products, the evidence is inadequate to allow a judgement regarding the evidence of a carcinogenic or a protective effect.

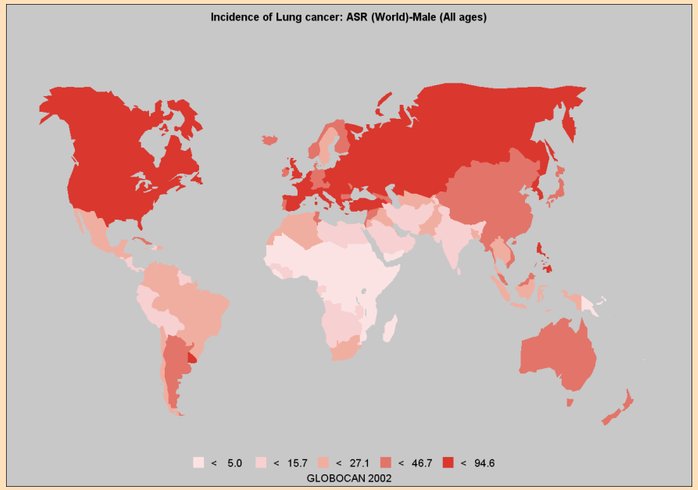
A large number of studies have reported a reduced risk of lung cancer for high intake of beta-carotene [9]. Similar results have been obtained in studies based on measurement of beta-carotene in prospectively collected sera. This evidence of a protective effect has been challenged by the results of intervention trials of beta-carotene supplementation [9]. In two of the studies, which included smokers and workers exposed to asbestos, an increase in the incidence of lung cancer was observed in the treated groups [10,11]: in the other studies, no difference was found between the treated and the control groups [12,13]. The differences in the results of observational studies and intervention trials can be explained either by a confounding effect due to other dietary components in observational studies, or by a paradoxical effect of beta-carotene at very high, non-physiological doses, in particular among smokers.

There is inadequate evidence of an increase in the risk of lung cancer from heavy alcohol drinking, independent from tobacco smoking , and for an association between body size and lung cancer risk [14].

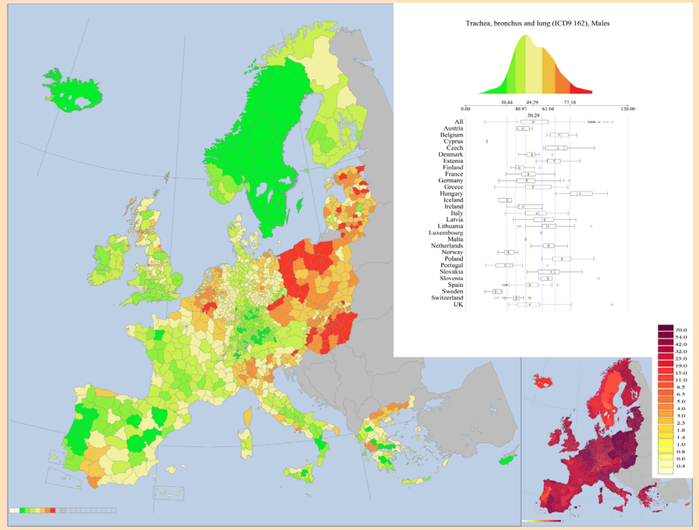
A positive familial history of lung cancer has been found to be a risk factor in several studies. Segregation analyses suggest that inheritance of a major gene, in conjunction with tobacco



World Map 5.10.1



World Map 5.10.2



European Map 5.10.1 *The most prominent feature of the geographical distribution of lung cancer in men in Europe is the large area of high rates extending from northern Italy through neighbouring Slovenia into Hungary, Slovakia, the Czech Republic, Poland, parts of northeast Germany and the Baltic Countries. There was a second, smaller, area with higher-than-average rates covering The Netherlands, Belgium and northern France. There were also small numbers of areas with high rates in central Scotland, southern Spain and the northern mainland of Greece. Rates were generally low in Portugal, central and northern Spain, southern France, Switzerland, southern Germany and Austria, as well as in all the Nordic Countries [1].*

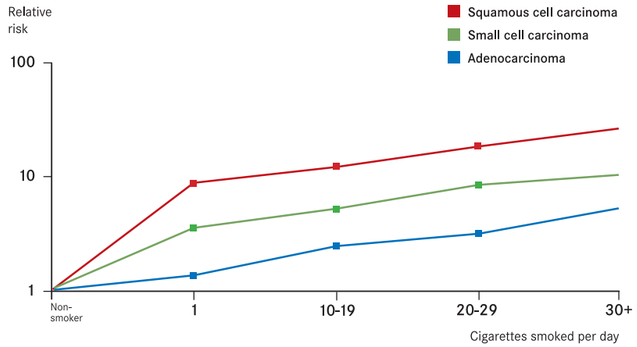


Fig. 5.10.2 *The relative risk of major histological types of cancer by average cigarette consumption*

smoking, might account for more than 50% of cases diagnosed below age 60 . A pooled analysis of high-risk pedigrees identified a major susceptibility locus to chromosome 6q23-25 . In addition, low-penetrance genes involved in the metabolism of tobacco carcinogens, DNA repair and cell cycle control might influence individual susceptibility to lung cancer [15]. Recently, three whole genome association studies have identified a susceptibility marker in chromosome 15q25.1, most likely located in a nicotine receptor gene [16-18]. It remains to be shown whether the effect of this gene is independent from tobacco dependence.

There is conclusive evidence that exposure to ionizing radiation increases the risk of lung cancer [19]. Atomic bomb survivors and patients treated with radiotherapy for ankylosing spondylitis or breast cancer are at moderately increased risk of lung cancer, while studies of nuclear industry workers exposed to relatively low levels of radiation, however, provided no evidence of an increased risk of lung cancer. Underground miners exposed to radioactive radon and its decay products, which emit alpha-particles, have consistently been found to be at increased risk of lung cancer [20]. The risk increased with estimated cumulative exposure and decreased with attained age and time since cessation of exposure .

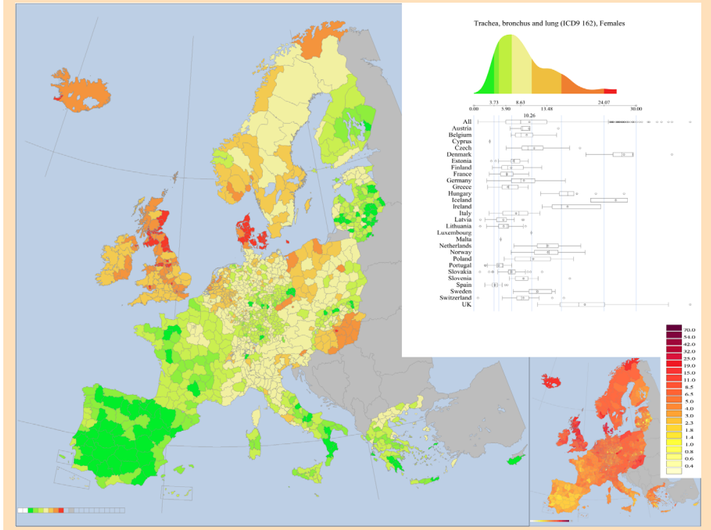
The risk of lung cancer is increased among workers employed in several industries and occupations. For several of these high-risk workplaces, the agent (or agents) responsible for the increased risk have been identified [21]. Of these, asbestos and combustion fumes are the most important. Occupational agents are responsible for an estimated 5–10% of lung cancers in industrialised countries.

Patients with pulmonary tuberculosis are at increased risk of lung cancer; it is not clear whether the excess risk is due to the chronic inflammatory status of the lung parenchyma or to the specific action of the mycobacterium. Chronic exposure to high levels of fibres and dusts might result in lung fibrosis (e.g. silicosis and asbestosis), a condition which entails an increase in the risk of lung cancer. Chronic bronchitis and emphysema have also been associated with lung cancer risk [22].

There is abundant evidence that lung cancer rates are higher in cities than in rural settings. Although this pattern might result from confounding by other factors, notably tobacco smoking and occupational exposures, the combined evidence from analytical studies suggests that urban air pollution might be a risk factor for lung cancer, although the excess risk is unlikely to be greater than 20% in most urban areas.

Indoor air pollution is thought to be responsible for the elevated risk of lung cancer experienced by non-smoking women living in several regions of China and other Asian countries. The evidence is strongest for coal burning in poorly ventilated houses, but also for burning of wood and other solid fuels, as well as for fumes from high-temperature cooking using unrefined vegetable oils such as rapeseed oil [23]. In some countries (e.g. Sweden), indoor exposure to radon decay particles may entail a sizeable increase of risk [22].

Control of tobacco smoking remains the key strategy for the prevention of lung cancer. Reduction in exposure to occupational and environmental carcinogens (in particular, indoor pollution and radon), as well as increase in consumption of fruits and vegetables are additional preventive opportunities. To date, no screening interventions have been demonstrated to be effective at reducing lung cancer mortality.



European Map 5.10.2 *The pattern of lung cancer mortality in women was quite different from that observed in males. The highest rates were in the United Kingdom (particularly the north), Ireland, Denmark and Iceland, and parts of Norway and Sweden, all of which had generally lower-than-average lung cancer mortality rates in males. There were, however, similar areas of higher-than-average rates in females as in males in Belgium and The Netherlands, in north and west Poland, and in Hungary. Low rates aggregated particularly in Portugal and Spain, but also in France, Greece, southern Italy and Finland. In terms of our understanding of lung cancer etiology, the current geographical patterns better represent the smoking habits in the various countries 20–30 years ago than those of today. In particular, the high mortality from lung cancer in women in Denmark and the United Kingdom reflects the early uptake of the smoking habit by large portions of females in those countries. An epidemic of tobacco-related lung cancer in women throughout Europe has yet to materialise (as it has previously in men) and effective intervention is now needed urgently to avoid this catastrophe [1].*

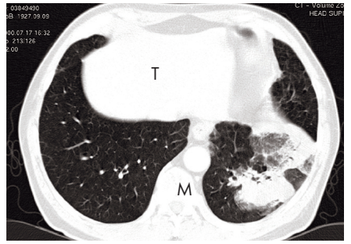


Fig. 5.10.3 *A lung tumour viewed by computed tomography. T= tumour, M= mediastinum*

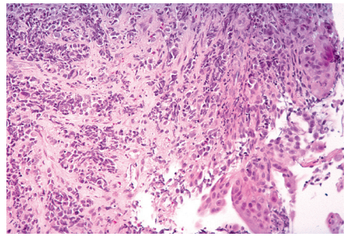


Fig. 5.10.4 *Biopsy of a small cell lung carcinoma, showing a monomorphic proliferation of small tumour cells with dense nuclei and poorly-defined cytoplasm, invading the deep parts of the bronchial wall*

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CANCER INSTITUTE PROFILE: AORTIC

(African Organization for Research and Training in Cancer, or l'Organisation pour la Recherche et l' Enseigment sur le Cancer [OAREC] in French).

This organisation was formed by expatriate African cancer care workers, scientists and their friends and is dedicated to the promotion of cancer control in Africa.

AORTIC Mission

AORTIC's mission is to stimulate and promote research into cancer in Africa, to support and develop standardised training programmes in all aspects of cancer care and management and to enable African countries to develop national cancer control programmes. AORTIC is committed to creating awareness of the extent of cancer in Africa and to ensure that programmes to prevent, diagnose, treat and palliate cancer in Africa are firmly on the continent's health agenda. The Organisation will achieve this by working with other non-profit organisations, government agencies and businesses to advocate for improved resources and access to care. AORTIC will also organise symposia, workshops, meetings and conferences that support this mission.

AORTIC Vision

The African Organisation for Research and Training in Cancer (AORTIC) seeks to become the continent's preeminent non-profit organisation working for cancer control. AORTIC will achieve this through the facilitation of research and training as well as the provision of relevant and accurate information on the prevention, early diagnosis, treatment and palliation of cancer. Our organisation is dedicated to providing all Africans with these benefits, as well as to increasing public awareness of cancer and reducing the stigma associated with it.

AORTIC Objectives

AORTIC's key objectives are to further research relating to cancers prevalent in Africa, support the management of training programs in oncology for healthcare workers, and to deal with the challenges of creating cancer control and prevention programmes, as well as raising public awareness of cancer in Africa.

The executive members of AORTIC are high-profile scientists from all over Africa volunteering as knowledge workers for the plight of the cancer patient in Africa. Their main value is their ability to gather and analyse information and make decisions that will benefit the cancer patient. They work collaboratively with other cancer organizations via conferences and the internet, sharing knowledge, learning from each other and disseminating relevant ideas and research to the cancer community.

AORTIC is actively connected to the global community, with a vast electronic database as well as paper and electronic newsletters sent out quarterly in English and French. AORTIC has been represented at numerous cancer conferences around Africa and the world, and looks forward to their upcoming seventh AORTIC conference in Tanzania in November 2009.

website: www.aortic.org

CANCER INSTITUTE PROFILE: Institut Jules Bordet

Located in the heart of Europe, the Institut Jules Bordet (IJB) was among the first European centres to be fully dedicated to cancer, and is currently the only one in Belgium. IJB belongs to the academic research network of the Université Libre de Bruxelles. As a Comprehensive Cancer Centre, IJB fully integrates three key missions: patient care, education and research.

IJB provides a full range of services, including prevention, screening, diagnostics, therapeutics and rehabilitation using state-of-the-art technologies and the most up-to-date methods. With a capacity of 154 beds and a 13-bed day-care Unit, IJB insures 6000 hospitalisation admittances (together with 2000 new diagnoses) and 71 000 outpatient consultations a year.

IJB collaborates closely with the International Agency for Research on Cancer (IARC) and coordinates large pivotal multicentric clinical trials. The top-quality translational and clinical research activities at IJB lead annually to more than 200 scientific articles with a high impact factor (820 in 2006). IJB belongs to the Organization of European Cancer Institutes (OECI) and is strongly involved in the European Organization for Research and Treatment of Cancer (EORTC), which is currently chaired by the IJB Head of Medical Department, Prof Martine Piccart.

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Belgium

www.bordet.be

5.11 Mesothelioma

Summary

> Mesothelioma of the pleura and the peritoneum is a rare cancer except in workers exposed to asbestos

> The clinical course of the disease is in most cases fatal

> Exposure to all types of asbestos increases the risk of developing mesothelioma, although the potency of amphibole asbestos (e.g. crocidolite, amosite) is greater than that of chrysotile asbestos

> Other known risk factors are environmental exposure to asbestos and asbestos-like fibres, as well as radiation

> Avoidance of exposure to asbestos and other fibres is the main approach to prevent mesothelioma

Mesothelioma is the most important primary tumour of the pleura. It can also originate from the peritoneum and the pericardium. Mesotheliomas were considered very rare tumours until large series of cases were reported in the 1960s among workers employed in asbestos mining and manufacturing. The descriptive epidemiology of pleural tumours, and mesothelioma in particular, is complicated by geographical and temporal differences in diagnostic accuracy. In most high-resource countries, the incidence of pleural mesothelioma is of the order of 1–1.5/100 000 in men and around 0.5/100 000 in women. Lower rates are reported from low-resource countries, where under-diagnosis might be a particularly serious problem. In areas with a high prevalence of occupational exposure to asbestos such as shipbuilding and mining centres, the rates might be as high as 5/100 000 in men and 4/100 000 in women [1]. Occurrence of mesothelioma has been linked conclusively to asbestos exposure, in particular to amphiboles such as crocidolite and amosite. Past occupational exposure to asbestos is the main determinant of pleural mesothelioma. High-exposure industries include mining, shipyard working, and especially asbestos, textile and cement manufacture [2].

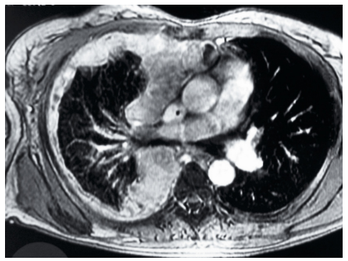
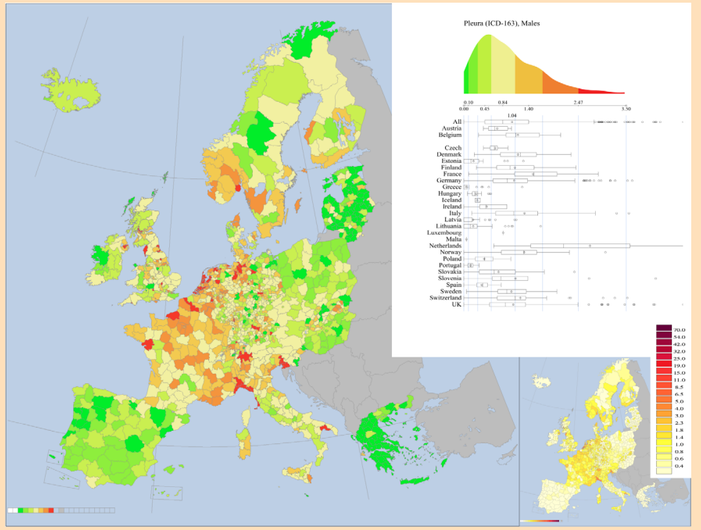


Fig. 5.11.1 *Diffuse malignant mesothelioma. In this CT scan, the pleura shows marked diffuse thickening by mesothelioma, with resulting encasement of the lung*

Despite a reduction or ban of asbestos use in many countries, the incidence of mesothelioma was increasing in the USA until the early 1990s, and in most Western European countries until the late 1990s, which reflects the long latency of the disease [3]. In the absence of occupational exposure to asbestos, incidence rates of the order of 0.1–0.2/100 000 are estimated in both genders. In heavily exposed workers, relative risks of the order of 1000 have been reported. There is evidence of an increased risk of pleural mesothelioma following environmental exposure to asbestos; epidemics of mesothelioma have been reported from areas with environmental contamination by other natural mineral fibres, such as some districts of central Turkey, where erionite, a fibrous substance similar to amphibole asbestos, contaminated the materials used for building construction.

In several populations, DNA of simian virus 40 has been reported in a high proportion of mesothelioma cases; however, a causal role of this virus, which contaminated polio vaccines used in the 1950s in many countries, has not been confirmed [4]. Exposure to ionising radiation entails an increased risk of pleural mesothelioma, as it has been shown in cohorts of patients treated with thorotrast, a radiological contrast medium [2]. Tobacco smoking, alcohol drinking and diet do not appear to be risk factors for pleural mesothelioma.

Peritoneal mesothelioma shares many of the epidemiological and biological features of the pleural form of the disease [5]. In particular, patients treated with thorotrast frequently developed peritoneal mesothelioma, probably because of local emission of alpha-particles by the contrast medium.



European Map 5.11.1 *This is the only form of cancer presented in the "Cancer Atlas of the Euroepan Union" in which the local rates are more important than the general geographic picture [Boyle and Smans, 2008].*

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5.12 Non-Melanoma Skin Cancer

Summary

> Non-melanoma skin cancer includes squamous and basal cell carcinomas

> These two forms of skin cancer are the most frequent cancer in light-skinned populations, but are rarely a cause of death

> Their public health importance resides in the huge economic burden their treatment entails, and the loss of quality of life due to disfiguring scars

Basal cell carcinomas (BCC) and squamous-cell carcinomas (SCC) are the two main forms of non-melanoma skin cancer, accounting for the large majority of all skin tumours [1]. Non-melanoma skin cancer is the most frequent form of cancer in light-skinned populations [2].

Epidemiology

Incidence. Non-melanoma skin cancer is a disease of light-skinned (white) populations. Hispanic and Asian populations develop less skin cancer, and it is even less frequent in black populations [3,4]. The Squamous-cell carcinomas occur almost exclusively on chronically sun-exposed skin areas, whereas BCC may also occur on body sites only intermittently sun-exposed [5].

In white populations residing in areas close to the equator (e.g. Queensland in Australia), non-melanoma skin cancer incidence surpasses that of any other cancer site. BCC has the highest incidence rate and is 3 to 4 times more frequent than SCC (Table 5.12.1). Incidence of BCC and SCC increases with age, mainly for SCC whose incidence rises sharply after 65 years of age [6]. The incidence of SCC is about three times higher in men than in women, and the incidence of BCC is twice as high in men as in women [4].

An important variability in incidence rate exists between Europe, the USA and Australia: incidence rates are about 5 times higher in the US and 20–40 times higher in Australia than in Europe. This can partly be explained by differences in latitude of residence. A correlation between incidence and latitude of residence was initially described in the USA [4]. This observation contributed to the hypothesis related to chronic sun exposure and the risk of non-melanoma skin cancer.

A continuous increase in incidence over time is observed in different parts of the world [3,7-13] with no sign of levelling off in the most recent investigations [14]. The increase was more rapid for BCC than for SCC [9].

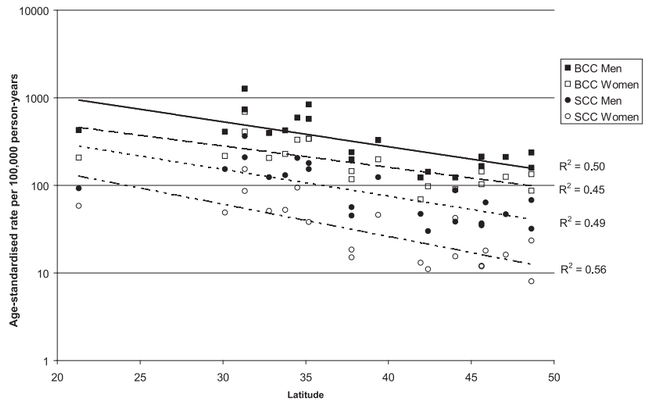


Fig. 5.12.1 *Incidence of BCC and SCC in the United States of America as a function of latitude in the white population from reports in peer-reviewed journals. R-squared corresponds to the log-linear correlation between incidence rate and latitude. Rates were standardised according to the US population of 1970*

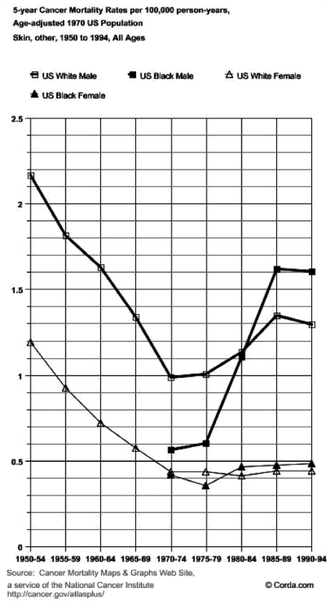


Fig. 5.12.2 *Non-melanoma skin cancer mortality rate in the USA*

Registration. In spite of its public health importance in white populations, and the continuous increase in incidence observed in all light-skinned populations, non-melanoma skin cancer remains poorly recorded by cancer registries. The main reason for the absence of registration data is the difficulty of obtaining systematic pathological assessment. Also, simultaneous BCC are often diagnosed, and both SCC and BCC have a high recurrence rate. In Australia, non-melanoma skin cancers are so frequent that around half of the population will develop a skin cancer during their lifetime, with many developing multiple recurrences. A complete registration of BCC and SCC in Australia would use all currently available resources for cancer registration and is therefore not feasible.

Mortality. BCC and SCC are slow-growing tumours that are locally invasive, but rarely result in distant metastasis. A small proportion of these cancers become life-threatening, and most countries with light-skinned populations record some deaths due to non-melanoma skin cancer. The majority of deaths are due to SCC, which are more invasive than BCC, and account for around 75% of all non-melanoma skin cancer deaths [15].

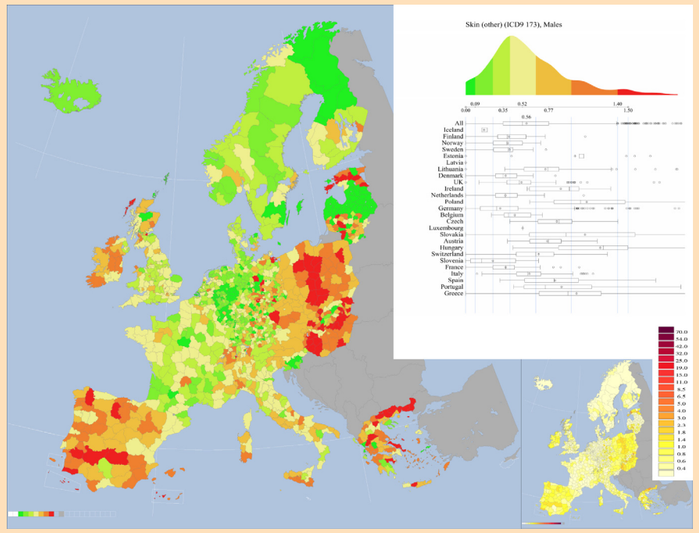
Etiology

Host factor - sun sensitivity. BCC and SCC arise predominantly in sun-sensitive people with light skin, red hair and an history of sunburn [16-18].

Publication	Geographical area	Years	BCC		SCC	
			Male	Female	Male	Female
North America*						
Scotto et al 1974	Dallas	1971-1972	394	205	124	51
	Iowa	1971-1972	123	69	47	13
	Minneapolis–Saint Paul	1971-1972	165	103	35	12
	San Francisco	1971-1972	198	117	45	15
Harris et al 2001	Southeastern Arizona	1996	936	497	271	112
Gallagher et al 1990	Canada	1973-1987	120	92	31	17
Australia**						
Giles et al 1988	Australia (survey)	1985	735	593	209	122
Marks et al 1993	Australia (survey)	1990	849	605	338	164
Buettner and Raasch 1998	Townsville, Australia	1997	2058	1194	1332	755
Europe**						
Osterlind et al 1988	Denmark	1978-1982	30	24	6.7	2.5
Holme et al 2000	South Wales, UK	1998	128	105	25	8.6
Hannuksela-Svahn et al 1999	Finland	1991-1995	49	45	7	4.2
Magnus 1991	Norway	1982,1984-1986	43	39	6.4	3.2
Coebergh et al 1991	Eindhoven, The Netherlands	1975-1988	46	30	11	3.4
Katalinic et al 2003	Schleswig-Holstein, Germany	1998-2001	54	44	11	5.3
Levi et al 1995	Vaud, Switzerland	1991-1992	69	62	29	18
Plesko et al 2000	Slovakia	1993-1995	38	29	6.7	3.8
Revenga et al 2004	Soria, Spain	1998-2000	65	53	23	13
Asia**						
Koh et al 2003	Singapore (Chinese)	1993-1997	6.4	5.8	3.2	1.8
	Singapore (Malay)	1993-1997	2.3	3.0	1.3	0.5
	Singapore (Indian)	1993-1997	1.2	1.4	1.8	1.9

Table 5.12.1 *Incidence per 100 000 person-years of BCC and SCC reported in different areas of the world*

** Standardised on the US population of 1970*
***Age-standardised incidence rate on the world population*



European Map 5.12.1 - *Mortality rates from non-melanoma skin cancer for men in Europe between 1993-1997*

Maps 5.12.1 and 5.12.2 present the distribution of mortality rates for men and women observed in the European Community including countries of the EFTA (Switzerland, Iceland and Norway). The main map represents the relative distribution of rates using a scale from lower rates in green to highest rates in red using percentiles of the distribution of rates (5,15,35,65,85 and 95). The second map represents the distribution of rates using an absolute scale and the upper right sub-figure contains the distribution of rates and boxplots of rates by country

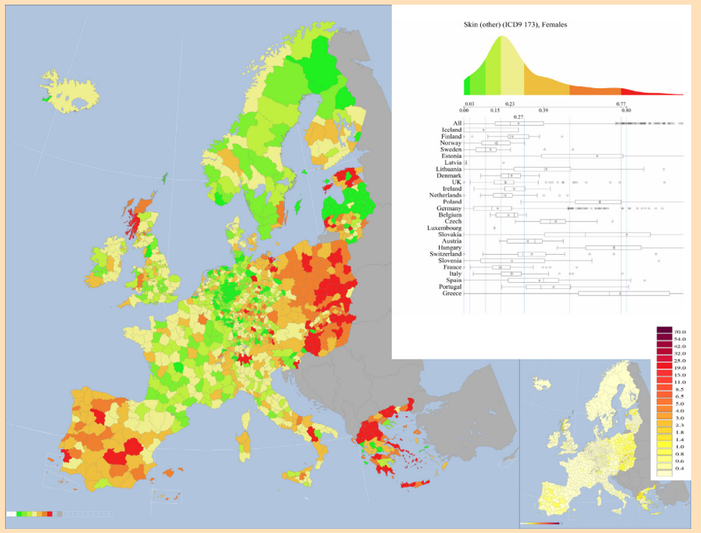
Sun exposure. The presence of actinic skin lesions, such as solar keratosis, lentigines, elastosis and telangiectasia, is frequently associated with BCC and SCC and reflects the role of chronic sun exposure in the risk of non-melanoma skin cancer [17]. The risk of SCC is strongly associated with increasing cumulative doses of sun exposure, independent of the pattern of sun exposure [19]. The association between sun exposure and BCC is more complex than that of SCC [16], and BCC seems more associated with intermittent exposure to high doses of solar radiation when compared to similar doses delivered more continuously [20].

Occupational exposure to untreated and mildly-treated mineral oil. The International Agency for Research on Cancer classified occupational exposure to untreated and mildly-treated mineral oil as carcinogenic to humans. This risk concerns squamous-cell carcinoma. These types of oils are used as lubricant bases for more refined oils such as engine oils, and the majority are used in automotive industries [21]. A case–control study evaluated that the risk of squamous-cell carcinoma is increased by 1.46 for those exposed to this carcinogen [22]. As the relative risk is low and the exposure concerns only a small fraction of the whole population, the number of SCC attributable to this exposure is very small.

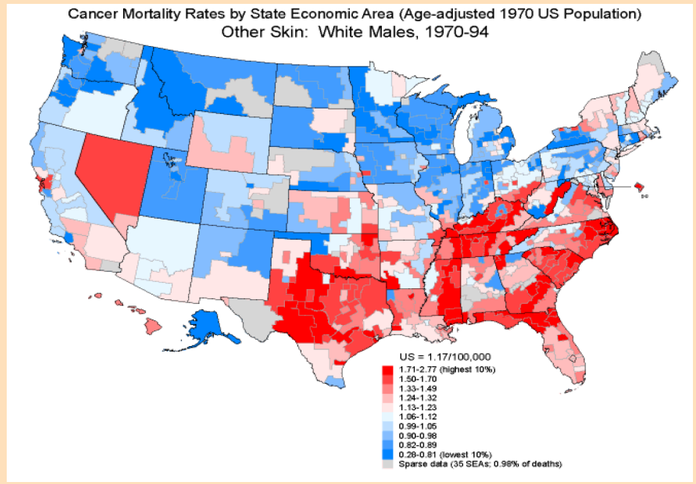
Immunodeficiency. Immunocompromised patients (renal transplant patients) have been repeatedly found to be at higher risk for non-melanoma skin cancer [23,24]. These observations strongly suggest that immune suppression could play a role in BCC and SCC etiology. This hypothesis could help in understanding the dramatic increase in the incidence of BCC and SCC with decreasing latitude, as solar radiation would cause SCC and BCC via two interacting mechanisms: the ultraviolet radiation-induced DNA damage of keratinocytes, and a decrease in immune control of carcinogenic events in the skin.

Skin infection with the Human papilloma virus. Non-melanoma skin cancer in immunocompromised subjects (e.g. organ transplant patients) was found to be associated with Human papilloma virus (HPV) infection of skin keratinocytes [25]. Persistent infections of the skin with high-risk genital HPV types (also known to be significant risk factors for cervical cancer) have also been found to represent a risk factor for non-melanoma skin cancer in non-immunocompromised subjects [26]. HPV infection of skin keratinocytes seems to be essentially associated with increased risk of SCC but not BCC [27] This association with HPV remains confined to SCC arising on chronically sun-exposed areas of the skin.

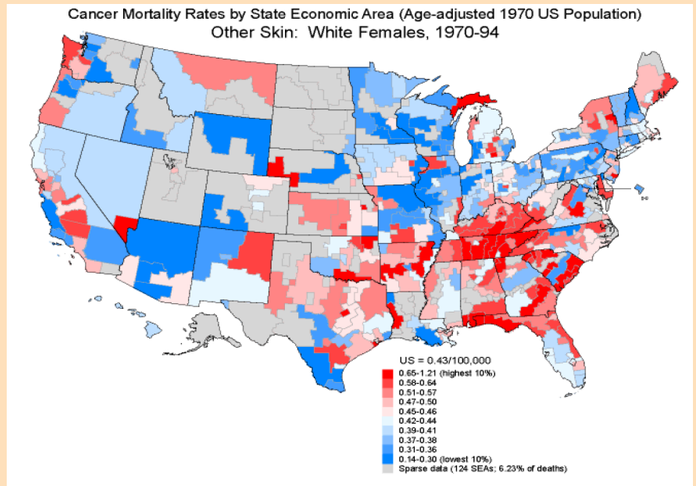
Genetics. Mutations of the TP53 gene are frequently observed in human SCC, and are associated with a history of sunburn [28]. In BCC, cell cycle regulatory factors other than TP53 are affected, such as mutations in the hedgehog signalling pathway genes [29].



European Map 5.12.2 *Mortality rates from non-melanoma skin cancer for women in Europe between 1993-1997*



US Map 5.12.1 *Mortality rates from non-melanoma skin cancer for men in US between 1970-1994*



US Map 5.12.2 *Mortality rates from non-melanoma skin cancer for women in US between 1970-1994*

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5.13 Cutaneous Melanoma

Summary

> The risk of developing malignant melanoma varies markedly according to racial background (skin pigmentation) and geography (sunlight-derived ultraviolet irradiation); highest incidence rates occur in white populations in Australia

> In Nordic countries, a steep increase in melanoma incidence has been attributed to excessive sun exposure during vacations in lower latitudes

> While prognosis for patients with localised melanoma is good, metastatic melanoma is largely resistant to current therapies

Melanoma is a malignant proliferation of melanocytes, the pigment-forming cells of the skin, which is the site of most (>95%) melanoma. There are about 160 000 new cases of melanoma worldwide each year, of which almost 80% are in North America, Europe, Australia and New Zealand. Incidence is similar in men and in women [2].

Malignant melanoma of the skin occurs predominantly in white-skinned populations ("Caucasians") living in countries where there is high-intensity ultraviolet radiation, but this malignancy afflicts all ethnic groups to some degree.

Assessed in relation to skin colour, melanoma incidence falls dramatically as skin pigmentation increases, and the disease is very rare in dark-skinned people. The highest incidence of melanoma occurs in Australia where the population is predominantly white. In this country, there is an average of six hours of bright sunlight every day of the year, and there is an essentially outdoors lifestyle. The lifetime risk of developing melanoma in Australia is 4–6% in men and 3–4% in women [2].

In Oceania, cutaneous melanoma is the third most common cancer in males (after prostate and lung cancers and before colon cancer), and the second in females (after breast cancer and before colon cancer). In North America, melanoma is the fifth most common cancer in males and the sixth in females. In Europe, melanoma is less common, being the eighth and the sixth most common cancer in males and females, respectively [3].

Dark-skinned people have a low risk of melanoma. In Africa and South America, the sole of the foot, where the skin is not pigmented, is the most frequent site affected in the context of a low incidence. Asian peoples have a low risk of melanoma despite their paler skins; naevi in Asian people, though common, are predominantly of the acral-lentiginous type which have low malignant potential.

Marked increases in incidence and mortality are being observed in both sexes in many countries, even where rates were formerly low, such as Japan. In the Nordic countries, for example, this averages some 30% every five years. In Sweden, between calendar periods 1960–1964 and 2000–2004, melanomas increased most rapidly on the upper limbs (men 885%, women 1216%) on the trunk (men 729%, women 759%) and on the lower limbs (men 418%, women 289%) in both genders. The incidence increase of head tumours was slower. Melanomas of the trunk and lower limbs dominate among patients <70 years, whereas tumours of the head are most common among patients ≥70 years. Tumours of the trunk formed an increasing proportion of all melanomas during the period studied, particularly in females. The relative shift of melanomas from the head to the trunk with mostly intermittent UV exposure coincides with behavioural and societal changes with regard to sun exposure [4] and probably also with increasing sunbed use. In, several populations, there are indications that greater awareness and surveillance may result in an increase in the diagnosis of early thin melanomas, but no clear reduction in the incidence rate of more deeply invasive melanomas.

Mortality rates are slightly higher in men than in women, with Australia and New Zealand registering rates of 5.1 and 6.1 for men, and 2.6 and 3.6 for women, respectively [2].

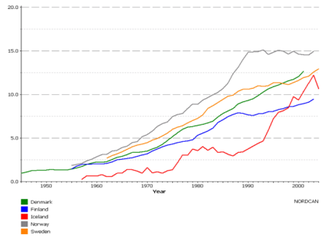


Fig. 5.13.1 *Melanoma of skin - Incidence: ASR (World), Male age (0-85+), (Rate per 100.000)*

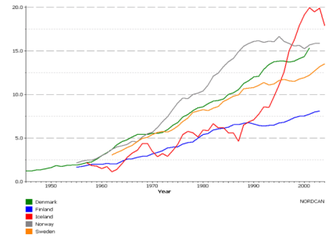


Fig. 5.13.2 *Melanoma of skin - Incidence: ASR (World), Female age (0-85+), (Rate per 100.000)*

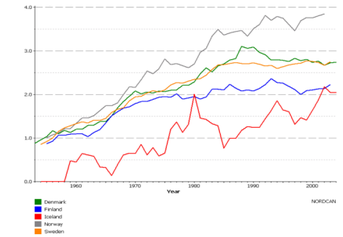


Fig. 5.13.3 *Melanoma of skin - Mortality: ASR (World), Male age (0-85+), (Rate per 100.000)*

Etiology

Melanoma risk factors include phenotypic pigmentation traits, naevi and sun exposure [5-7].

It is estimated that 80% of melanoma is caused by ultraviolet damage [8] to sensitive skin, i.e. skin that burns easily, fair or reddish skin, multiple freckles, skin that does not tan and develops naevi in response to early sunlight exposure. Prevention of melanoma is based on limitation of exposure to ultraviolet radiation, particularly in the first 20 years of life.

Ultraviolet radiation is particularly hazardous when it involves sporadic intense exposure and sunburn. Most damage caused by sunlight occurs in childhood and adolescence, making this the most important target group for prevention programmes. Other established risk factors include congenital naevi, immunosuppression and use of solaria [9].

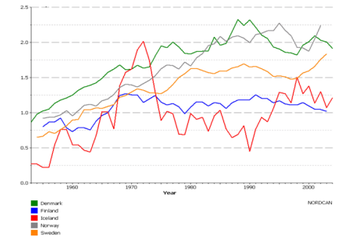


Fig. 5.13.4 *Melanoma of skin - Mortality: ASR (World), Female age (0-85+), (Rate per 100.000)*

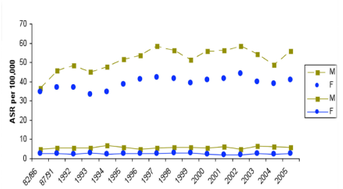
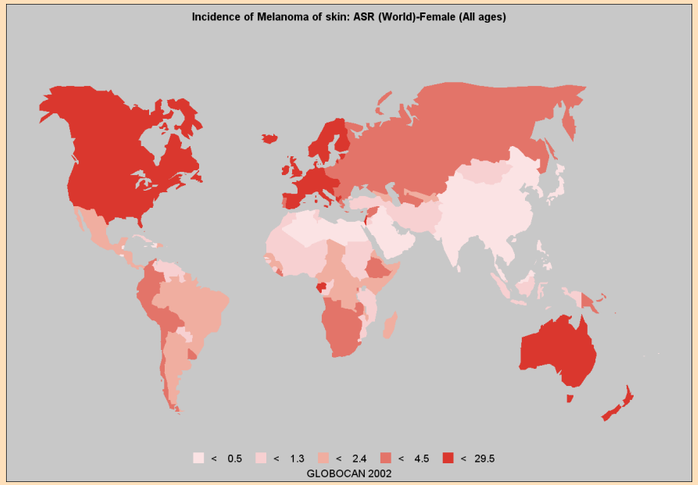
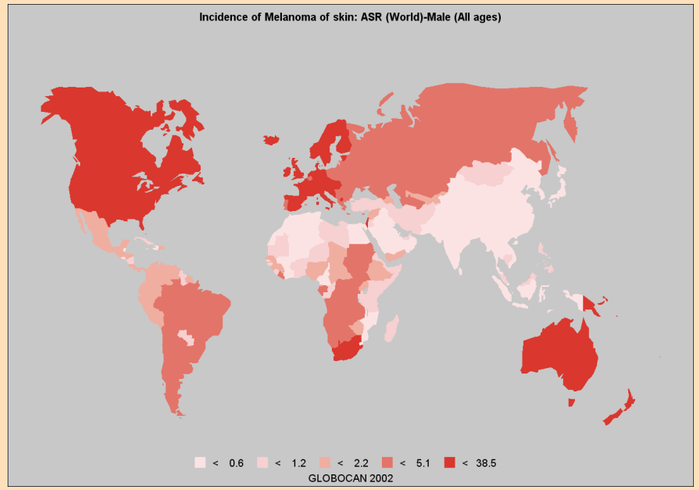


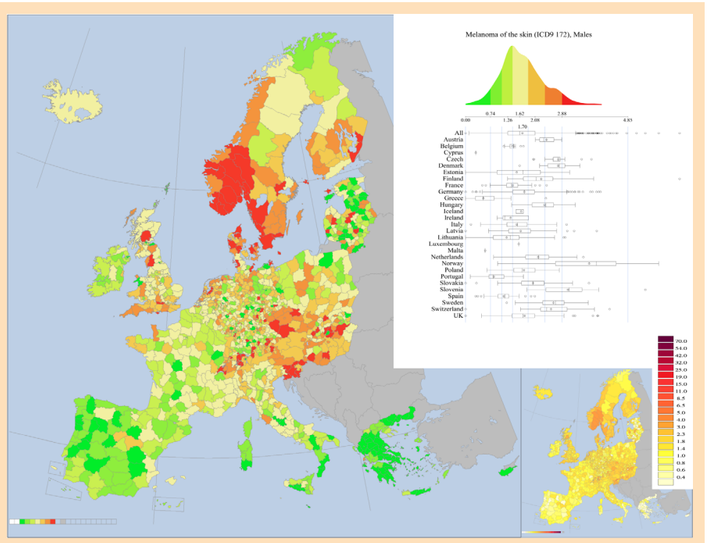
Fig. 5.13.5 *Incidence and mortality from cutaneous melanoma in Queensland, Austral (Queensland Cancer Registry (ASR per 100.000)*



World Map 5.13.1



Map 5.13.2



European Map 5.13.1 *The prominent features of the geographical distribution of melanoma in men are the high levels across (southern) Finland, Norway, Sweden and Denmark and into northern Germany and The Netherlands, in Austria, Switzerland, the Czech Republic, Slovakia, Hungary and Slovenia, and in southern England. Rates were low in most of Spain, Portugal, southern Italy and Greece [1].*

While melanoma may occur anywhere on the skin, the majority of melanoma in men is on the back, while in women the majority is on the legs. This difference in site incidence is not completely explained by differential exposure to ultraviolet light.

There is evidence from epidemiological studies that cutaneous melanomas arise through different causal pathways. Patterns of age-specific incidence of melanoma at different anatomical sites in fair-skinned populations show that melanomas arising on intermittently exposed body sites are significantly more common among younger and middle-aged adults, whereas melanomas of the head and neck are most common among older people. In younger patients the incidence of melanoma is higher on intermittently exposed skin areas than on continuously exposed areas: in both men and women under age 50 the highest melanoma density is on the back, while at ages over 50, the greatest density occurs on fully exposed sites, such as the face. Thus, intermittent sun exposure may have a greater potential for producing melanoma than continuous exposure at ages below about 50, though at older ages melanoma is more common on body sites with continuous sun exposure [10]. It was further shown that melanomas at different body sites arise through different pathways that have different associations with melanocytic nevi and solar keratoses. Patients who develop melanoma of the head and neck tend to have fewer naevi, greater lifetime exposure to sunlight and more evidence of chronic solar damage than those who develop melanoma of the trunk. Patients with Lentigo Maligna melanomas are also less likely than patients with truncal melanomas to have numerous naevi and tend toward more solar keratoses. Cutaneous melanomas may arise through two pathways, one associated with melanocyte proliferation and the other with chronic exposure to sunlight [11]. Most recently, molecular epidemiological studies have brought support to these views:

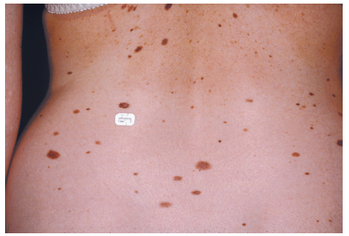


Fig. 5.13.6 *Dysplastic naevus syndrome, predisposing to non-familial malignant melanoma. The patient shows atypical cutaneous naevi, usually exceeding 5mm in diameter, with variable pigmentation and ill-defined borders*

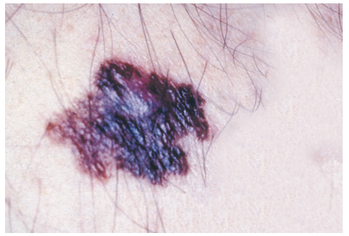


Fig. 5.13.7 *Primary melanoma with a coastline border and multiple colours, including classic blue black pigmentation*

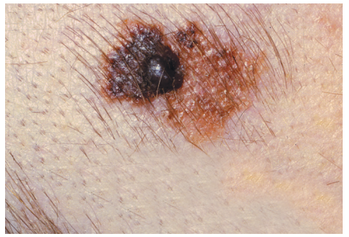
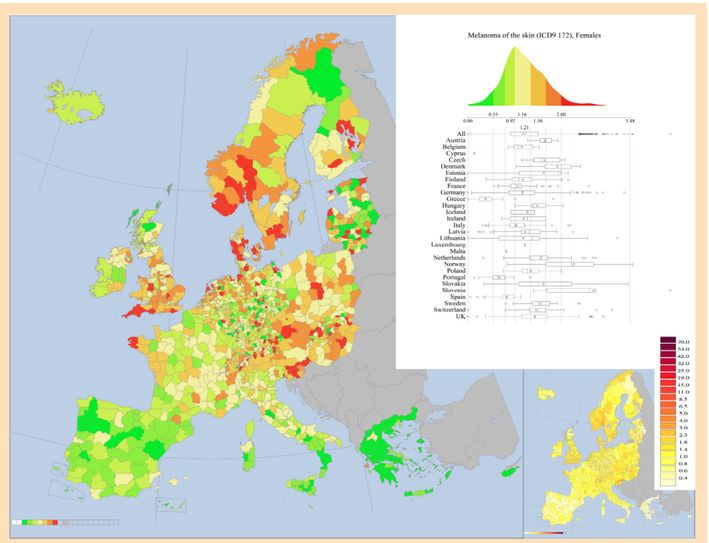


Fig. 5.13.8 *Melanoma with an elevated nodule*



European Map 5.13.2 *In females, the pattern was quite similar in broad terms with higher-than-average levels across (southern) Finland, Norway, Sweden and Denmark and into northern Germany and The Netherlands, in parts of Austria, Switzerland, the Czech Republic, Hungary and Slovenia, and in southern England. As in males, there were lower-than-average rates in Spain, Portugal, southern Italy and Greece [1].*

BRAF mutant melanomas tend to arise on the trunk and occur among younger people with many naevi.

Detection

Melanoma is usually asymptomatic, but a person with melanoma sometimes complains of an intermittent itch. Pain, bleeding and ulceration are rare in early melanoma. A melanoma often arises from a pre-existing pigmented lesion of the skin (a mole or "naevus") but these tumours can also develop in unblemished skin. The common predisposing skin lesions are dysplastic naevi, junctional and dermal naevi and blue naevi. However, the risk for melanoma development from mature dermal, junctional and blue naevi is quite small, estimated at approximately 1 in 200 000. Congenital naevi are also known precursors of melanoma, but the risk for malignant change is related specifically to the size of the naevus. Naevi greater than 20mm in diameter and, in particular, the large bathing trunk naevi have a high risk of malignant degeneration. The highest risk naevus is the dysplastic (atypical) naevus. These are naevi that are larger than 6mm in diameter, have irregular pigmentation, an ill-defined margin and often exist in multiples. Of particular risk is the dysplastic naevus syndrome (familial atypical mole syndrome) (Figure 5.13.6), in which the patient may have more than 100 of these irregular naevi; risk is highest in those patients with dysplastic naevus syndrome who have a near relative diagnosed with melanoma [12].

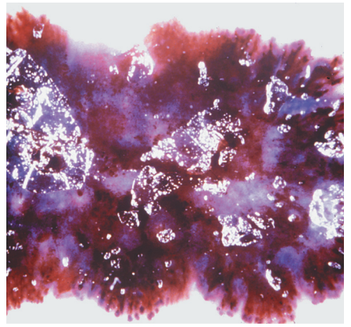


Fig. 5.13.9 *Surface microscopy of a melanoma, showing pseudopods, blue-grey veil and multiple colours*

The clinical features of melanoma are asymmetry (A), a coastline border (B), multiple colours and quite often some areas of blue/black pigmentation (C), and a diameter greater than 6mm (D). As the melanoma progresses, part or all of the lesion will become elevated (E) (Figure 5.13.7 and Figure 5.13.8). This ABCDE system has been the basis for clinical diagnosis for melanoma for many years. Surface microscopy [13] (dermoscopy, epiluminescence microscopy) has developed as an aid to the clinical diagnosis of melanoma. In this technique, the skin surface is rendered translucent by the application of oil, and a hand-held instrument providing magnification of at least ten times is used to view the internal details of the tumour. Many additional characteristics, such as pseudopods, radial streaming, blue/grey veil, peripheral black dots and multiple colours are visible and have been used in diagnostic systems now readily accessible to the clinician with an interest in cutaneous diagnosis (Figure 5.13.9).

Pathology and genetics

Melanoma occur primarily in the skin (where more than 95% of cases occur) but are also found in the mucous membranes of the mouth, nose, anus and vagina and, to a lesser extent, the intestine; melanocytes are also present in the conjunctiva, the retina and the meninges. The morphological classification system for melanoma defines four types: superficial

spreading melanoma, nodular melanoma, acral-lentiginous melanoma, and lentigo maligna melanoma. However, this classification has been superseded by a system based on the histopathological parameters of the excised lesion. Melanoma is now classified essentially on the vertical diameter of the lesion from the granular cell layer of the epidermis to the deepest detectable melanoma cell (tumour thickness). In recent years, one additional criterion, ulceration, has been shown to be important in prognosis and is included in the AJCC/UICC classification system (Table 5.13.1).

While it is clear that the genetic make-up of the melanoma-prone populations is very important, few melanomas can be ascribed to specific genetic defects in these populations. Loss-of-function mutations in the human melanocortin-1 receptor (MC1-R) have been associated with red hair, fair skin freckles and decreased ability to tan [14], all physical characteristics that affect susceptibility to skin cancer. While 10% of melanoma patients have a first-degree relative affected, less than 3% of melanomas in Australia (where the incidence of melanoma is high) can be ascribed to an inherited gene defect. Familial melanoma is even rarer in lower-incidence countries.

The familial melanoma syndromes are associated with germline mutations in highly penetrant genes [15]. About 20% of melanoma-prone families possess germline mutations in the CDKN2A gene, which encodes p16INK4A and p14ARF. Mutations in the pl6 binding domain of the gene encoding CDK4 have been identified in melanoma families without mutation of CDKN2A but are extremely rare [16]. The penetrance of the CDKN2A melanoma-predisposing gene varies with melanoma population incidence rates and is largely influenced by ultraviolet exposure across geographic latitude [17].

However, melanoma susceptibility genes identified in melanoma-prone families are rarely mutated in sporadic melanomas. Contrary to other skin cancers, only a small percentage (20%) of melanomas harbour mutations in the p53 gene. Nodular melanomas may display amplification of the MYC oncogene. Inactivation of p16INK4A is associated with a poorer prognosis. Different oncogenes and tumour suppressor genes may be involved in melanoma occurrence. Genes identified as having a role in sporadic melanoma development include CDKN2A, PTEN and BRAF, while cytogenetic studies have observed that genes located on chromosomes 1p, 6q, 7p, 9p and 11q are involved in the pathogenesis of melanoma. A high frequency of mutations of the BRAF gene, which resides on chromosome 7q, has been reported in primary melanomas [18]. The function of BRAF mutation in melanoma occurrence and development is currently being actively investigated. BRAF mutations are more common in melanomas arising on intermittently sun-exposed skin, but do not have the standard UVB signature [19]. It has recently been shown that genes involved in cellular signalling pathways may be inactivated in primary melanomas not only by mutation but also by deletion or epigenetic events [20]. Current data support a model in which genesis of melanoma requires changes that initiate clonal expansion, overcome cell senescence and reduce apoptosis. The inactivation of one critical pathway in the response to UV irradiation (such as p16 inactivation) may increase susceptibility to melanoma.

Cutaneous melanoma develops in a spatio/temporal sequence. Changes in expression of numerous melanoma associated genes can trace steps of melanoma progression from the early benign melanocytic lesions, to dysplastic naevi, to primary melanoma with radial (RGP) then vertical (VGP) growth pattern, to the acquisition of metastatic capacities. However, this sequence is currently challenged by the recent identification of malignant melanoma stem cells [21]. One of the major findings in cancer biology of recent years has been the identification of cells within tumours with stem cell-like properties. Such cancer stem cells were first identified in haematologic malignancies [22], then in solid tumours (breast cancers, glioblastomas, colon cancers and melanomas). It is not clear yet whether cancer stem cells arise from the malignant transformation of long-lived normal tissue stem cells or alternatively from the malignant transformation of lineage-restricted-progenitors or from differentiated cells [23]. Cancer stem cells share with normal tissue stem cells properties of self-renewal and the capacity to generate other sub-populations of cells within the tumour. Serial xenotransplantation experiments have shown that only a fraction of the cells in a tumour are essential for its propagation. Stem-like cancer cells are involved in the processes of progression and metastasis, and have been found to be highly resistant to drugs and toxins; hence they may constitute the small reservoir of drug-resistant cancer cells that survives chemotherapy and drives tumour recurrence and metastatic disease.

Classification	Melanoma thickness	Surgical excision margins
Tis	*in situ* melanoma/no invasion of the dermis	5 mm
T1	≤ 1 mm (in thickness)	10 mm
T2	1.1 mm – 2.0 mm	10 mm
T3	2.1 mm – 4.0 mm	Minimum 10 mm, maximum 20 mm
T4	> 4 mm	Minimum 20 mm, maximum 30 mm
Each T level is classified: A – if ulceration is present B – if no ulceration is present	There is no evidence that a margin greater than 1 cm improves survival but it may decrease local recurrence	There is no evidence that a margin greater than 1 cm improves survival but it may decrease local recurrence

Table 5.13.1 *Classification of melanoma (American Joint Committee on Cancer/International Union Against Cancer) and corresponding recommended excision margin*

Management

Treatment of primary melanoma is essentially surgical; the primary tumour is excised with a margin of normal skin, the excision being based on the tumour thickness measurement (Table 5.13.1) [24]. As the primary melanoma becomes thicker (deeper), the risk for metastatic spread rises; survival outcomes are thus related specifically to the tumour thickness measurement (Figure 5.13.10). Melanoma metastasises via the lymphatic system and also via the systemic circulation. Approximately 50% of melanomas metastasise first to the lymph nodes, thus making the management of lymph node metastases an important part of the treatment. Elective lymph node dissection (i.e. prophylactic removal of lymph nodes) is now rarely practised in the management of primary melanoma. The standard management for lymph nodes in patients with primary melanoma is an observation policy, with therapeutic node dissection if lymph nodes become involved. However, selective lymphadenectomy [25] is under clinical trial at the present time. This technique enables mapping of the lymphatics in the skin by lymphoscintigraphy: radioactive tracer is injected at the site of the primary and its flow through the skin to the first lymph node that takes up the tracer (the sentinel node) is identified. This lymph node is then removed for histopathological examination; only patients with positive lymph nodes are subjected to full lymph node dissection. An international trial has shown that the staging of intermediate-thickness (1.2–3.5mm) primary melanomas according to the results of sentinel-node biopsy provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy [26].

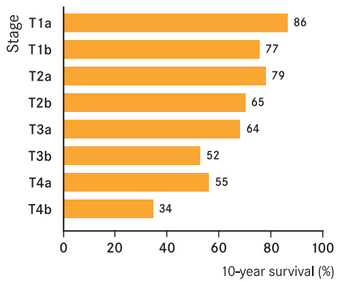


Fig. 5.13.10 *Ten-year relative survival for melanoma, according to stage*

The greater the number of nodes involved by melanoma cells, the higher the risk of systemic metastases and poor prognosis. As the thickness of the melanoma increases and as the number of lymph nodes involved rises, the risk of systemic metastases becomes greater. Melanoma metastasises widely, with the lungs, liver and brain being the most common sites. Vitiligo (a skin condition characterised by failure to form melanin) is a favourable prognostic sign in metastatic melanoma. At the present time, only a small proportion of people (<5%) live more than two years once systemic metastases become evident. The mainstay for the treatment of systemic metastases is chemotherapy. However, since the original introduction of dacarbazine 40 years ago, clinical trials conducted to date have failed to demonstrate a meaningful impact on survival. No highly effective single agent or combination has yet been developed, and metastatic melanoma is characterised by drug resistance [27]. Spontaneous regression of primary or metastatic melanoma, possibly as a result of natural and induced immune rejection, is rare but not uncommon (0.2–0.4% of cases), and this has led to increasing interest in immunotherapy. At the present time this modality remains experimental, although response rates of 15–20% to cytokines, such as interferon-α and interleukin-2, have been reported, and clinical trials of vaccines containing whole cells, lysates, dendritic cells or melanoma-associated antigens, such as MAGE, TRP and MART, are underway [28].

Recent progress in the understanding of melanoma biology has led to the identification of genetic lesions and intracellular signalling pathways that could serve as targets for novel therapy. An increasing number of new agents that have been shown to interfere with signalling pathways in melanoma, or to decrease proliferation, survival, migration or invasion, or to interfere with stromal components of melanoma such as angiogenesis and components of the immune system, are currently under evaluation [29].

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CANCER INSTITUTE PROFILE: European Institute of Oncology (IEO)

The European Institute of Oncology (IEO) in Milan, Italy is the fastest-growing comprehensive cancer centre in Europe. The brainchild of Professor Umberto Veronesi, it opened in 1994, and the hospital has grown such that in 2007 over 11 000 new cancer patients were treated, 3000 of whom were suffering from breast cancer. A new Day Hospital and Hotel will be completed within eighteen months, adding 50% to our clinical capacity.

The science base has grown in parallel such that the total number of full-time scientists including the IFOM-IEO science campus is now over 380. In 2007 IEO staff published 322 peer-reviewed articles with a total impact factor of 1870.

Last year the hospital staff succeeded in entering around half of its patients in clinical trials ranging from prevention, imaging, staging and therapy to pain control and supportive care. The personnel at the hospital were the first to carry out a random trial of breast cancer conservation, the first to show the value of sentinel node imaging and biopsy, and the first to complete a random trial of intra-operative radiotherapy (IORT) in breast cancer.

A key focus in the science labs is the molecular biology of normal tissue stem cells and their cancerous counterparts.

In addition, IEO has recently launched the first new online Open Access cancer journal, www.ecancermedicalscience.com.

website: www.ieo.it/inglese/index.asp

5.14 Breast Cancer

Summary

> Breast cancer is the most common cancer in women worldwide. Mortality from breast cancer has been declining in developed countries over the last two decades due to improved diagnosis (mammography) and (mainly) improved treatment

> Breast cancer risk is related to nulliparity and late first birth, early menarche and late menopause; it is reduced by breastfeeding

> Current use of oral contraceptives and of combined HRT is associated with increased breast cancer risk, which reduces to that of never-users 5 to 10 years after stopping use

> Family history of breast cancer and high mammographic density are among the best recognised breast cancer risk factors, which assist in identifying high-risk women for screening purposes

Breast cancer is the most common cancer among women worldwide. It was estimated that 636 000 incident cases occurred in developed countries and 514 000 in developing countries during 2002 [2]. Breast cancer is also the most important cause of neoplastic deaths among women; the estimated number of deaths in 2002 was 410 000 worldwide. The incidence of breast cancer is low (less than 20/100 000) in most countries from sub-Saharan Africa, in China and in other countries of eastern Asia, except Japan. The highest rates (80-90/100 000) are recorded in North America, in regions of South America, including Brazil and Argentina, in northern and western Europe, and Australia. With reference to time trends in incidence and mortality from breast cancer, the incidence has grown rapidly during the last decades in many developing countries, and slowly in developed countries. Mortality rates have remained fairly stable between 1960 and 1990 in most of Europe and the Americas, then showed appreciable declines, which have reached 25-30% in northern Europe [3]. The incidence increases linearly with age up to menopause, after which a further increase is less marked, or almost absent in developing countries.

Over 80% of the neoplasms of the breast originate from the ductal epithelium, while a minority originate from the lobular epithelium. However, the proportion of ductal carcinomas has been increasing over recent calendar periods. Survival from breast cancer has slowly increased in developed countries, where it now achieves 85%, following improvements in screening practices and treatments. On the other hand, survival in developing countries remains around 50-60%.

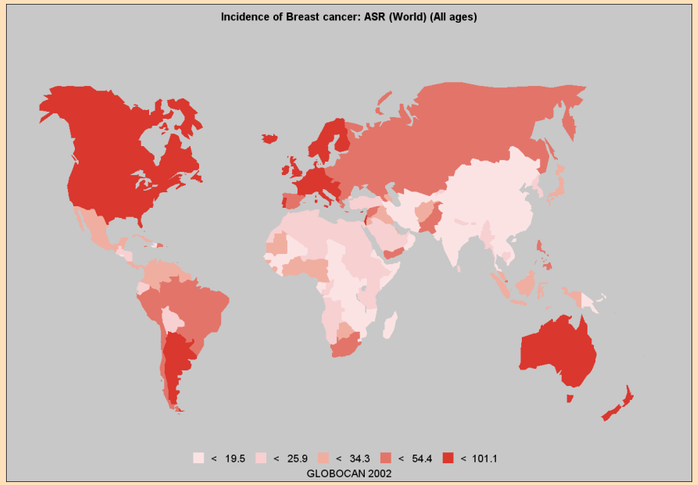
The risk of breast cancer increases with cumulative number of ovarian cycles. The risk decreases by about 15% for each year of delay in age at menarche and increases by 3% for each year of delay in age at menopause. Artificial menopause exerts a similar or somewhat stronger protective effect than natural menopause [4].

Pregnancy increases in the short term the risk of breast cancer, probably because of increase in the level of free estrogens during the first trimester. In the long run, however, pregnancy has a beneficial effect, since parous women have a higher level of prolactin and a lower level of sex hormone-binding globulin than nulliparous women. These two effects result in a protective role of early age at first pregnancy and a small residual protective effect of other pregnancies. An additional protective effect of lactation has been shown in several populations, probably attributable to the suppression of the ovulatory function caused by nursing. In a collaborative reanalysis of 47 studies, breast cancer risk decreased by 4.3% for each year of lactation (Figure 5.14.1) [5]. The Collaborative Group also reconsidered data from 53 epidemiological studies providing information on history of spontaneous or induced abortions, and found no association with breast cancer [6].

With reference to exogenous hormones, the risk of breast cancer is 15-25% higher in current and recent users of oral contraceptives (OC) as compared to never users (Figure 5.14.2) [7]. Further, 10 or more years after stopping OC use the risk levels off to approach that of never users, independently from duration of use. This is of particular importance since most women who use OC are young and have low baseline incidence of breast cancer. Therefore, their increased risk during and shortly after OC use has little relevance [8]. The evidence derived both from observational epidemiological studies (cohort and case-control) and randomised clinical trials indicates that the risk of breast cancer (mainly ductal cancer) is elevated among women using (combined) hormonal replacement therapy (HRT) [9]. The risk of breast cancer depends on duration of HRT use and is reduced after cessation of use, levelling off after 5 or more years since quitting HRT. The Women's Health Initiative, a randomised controlled trial conducted on post-menopausal women, provided comprehensive information on the risk of breast cancer in users of conjugated estrogen alone or in combination with progestin. In the estrogen-alone trial, after about 7 years of follow-up, there was no significant difference in breast cancer incidence comparing conjugated estrogen users to the placebo group (hazard ratio, HR=0.80) [10]. On the other hand, a higher incidence of invasive breast cancer was observed in the estrogen plus progestin group as compared to women receiving placebo. Further, breast cancers were diagnosed at a more advanced stage in the estrogen plus progestin group [11].

First-degree relatives affected with breast cancer	Cases : Controls	Risk ratio (99% FCI)
0	50,713 : 94,548	1.00 (0.97-1.03)
1	6810 : 6998	1.80 (1.70-1.91)
2	603 : 404	2.93 (2.37-3.63)
≥3	83 : 36	3.90 (2.03-7.49)

Table 5.14.1 *Risk ratios of breast cancer and 99% floating confidence intervals (FCI) in relation to family history of breast cancer in first-degree relatives. RRs are stratified by study, age, menopausal status, parity, age at first birth and number of sisters. (Data from Lancet (2001) 358, 1389-99)*



World Map 5.14.1

Besides exogenous hormones, the combined evidence from reproductive factors points towards a role of endogenous hormones in breast carcinogenesis. A direct assessment of the role of estrogen and testosterone is also available from recent prospective studies collecting epidemiological data and biological samples. Estradiol concentrations in the blood have been directly associated with breast cancer risk in post-menopausal women, particularly with estrogen and progesterone receptor positive tumours. Similarly, testosterone and other androgens have been found to increase breast cancer risk, but the data are inconsistent for all endogenous hormones across major cohort studies [12].

Fibrocystic disease and fibroadenoma, the most common benign breast diseases, are associated with a 2-3-fold higher breast cancer risk. Likely, these lesions are not pre-neoplastic conditions, but epithelial proliferation, linked to hormonal alterations, is a feature they share with breast cancer.

Family history of breast cancer is associated with a 2-3-fold higher risk of the same disease, and risk increases with the number of affected first-degree relatives (Table 5.14.1) [13]. This role of familial history is likely to result from low-penetrance genes associated with hormonal metabolism and regulation, DNA damage and repair. There is some evidence of an increased risk of breast cancer associated with polymorphisms of genes involved in the biosynthesis of estradiol, particularly the CYP19 gene. Several other low-penetrance genes have been analysed, but studies have generally reported null or inconsistent findings. In addition, breast cancer risk is greatly increased in carriers of mutations of several high-penetrance genes, in particular BRCA1, BRCA2 and p53. Although the cumulative lifetime risk in carriers of these genes might be over 50%, they are rare in most populations and explain only a small fraction (2-5%) of total cases.

Although a role of nutrition in breast cancer risk is strongly suggested by international comparisons, the combined evidence from epidemiological studies is inconclusive for most aspects of diet [14]. Several studies have been conducted to investigate whether intake of fruit, vegetables and related micronutrients, dietary fibre, total and saturated fats, dairy products, glycaemic index and load, and intake of phytoestrogens have an influence on breast cancer risk. No association emerged consistently from prospective studies, although there is some evidence for a protective role played by soy intake [15] and folate (by neutralising the enhancing effect of alcohol in moderate and high drinkers) [16]. Hormonal levels and nutritional factors during the intrauterine period and childhood are also likely to be important in breast carcinogenesis. In fact, energy intake during childhood is one of the determinants of adult height, which in turn has been directly associated with breast cancer risk in most epidemiological studies [17].

Besides height, other anthropometric factors are involved in the etiology of breast cancer. Weight gain during adult life has been consistently associated with postmenopausal breast

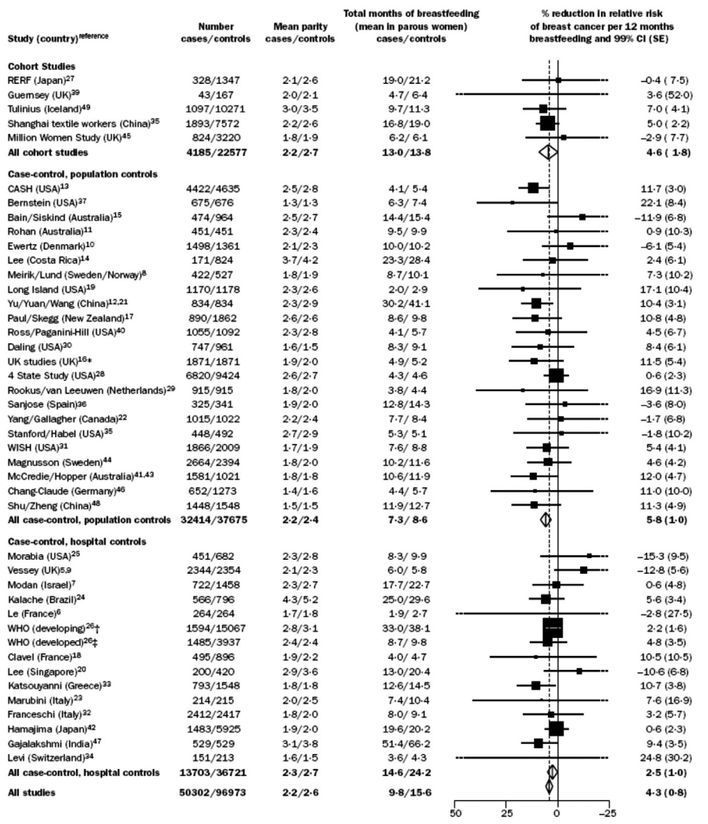


Fig. 5.14.1 *Details and results from cohort and case–control studies that contributed data on breastfeeding and breast cancer. (Figure from Lancet (2002), 360, 187-95)*

cancer incidence [14]. There is an inverse relationship between body mass index and breast cancer in pre-menopausal women and a direct relationship in post-menopausal women [18]. Further, in post-menopausal women, there is consistent evidence of a modifying effect of HRT use, as the increase in risk of breast cancer related to a high body weight and/or weight gain is stronger or limited to non-users of HRT.

Alcohol drinking is an established aetiological factor for breast cancer. Consumption of three or more alcoholic drinks per day increases the risk by 30–50%, with each daily drink accounting for an about 7% higher risk (Figure 5.14.3) [19]. It is likely that both obesity and heavy alcohol drinking act on breast cancer through mechanisms involving hormonal levels or metabolism. With reference to other lifestyle factors, tobacco smoking is not associated with development of breast cancer, while frequent physical activity is likely to moderately decrease the risk. Studies of occupational factors and of exposure to organochlorine pesticides have failed to provide evidence of an etiological role.

Male breast cancer is a rare disease. Less than 1% of all breast cancer patients are men [20]. Incidence rates in developed countries provide limited evidence of geographical and interracial variations, except for Jewish men who have higher than average rates. There is no clear correlation between incidence rates in men and women. Conditions involving high oestrogen level, such as gonadal dysfunction and liver damage, alcohol abuse and obesity, are risk factors for breast cancer in men. BRCA2 mutations are more frequent than BRCA1 in male familial breast cancers [21].

Primary prevention of breast cancer has been attempted via nutritional intervention, involving reduction of energy intake, reduction of proportion of calories from fat, and increase in fruit and vegetable consumption. No evidence of efficacy has been produced so far. However,

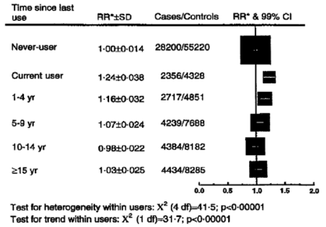


Fig. 5.14.2 *Relative risks (RR) of breast cancer and 99% confidence intervals (CI) in relation to time since last use of combined oral contraceptives. RRs are stratified by study, age, parity, age at first birth and age when risk of conception ceased. (Figure from Lancet (1996), 347, 1713-27)*

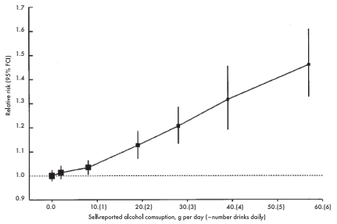
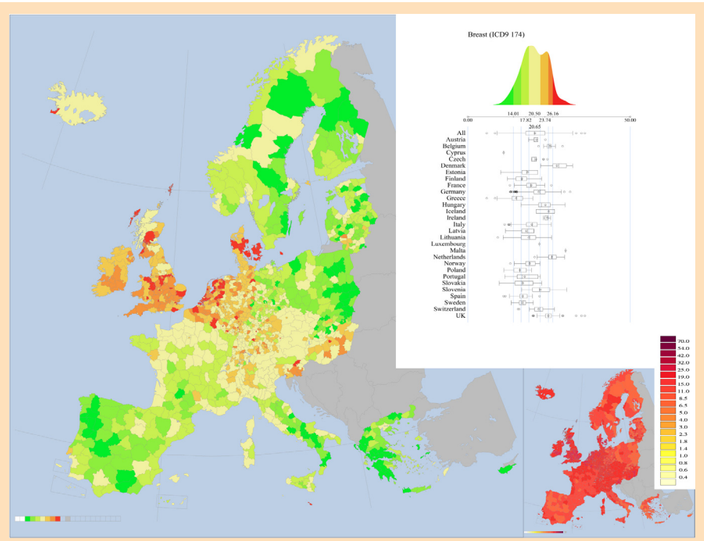


Fig. 5.14.3 *Relative risks (RR) of breast cancer and 95% floated confidence intervals (FCI) in relation to self-reported alcohol consumption. RRs are stratified by study, age, parity, age at first birth and smoking. (Figure from Br J Cancer (2002) 87, 1234-45)*

control of weight gain and of overweight and obesity in postmenopausal women would have favourable implications in breast cancer risk.

Tamoxifen, an anti-oestrogen drug used in chemotherapy, has shown a chemopreventive action against breast cancer, although the magnitude of the protection is uncertain [22]. Aspirin and other nonsteroidal anti-inflammatory drugs might also have a chemopreventive effect on breast cancer risk, although results from epidemiological studies are heterogeneous [23].

Secondary prevention through mammography is the most suitable approach for breast cancer control. The effectiveness of screening by mammography in women older than 50



European Map 5.14.1 *There are several notable features of the geographic distribution of breast cancer mortality in women in Europe.*
There is an aggregation of high rates that covers Denmark and westwards through northern Germany, The Netherlands and Belgium and then across to the United Kingdom and Ireland; mortality was also slightly above average in parts of Slovenia and Hungary. Rates were low in the Nordic Countries (apart from Denmark), Portugal, Spain, France, southern Italy and Greece.
There is nothing known about the etiology of breast cancer that can explain the geographic pattern demonstrated on the map. The pattern will change in the future as national breast screening programmes make their effects in reducing breast cancer mortality [1].

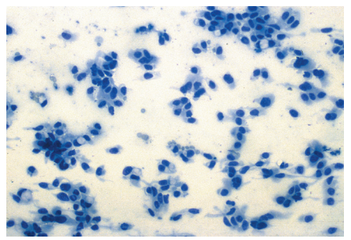


Fig. 5.14.4 *Fine needle aspirate of cells from a breast tumour*

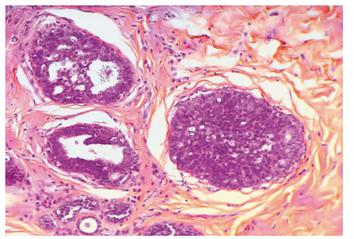


Fig. 5.14.5 *An example of lobular carcinoma in situ, comprising a well-differentiated malignant proliferation without signs of invasion*

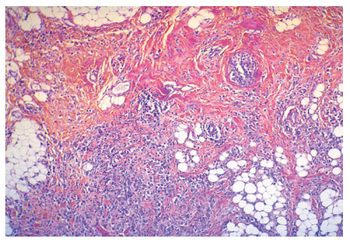


Fig. 5.14.6 *Infiltrating ductal carcinoma. This is a poorly-differentiated adenocarcinoma infiltrating the adipose tissue*

years has been demonstrated, and education programmes have been established in various countries. The effectiveness in women younger than 50 is not yet demonstrated, though there is some evidence for a reduction in risk of dying from breast cancer in women aged 40–49 years who undergo annual mammography. MRI has also been valuable in the screening of high-risk (BRCA-positive) young women [24].

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5.15 Cervical Cancer

Summary

> Cervical cancer is the second most common cancer among women worldwide; more than 80% of the global burden of cervical cancer is found in developing countries

> Cervical cancer is caused by persistent infection with one or more of the 15 oncogenic types of human papillomaviruses (HPV)

> Invasive cervical cancer is preceded by well-defined precancerous lesions that can be detected early by screening tests

> Population-based screening, leading to early detection of cervical precancerous lesions and their treatment, has led to greatly reduced cervical cancer incidence and mortality in developed countries

> HPV vaccination offers a promising option for cervical cancer prevention

Cervical cancers arise in the epithelium covering the uterine cervix, particularly at the junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix, a site of continuous metaplastic change, especially *in utero*, at puberty and after first pregnancy through to menopause. Persistent infection of the cervical epithelium with one or more oncogenic types of human papillomaviruses (HPV) lead to the development of precancerous lesions therein, a proportion of which, if not detected and treated, progress to invasive cervical cancer over a period of 10–20 years. Squamous-cell carcinomas are the most common type of epithelial tumours of the cervix, accounting for 85–90% of the epithelial cancers. Adenocarcinomas and adenosquamous cancers, among others, constitute the remaining 10–15%. Adenocarcinoma cases constitute a quarter of cervical cancer cases in western countries as a consequence of cytological screening.

Epidemiology

Cervical cancer is an important global public health problem. It accounted for an estimated 493 000 incident cases, 1.4 million prevalent cases and 273 000 deaths in the world in 2002, constituting approximately 8% of the global burden of cancer among women and the second most common cancer among women worldwide. Developing countries accounted for four fifths of this global burden, reflecting the grim reality of the lack of effective control measures in many high-risk countries. It is a major cause of mortality and premature death among women in their most productive years in low- and medium-resource countries in Asia, Africa and Latin America, despite the fact that it is an eminently preventable cancer.

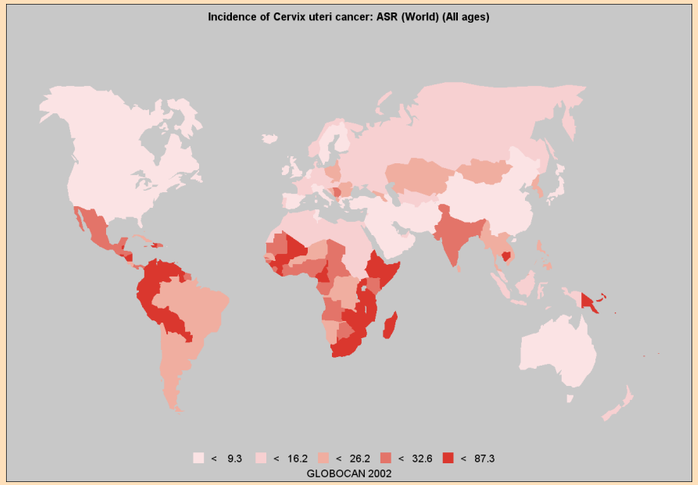
There is a more than twentyfold difference between the highest and lowest incidence rates of cervical cancer worldwide (Figure 5.15.1) [2,3]. In sub-Saharan Africa, Central and South America, South Asia and Southeast Asia, age-standardized incidence rates of cervix cancer exceed 25/100 000 in many countries. Rates lower than 7/100 000 women are observed in West Asian countries and in urban China, while these are lower than 10/100 000 women in most developed countries. The highest risk is observed in sub-Saharan Africa, Melenasia, Latin America and the Caribbean, and South and East Asia (World map 5.15.1). The incidence of cancer of the cervix begins to rise at ages 30–39, and then increases rapidly to reach a peak in the fifth or sixth decade of life. The high incidence rates in developing countries are mainly due to the lack of or ineffective screening programmes. Estimated age-adjusted cervical cancer mortality rates range between 3–8/100 000 women in most developed countries and 10–25/100 000 women in most developing countries [2]. The high mortality in developing countries is due to advanced clinical stage at presentation and to the fact that a significant proportion of patients do not avail themselves of or complete prescribed courses of treatment due to deficiencies in treatment availability, accessibility and affordability. Incidence and mortality declined markedly over the 5 decades after the introduction of population-based cervical screening programmes in the 1950s and 60s in Western Europe, USA, Canada, Australia and New Zealand. However, in recent years, notably in the UK, Nordic countries, Australia, New Zealand and eastern Europe. Increases in incidence have been observed in young women, particularly for adenocarcinoma [4,5].

A large variation in survival from cervical cancer is observed among countries due to the differences in clinical stages at presentation and the level of development of cancer-related health services. Five-year survival rates less than 25% are reported for black patients in Uganda [6] and Zimbabwe [7]; survival ranged between 30–50% in Cuba, India, and Philippines; 50–60% in Thailand and mainland China [8]; and 65% in Singapore [9]; rates range between 60–75% in developed countries [10,11].

Etiology

Persistent infection with one or more of the oncogenic types of HPV is the central and necessary cause of cervical cancer [12,13]. The recent IARC monograph concluded that there is sufficient evidence in humans for the carcinogenicity of HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 in the cervix [14]. HPV DNA has been detected in virtually all cervical cancer specimens [15,16]. The association of HPV with cervical cancer is equally strong for the two main histological types: squamous-cell carcinoma and adenocarcinoma.

However, since most cervical abnormalities caused by HPV infection are unlikely to progress to high-grade CIN or cervical cancer, as most of them regress by themselves, other exogenous or endogenous factors acting in conjunction with HPV may be necessary for progression of the disease. Epidemiological studies have identified a number of other risk factors that contribute to the development of cervical cancer precursors and cervical cancer. These include sexual intercourse at an early age, multiple sexual partners, multiparity, long-term oral contraceptive use, tobacco smoking, low socioeconomic status, infection with Chlamydia trachomatis, and micronutrient deficiency in vegetables and fruits. [12,13,17]. It is now clear that the well-established risk factors associated with sexual behaviour, such as multiple sexual partners and early age at initiation of sexual activity, simply reflect the probability of being infected with HPV. The assessment of the role of these co-factors requires that the central and strong effect of HPV be taken into account. A review of studies fulfilling this requirement has revealed that high parity, smoking and long-term use of oral contraceptives are co-factors that increase the risk of cervical cancer [18]. Additional co-factors such as herpes simplex virus type 2 (HSV-2), *Chlamydia trachomatis* infection, HIV and immunosuppression, certain micronutrient deficiencies and genetic susceptibility, are also implicated in cervical carcinogenesis [19-23].



World Map 5.15.1

Natural history

The cervical columnar epithelium is replaced by metaplastic squamous epithelium over several years after first pregnancy. The area of the cervical epithelium where this squamous metaplasia occurs is called the transformation zone (TZ), and this is where cervical neoplasia occur. The peak risk of HPV infection occurs soon after the onset of sexual activity, and HPV infects the basal cells or parabasal cells of the metaplastic epithelium. In most women HPV infection resolves spontaneously, but it may persist in some. If the infection persists, integration of viral genome into the host cellular genome may occur. The normal differentiation and maturation of the immature squamous metaplasia into the mature squamous metaplastic epithelium may be disrupted as a result of expression of E6/E7 oncoproteins and the loss of normal growth control. This may then lead to the occurrence, persistence and progression of precancerous lesions such as cervical intraepithelial neoplasia (CIN), particularly grade 3 CIN and adenocarcinoma *in situ* in some women. If undetected and untreated, these precursor lesions may progress traversing the basement membrane invading cervical stroma over a period of 5–20 years. The invasion may then involve blood and lymphatic vessels and the disease may spread to the lymph nodes and distant organs. While early detection of asymptomatic precancerous lesions by screening and their effective treatment lead to the prevention of invasive cervical cancer, prevention of oncogenic HPV infection by vaccination is an important emerging prevention option.

Pathology

Persistent HPV infection followed by a long phase of preinvasive disease precedes invasive cervical cancer. Precursor lesions of the cervix microscopically present as a spectrum ranging from cellular atypia to various grades of dysplasia or CIN. CIN are subclassified into 3 grades depending upon the thickness of the epithelium affected by the dysplastic cells. In grade 1, dysplastic cells are confined to the lower third of the epithelium (Figure 5.15.2), while CIN 2 is characterised by dysplastic cells restricted to the lower half of the epithelium (Figure 5.15.3). In CIN 3, differentiation and stratification may be totally absent and dysplastic cells present throughout the thickness of the epithelium, but the basement membrane is intact (Figure 5.15.4). In the case of adenocarcinoma *in situ* (AIS), normal columnar epithelium is replaced by dysplastic glandular epithelium showing loss of polarity and dysplastic features.

Histologically 85–90% of invasive cervical cancers are squamous-cell carcinoma, appearing as infiltrating networks of neoplastic cells in the stroma, with varying degree of differentiation, with or without keratinization (Figure 5.15.5). Other uncommon types of squamous carcinoma include verrucous carcinoma, papillary squamous-cell carcinoma, squamo-transi-

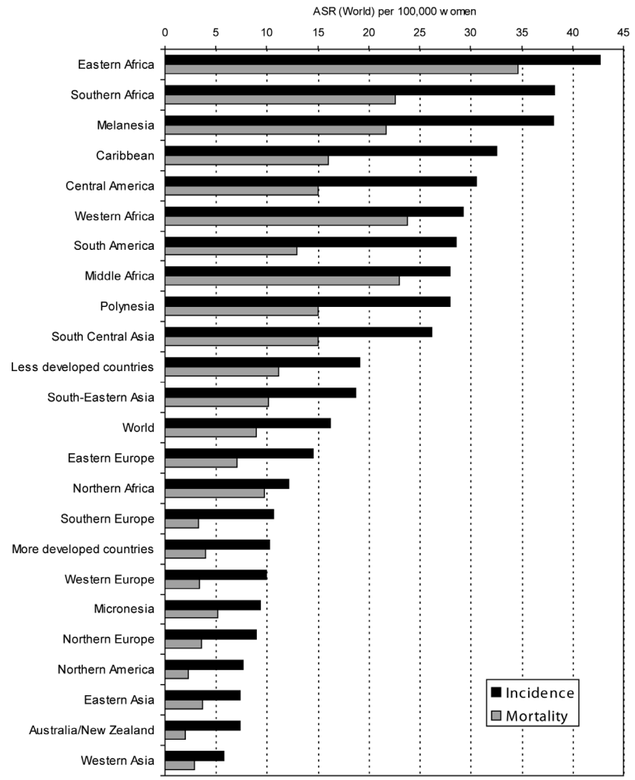


Fig. 5.15.1 *Cervical cancer incidence and mortality rates in selected regions*

tional cell carcinoma and lympho-epithelioma cell-like carcinoma. Adenocarcinoma and its variants constitute 10–15% of cervical cancers.

The most common type of adenocarcinoma is the endocervical cell type showing abnormal glands with varying size and shape with budding and branching, infiltrating the stroma (Figure 5.15.6).

Prevention by HPV vaccination

Primary prevention through vaccination offers a promising new tool to prevent cervical cancer. However, vaccines are currently expensive and there are several challenges and uncertainties in the widespread implementation of HPV vaccines. The currently available HPV vaccines based on virus-like particles produced by recombinant technology target preventing infection by HPV types 16 and 18, and are given using a regimen of three intramuscular injections over a six-month period. Monovalent (HPV 16), bivalent (HPV 16 and 18) and quadrivalent (HPV 6, 11, 16 and 18) virus-like particle (VLP) vaccines have been evaluated in randomised Phase II and III trials. Recent studies indicate that HPV vaccines are safe, highly immunogenic inducing high levels of serum antibodies in virtually all vaccinated women, and confer a high degree of protection (~99%) against HPV 16/18 infection and related CIN in fully vaccinated women [24,25]. The current information is based on a maximum of 5-year follow-up after vaccination and long-term immunogenicity and efficacy in preventing cervical neoplasia, cross-protection against HPV types not targeted by the vaccine antigens, the need for boosters and the efficacy of different, more logistically feasible dose regimes in inducing and maintaining immunogenicity, remain to be established.

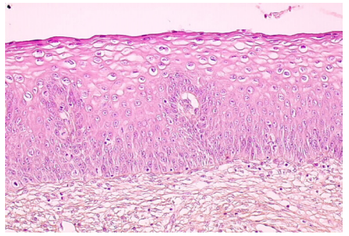


Fig. 5.15.2 *Histology of CIN 1 characterised by the dysplastic cells confined to the lower third of the epithelium*

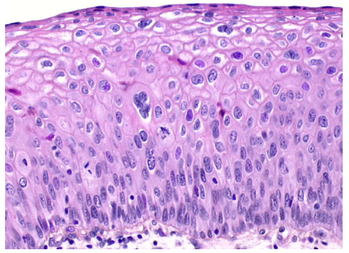


Fig. 5.15.3 *Histology of CIN 2 characterised by dysplastic cells restricted to the lower half of the epithelium*

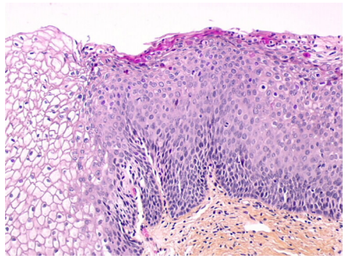


Fig. 5.15.4 *Histology of CIN 3 characterised by lack of differentiation and stratification and dysplastic cells are present throughout the thickness of the epithelium while the basement membrane is intact*

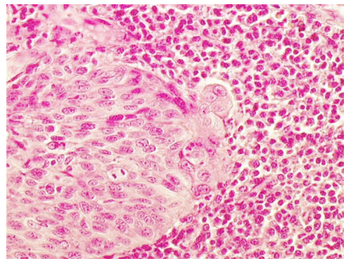


Fig. 5.15.5 *Squamous-cell carcinoma: note infiltrating networks of neoplastic cells in the stroma, varying degrees of differentiation, with keratinization*

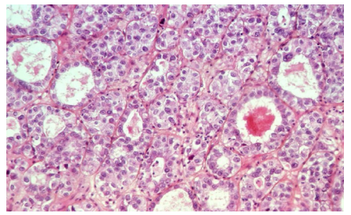
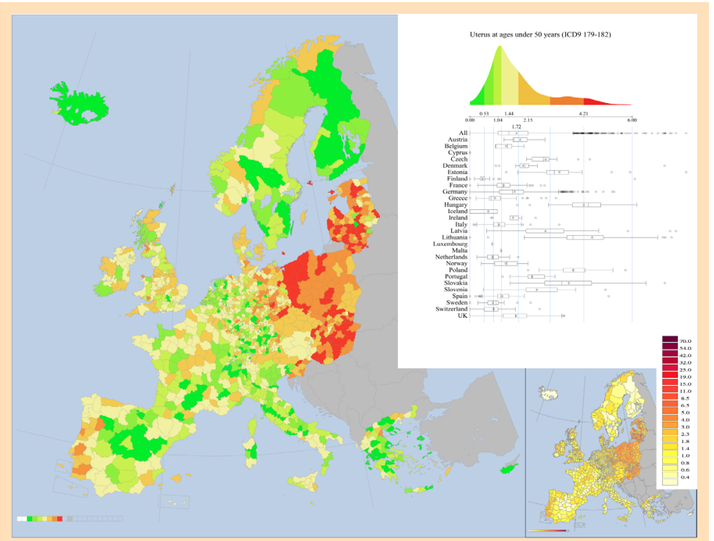


Fig. 5.15.6 *Adenocarcinoma of the cervix showing abnormal glands of varying sizes and shapes infiltrating the stroma*



European Map 5.15.1 *When consideration is restricted to mortality in women under the age of 50, the band of higher rates from Denmark southwards to Austria and Slovenia was still present but less prominent, as were the higher rates in Portugal. Rates were again highest in central Europe and low in Italy and Greece as well as Finland and Sweden [1].*

Prevention by screening

Early changes in the cervix, specifically CIN, can be detected years before invasive cancer develops by screening tests such as conventional cytology (Pap smear), liquid-based cytology, HPV testing and visual screening with acetic acid or Lugol's iodine [26]. An affordable, fast and simple new HPV test (careHPV) developed to detect 14 high-risk types of HPV is a promising test to screen women in developing countries [27]. Women with abnormal screening results are further investigated with colposcopy (a 4–20X magnified inspection of the cervix with a binocular endoscope), directed biopsies from abnormal areas identified on colposcopy [28]. For women whose TZ is not or only partially visible, a tissue specimen may be obtained using endocervical curettage (ECC) or by excising the cervical tissue by the loop electrosurgical excision procedure (LEEP) and subjecting these for histological examination.

The treatment of CIN has evolved from in-patient procedures like hysterectomy and cold knife conisation towards more conservative, safer, simpler and more effective approaches. CIN may be treated by destructive therapy such as cryotherapy, electrocoagulation, cold coagulation or laser vaporisation or by local excision methods such as the LEEP, large loop excision of the transformation zone (LLETZ), or laser excision. The basic principle of treatment of CIN is that the entire TZ of the cervix including the extension into the crypts (average depth 5mm) should be destroyed or removed [28]. Currently, cold knife conisation under local or general anaesthesia is reserved only for the treatment of micro-invasive cancer where evaluation of the margin is of prime importance. Hysterectomy should be reserved only for a

select few cases of CIN coexisting with associated gynaecological conditions requiring removal of the uterus.
CIN 2 and 3 being true cervical cancer precursors are always treated. CIN 1 lesions should be treated if follow-up cannot be ensured (as in most low-resource settings) or the lesion persists for 2 years or worsens in grade or size.

Diagnosis and management of invasive cervical cancer

Public and professional awareness are important in the early detection and management of invasive cervical cancer. Awareness of early symptoms and signs lead to clinical early diagnosis. Education and awareness are critical for the success of this approach. Clinical early diagnosis has been responsible for the reduction in mortality from cervical cancer achieved in developed countries before cervical screening programs were introduced [29,30].

Early, aymptomatic preclinical invasive cervical cancers may be detected during colposcopic assessment of screen-positive women. As invasion progresses, symptoms manifest with characteristic clinical features, depending on the clinical spread of the disease. Women with invasive cervical cancer often present with one or more of the following symptoms: intermenstrual bleeding, postcoital bleeding, heavier menstrual flows, excessive seropurulent discharge, recurrent cystitis, backache and lower abdominal pain. In advanced stages, patients may present with breathlessness due to severe anemia, edema of the lower limbs, haematuria, bowel obstruction, cachexia, a non-functioning kidney (due to ureteral obstruction), invasion of sacral nerve branches or extranodal extension.

Awareness of symptoms and signs of invasive cancer should prompt visual inspection of the cervix to rule out cancer. Clinical suspicion and speculum examination are important in the early detection of invasive cancer. Once a diagnosis of invasive cancer is made, it is mandatory to stage the clinical extent of disease, according to the International Federation of Gynaecology and Obstetrics (FIGO) classification, to guide treatment and prognosis (Table 5.15.1).

A diagnosis of invasive squamous-cell carcinoma or adenocarcinoma requires prompt referral for definitive treatment with surgery or radiotherapy, with or without chemotherapy. Women with microinvasive (stage I A) cancers may be treated with cold knife conisation or simple hysterectomy. Early cervical cancers (stage I B and IIA) may be treated with radical surgery or radiotherapy. Radical surgery for these stages involves the removal of the uterus with a cuff of vagina and the parametrial tissue. Radiotherapy with or without concomitant chemotherapy with platinum compounds is the treatment of choice once the disease has spread beyond the confines of the cervix and vaginal fornices (stages IIB and III). The management of cervical cancer with radical radiotherapy involves a combination of external beam therapy and intracavitary radiation. Concomitant chemotherapy with radiotherapy has improved local control rates in advanced cervical cancer. Treatment for locally very advanced stage IV A and distally spread (IVB) cancers is often palliative.

Clinical stage of disease at presentation is the single most important predictor of long-term survival; survival rates also decline with advancing age. The 5-year survival in stage I A disease ranges from 90–95%, 80–85% in stage I B, 50–65% for stage IIA, 25–35% for stage III and <5% for stage IV disease (Table 5.15.1).

Stage	Description of the stage of disease	5-year survival %
IA	Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm. Stage IA_1: Measured invasion of the stroma 3 mm or less in depth and 7 mm or less in diameter. Stage IA_2: Measured invasion of stroma more than 3 mm but 5 mm or less in depth and 7 mm or less in diameter.	90-95%
IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA. Stage IB_1: Clinical lesions 4 cm or less in size. Stage IB_2: Clinical lesions more than 4 cm in size.	80-85%
II	Stage II is carcinoma that extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina but not as far as the lower third section. Stage IIA: No obvious parametrial involvement. Involvement of as much as the upper two thirds of the vagina. Stage IIB: Obvious parametrial involvement but not onto the pelvic sidewall.	50-65% for II A disease 40-50% II B disease
III	Carcinoma that has extended onto the pelvic sidewall and/or involves the lower third of the vagina. On rectal examination, there is no cancer-free space between the tumor and the pelvic sidewall. All cases with a hydronephrosis or nonfunctioning kidney are stage III B, unless they are known to be due to other causes. Stage IIIA: No extension onto the pelvic sidewall but involvement of the lower third of the vagina. Stage IIIB: Extension onto the pelvic sidewall or hydronephrosis or nonfunctioning kidney.	25-30%
IV	Carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum. Stage IVA: Spread of the tumor onto adjacent pelvic organs such bladder or rectum. Stage IVB: Spread to distant organs.	<5%

Table 5.15.1 *Clinical staging and survival of cervical cancer*

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5.16 Ovarian Cancer

Summary

> Parity and oral contraceptive use reduce ovarian cancer risk. Late menopause and use of hormonal therapy in menopause are associated with moderate excess risk

> Overweight and obesity are moderately related to the risk

> The prevention of ovarian cancer is hampered by the lack of availability of early diagnostic techniques and the absence of a proven screening test

Most malignant neoplasms of the ovary originate from the coelomic epithelium; less frequent tumours originate from the germ cells (dysgerminomas and teratomas) and the follicular cells (granulosa cell tumours). In 2002 the estimated number of new cases worldwide was 204 000 with 125 000 cancer deaths, ranking ovarian cancer as the 6th most common cancer in women, and 7th most common cause of cancer death. High incidence rates (on the order of 10–12/100 000) are found in western and northern Europe and in North America; the lowest rates (<3/100 000) are from China and central Africa. In high-risk countries the rates have remained stable in recent decades.

Menstrual, reproductive and hormonal factors are the most widely investigated and best-recognised risk factors for ovarian cancer. Early age at menarche is a risk factor, but only has a modest effect on ovarian cancer risk. Lifelong number of menstrual cycles has also been associated with ovarian cancer risk, suggesting that ovulation may be implicated in the process of ovarian carcinogenesis. Several studies showed a direct relation between late age at menopause and the risk of ovarian cancer [2].

Nulliparity and low parity have been consistently related to ovarian cancer. Most studies showed a decline in risk associated with number of full-term pregnancies beyond the first one, thus suggesting that the inverse association is not due to infertility per se, and additional risk reduction is conferred by events accompanying each pregnancy [3].

The protection afforded by combined oral contraceptives (OC) is the other established, and most important from a public health perspective, feature of epithelial ovarian cancer. The overall estimated protection is approximately 40% in ever OC users and increases with duration of use to about 60% for users for 10 years or longer. The favourable effect of OC against ovarian cancer risk seems to persist for at least 15–20 years after OC use has ceased, and it is not confined to any particular type of OC formulation [4]. The issue of fertility drugs and ovarian cancer has also attracted lively interest, but the findings of various studies remain inconsistent. Hormone therapy in menopause has also been related to increased ovarian cancer risk, although the association is less consistent than that of breast cancer [5].

The implication of reproductive factors in the etiology of ovarian cancer suggests a major role of endogenous hormones in the disease. Several hypotheses have been postulated, as excessive gonadotropins stimulation [6] (see *Reproductive factors*, Chapter 2.7). To date, however, the epidemiological evidence of such an involvement is rather limited: only a few studies with limited sample size have been published on the association of endogenous sex steroids and ovarian cancer risk, with discordant results. Conversely, two case–control studies nested within large cohorts have shown an increase in ovarian risk with increasing circulating insulin-like growth factor concentrations in blood in young women (pre or peri-menopausal age)[7,8].

Additional support for an involvement of hormones in ovarian cancer comes from studies exploring the relationship between endometriosis and ovarian cancer risk. Endometriosis is an inflammatory disease, very often becoming clinically apparent during the reproductive years, that seems to be regulated by estrogens and progestins. Risk factors for endometriosis are similar to those for ovarian cancers, viz. age at menarche, irregular menstrual cycles and height, while pregnancy and oral contraceptive use seem to lower the risk of developing the disease. Apart from hormones, the chronic inflammatory state caused by endometriosis may also explain its implication in the disease, since other known epidemiological risk factors, such as talc use and pelvic inflammation, are related to chronic inflammation. A consistent association between endometriosis and ovarian cancer risk has been shown in many epidemiological and clinical studies. Prospective as well as case–control studies suggest an overall doubling in ovarian cancer risk in women who have endometriosis compared to women who do not [9].

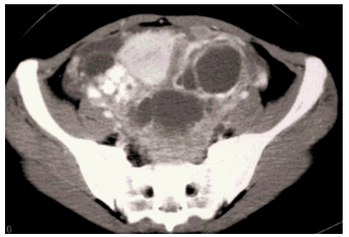


Fig. 5.16.1 *Magnetic resonance image (MRI) of a large, partly cystic ovarian carcinoma*

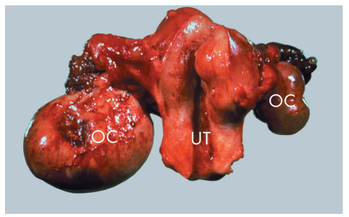


Fig. 5.16.2 *Surgical specimen of a bilateral ovarian carcinoma (OC). UT = uterus*

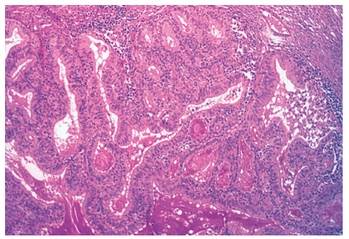
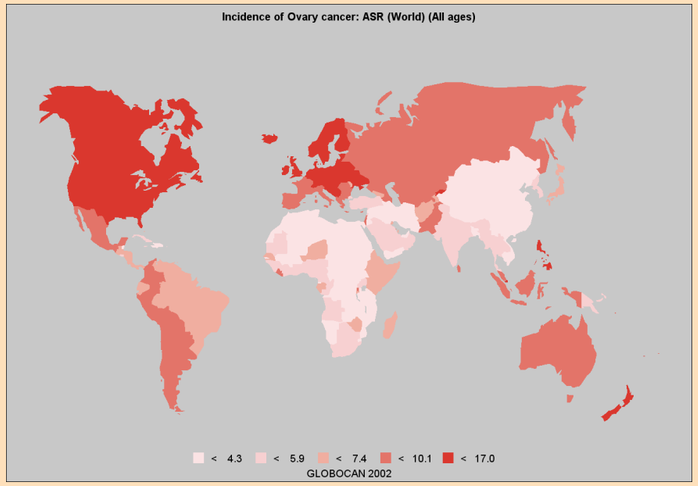


Fig. 5.16.3 *Histopathology of a well-differentiated, mucus-secreting, endometrial-like adenocarcinoma of the ovary*

Factors leading to greater adult height, including genetic, environmental, hormonal and nutritional factors, have been judged by the World Cancer Research Fund panel experts to be probable causes of ovarian cancer [10]. Results from cohort studies suggest an overall 15% increase in ovarian cancer risk with a 10cm increase in adult height, even though this relationship with risk is not supported by results from case–control studies. The association between ovarian cancer risk and adult height seems to be more related to specific subtypes of cancer (borderline mucinous) [11].

Potential links between ovarian cancer and diet were originally suggested on the basis of international differences or correlation studies. Overweight and obesity are moderately related to the risk of ovarian cancer: The estimated RR was 1.14 (95% CI 1.03–1.27) in the Million Women study [12]. Positive correlations were observed with fat, protein and total caloric intake and are generally in the same direction as those of endometrial and breast cancer. A relationship between ovarian cancer and intake of meat and fats has also been reported from some cohort and case–control studies, whereas fruit and vegetables appear to be inversely related. Some case–control studies found direct associations between measures of fat intake and risk of ovarian cancer. Starchy foods, and consequently diets with a high glycemic index and glycemic load, have also been related to excess ovarian cancer risk. The possibility that the milk sugar lactose or its metabolites have some effect on oocytes with a compensatory gonadotropic stimulation resulting in excess ovarian cancer risk has been investigated. Several, but not all, studies have found excess risk with lactose consumption and absorption, but the issue remains unsettled. Studies from Greece and Italy suggested that monounsaturated fats (olive oil) and fibre intake may be protective [13,14]. The role of diet on ovarian cancer incidence and mortality rates across Europe remains, however, unquantified [15].

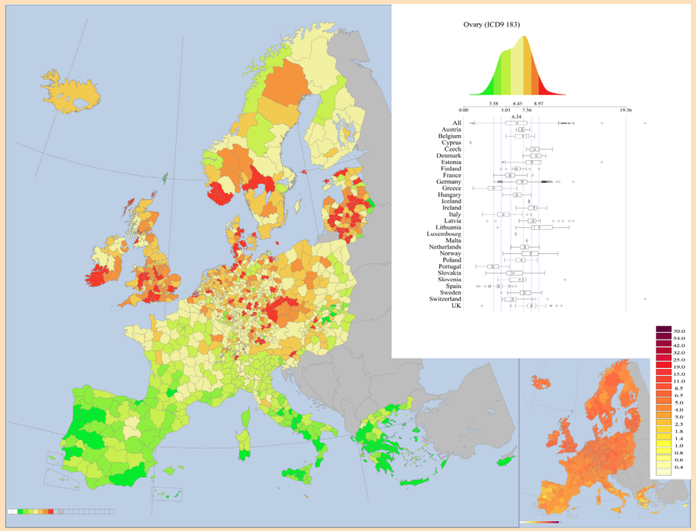


World Map 5.16.1

A relationship between smoking and ovarian cancer risk has also been suggested, even though results from studies are not totally consistent and largely negative. A recent meta-analysis including 910 women with mucinous ovarian cancer and 5564 women with non-mucinous ovarian cancer suggests a doubling in mucinous ovarian cancer risk in current smokers compared to never-smokers, but no increase in risk with other types of ovarian cancer [16].

There have long been clinical observations suggesting familial aggregations of ovarian cancer. Besides the clustering of ovarian cancer, an excess of breast cancer and a more general excess of several cancers (including colon and endometrium) have been described. These patterns are consistent with an autosomal dominant gene with variable penetration. The estimated relative risks from case–control studies that included data on family history range between 3 and 5 in most studies [17]. Women carrying BRCA1 or BRCA2 mutations have been seen to be at higher risk of developing ovarian cancer. The average cumulative risk of developing ovarian cancer by the age of 70 is 39% (22–51%) in BRCA1-mutation carriers and 11% (4.1–18%) in BRCA2 carriers [17].

The prevention of ovarian cancer is currently hampered by the limited knowledge of its causes and the lack of availability of early diagnostic techniques.



European Map 5.16.1 *While there are certain similarities with breast cancer in the geographic distribution of mortality from cancer of the ovary, there are also some potentially interesting differences [1].*

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CANCER INSTITUTE PROFILE: Karolinska Comprehensive Cancer Centre

Recently there was a merger of the two university hospitals in Stockholm, Sweden into the Karolinska University Hospital. The aim was to integrate research and education at the Karolinska Institute with the health care system in Stockholm and build a structure for translational medicine. The hospital and the campus of the Karolinska Institute together form an organisation with more than 18 000 employees. The decision has been made to develop a more visible and functional comprehensive cancer centre within this structure in order to form an environment for improved translational cancer research. With about 120 research groups involved in cancer research, there is a strong platform for basic, preclinical and epidemiological research. There is also important infrastructure for translational research, with experimental cancer research laboratories linked to oncological health care (Cancer Center Karolinska, a translational research structure), patient data registries containing population-based data, a clinical trial unit, a structure for biobanking and a platform for biomics. A particularly strong area of interest is proteomics, evidenced by the collaboration with the human proteome resource at the Royal School of Technology. The Centre provides oncologic service for the 2 million inhabitants in the Stockholm area. About 700 to 800 scientific reports in the area of cancer are published each year, as well as around 80 PhD theses.

5.17 Endometrial Cancer

Summary

> The "unopposed estrogens" hypothesis (long-term exposure to relatively high levels of estrogens, not counterbalanced by the presence of progesterone) is the most widely accepted hypothesis on the etiology of endometrial cancer

> Obesity is the most important risk factor for endometrial cancer worldwide, and has been estimated to account for up to 40% of endometrial cancer incidence

> The use of oral contraceptives is associated with a long-lasting decrease in endometrial cancer risk

> Much of the effects of dietary habits and physical activity on endometrial cancer risk may be explained by the link between energy intake, expenditure and body weight

Endometrial cancer is the seventh most-common cancer in women worldwide, and the fourth in developed countries, after breast, lung and colorectal cancers. This cancer appears more important in terms of number of new cases than in terms of mortality (representing 3.9% of new cancer cases in women compared to 1.7% cancer deaths) [2]. The highest incidences are in North America and in Western Europe, where it is about 10 times higher than in Asia or in rural Africa[2] . In these areas, endometrial cancer is the most common cancer of the female genital tract. The wide differences in incidence of endometrial cancer between rural and urban areas, as well as results of studies on migrations from low- to high-risk areas, strongly suggest strong environmental rather than genetic risk factors.

The overall incidence of endometrial cancer is rising as life expectancy increases. This cancer mostly arises in post-menopausal women: more than 90% of cases occur in women who are older than 50, with the highest incidence reached after 65 years of age [2]. Survival is rather good and parallels that of breast cancer (86% according to the SEER registries, and 78% in European registries) [2].

There are two major types of endometrial cancers. About 80% are of endometrioid type, are well to moderately differentiated, and are generally associated with endometrial hyperplasia (type I). They have favourable prognosis, and are strongly related to hormonal imbalances [3]. About 10% of endometrial cancers are type 2 (high-grade or poorly differentiated). Type 2 tumours are more often serous papillary, squamous cell or clear cell carcinomas, and seem to be unrelated to estrogens [3]. Women with type 2 tumours are at high risk of relapse and of metastatic disease. Type-I carcinomas are associated with mutations in the ras oncogene and PTEN tumour suppressor gene, as well as with microsatellite instability, while the majority of type-2 tumours are associated with p53 mutations.

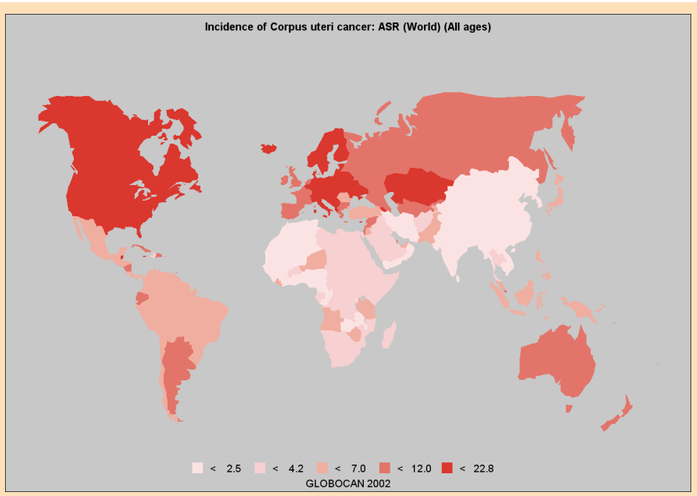
Since endometrium is a tissue that is very responsive to hormone stimulation, hormones seem to play an important role in the etiology and in the development of this cancer. Endometrial cell mitotic rate is sensitive to estrogens, especially to estrogens that are unopposed by progestins: the proliferation rate of endometrial cells seems to reach its maximum during the first 18 days of the menstrual cycle (follicular and early luteal phases), phases in which progesterone levels are particularly low. The "unopposed estrogens" hypothesis (long-term exposure to relatively high levels of estrogens, not counterbalanced by the presence of progesterone) [4] is the most widely accepted hypothesis on the etiology of endometrial cancer and can explain most of the risk factors already identified: early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity. An early age at menarche and a late age at menopause increase the exposure of a woman to estrogens over her lifespan, while pregnancies mainly increase her exposure to progestogens (through placental production).

Obesity is the most important risk factor for endometrial cancer worldwide, and has been estimated to account for about 40% of endometrial cancer incidence. In pre-menopausal women, obesity is associated with anovulatory cycles during which the endometrial tissue receives continuous stimulation. In post-menopausal women, increased body fat mass increases the concentration of endogenous estrogens, because in this population estrogens are not produced by the ovary anymore, but are mainly produced by the aromatisation of androgens in the adipose tissues. Excess weight is associated with insulin resistance and chronically elevated insulin concentrations in blood, and with increasing concentrations of bioavailable sex steroids [5], factors that are associated with increased endometrial cancer risk (Figure 5.17.1). Type-2 and type-1 diabetes are strongly associated with an increase in endometrial cancer risk, as well as hypertension. Hyperglycaemia has also been associated with an increase in endometrial cancer risk, especially in overweight women.

	Premenopausal		Postmenopausal
	Normoandrogenic	Hyperandrogenic (PCOS)	
SHBG	↓	↓	↓
E_1	↑	↑	↑
E_2 (total)	~	~	↑
E_2 unbound to SHBG	~	~	↑
Δ-4A	~	↑	~↑[α]
T (total)	~	↑	~↑ [α]
T unbound to SHBG	↑	↑↑	↑

Fig. 5.17.1 *Effects of obesity and chronic hyperinsulinemia on plasma sex steroids in women [5]*
[α]Observed relationships between obesity/plasma insulin and plasma androgen levels in postmenopausal women are inconsistent across studies, and might depend on genetic factors predisposing to hyperandrogenism.

The use of OC is associated with a long-lasting decrease in endometrial cancer risk, but only when the contraceptives used contain progesterone in addition to estrogens [6] (Figure 5.17.2). Since in these drugs the concentrations of progestagens are dominant compared to oestrogen concentrations, the proliferation of endometrial cells happens only during the few days of the menstrual cycle when OC are not taken. Based on this assumption, the decrease in endometrial cancer risk has been calculated to be about 10% per year of OC use. Oestrogen-containing pills only, conversely, increase the risk of endometrial cancer. The use of HRT in post-menopausal women increases about twofold the risk of developing endometrial cancer [7] (Figure 5.17.3), and the risk increases with duration of use and with increasing oestrogen concentrations in the medications. Adding progesterone daily to estrogen therapy seems to lower the risk of endometrial cancer similar (or lower) to that of non-estrogen users [6]. A recent publication suggests that the risk of endometrial cancer in women taking HRT may be associated with relevant genotypes regulating steroid hormone sulfation.



World Map 5.17.1

Relatively higher endogenous estrogen concentrations in blood are associated with an increase in endometrial cancer risk mainly in post-menopausal women, while higher endogenous androgen concentrations are associated with an increase in endometrial cancer risk in both pre- and post-menopausal women [5]. Polycystic ovary syndrome (PCOS) (a syndrome associated with increased blood androgen levels, and with infertility, amenorrhea, hirsutism and diabetes) has been repeatedly associated with an increase in endometrial cancer risk [5].

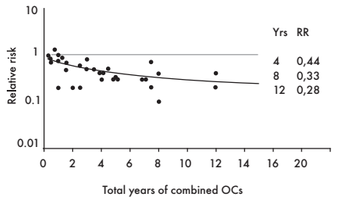


Fig. 5.17.2 *Relative risk of endometrial cancer by duration of use of combined oral contraceptives [11]*

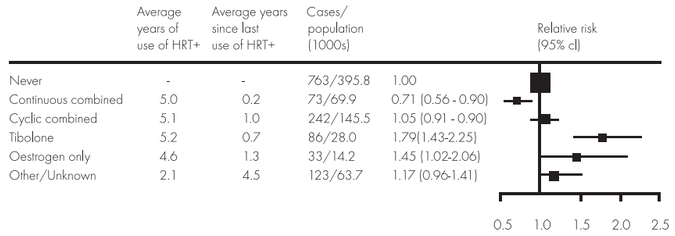


Fig. 5.17.3 *Relative risk of endometrial cancer according to type of hormone replacements therapy used (Million Women study) [7]*

In respect to dietary factors, phytoestrogen, antioxidant and vegetable consumptions have been associated with a decrease in risk of endometrial cancer [8,9]. Conversely, recent publications have suggested an increase in endometrial cancer risk with high consumption of meat.

Women who develop breast cancer are at increased risk of developing endometrial cancer, and are more likely to develop type-2 rather than type-I endometrial carcinoma. This increase in risk could be partly explained by common risk factors between breast and endometrial malignancies (as nulliparity or late age at menopause), but the use of tamoxifen for the treatment of breast cancer has also been questioned: women under tamoxifen therapy had more than a twofold increase in endometrial cancer risk compared to non-users. Physical activity has been shown to decrease the risk of endometrial cancer, although further studies are needed to finally assess its influence on the disease. Epidemiological evidence suggests that smoking may be protective against endometrial cancer in post-menopausal women, but it seems to be associated with an increase in endometrial cancer risk in pre-menopausal women. Much, if not all, of the reported effects of dietary habits and physical activity on endometrial cancer risk may be explained by the link between energy intake and expenditure, and body weight. The same may be true for the apparent lower risk among smoking women, as they tend to be leaner than non-smoking women.

As stated previously, genetic causes of endometrial cancer are uncommon, although having a first-degree relative with endometrial cancer has been associated with double the risk of developing the disease, and an association with hereditary non-polyposis colon cancer (HNPCC) syndrome has been observed [3]. Screening for endometrial cancer does not seem to improve survival or reduce mortality from endometrial cancer, since most of the cancers detected with screening would be most likely low-risk cancers [3,10]. Post-menopausal bleeding is the most common symptom of endometrial cancer, which is present in 75% of women with the disease. Women should therefore be aware of the importance of detecting post-menopausal bleeding or spots. Conversely, no tests have so far been validated or are recommended for endometrial cancer screening [10].

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BRIEF REPORT FROM THE WHO REGIONAL OFFICE FOR AFRICA

Cancer is an emerging public health problem in the WHO African Region. The commonest cancers are Kaposi sarcoma and cancers of the liver and prostate gland in men, and cancers of the cervix and breast in women. In Africa the cancer situation is characterised by 80–90% of cancer cases being incurable at presentation, 10–15% curable when given appropriate treatment and less than 5% prevention actions implemented. According to GLOBOCAN, 412 100 people in sub-Saharan Africa died from cancer in 2002. If no interventions are put in place, it is projected that by the year 2020 the number of new cancer cases will be 804 000 and the number of deaths due to cancer will be 626 400. The main risk factors for cancer are infectious conditions, tobacco use, unhealthy diet, environmental pollution, excessive alcohol intake and physical inactivity. Use of traditional diets, farming and pasturing are protective factors.

In the WHO African Region, a few countries including Guinea, Senegal, South Africa and Tanzania have national cancer control policies and programmes. Data on the magnitude of cancer are scanty or nonexistent. Cancer registries exist but not many countries have published national data in global outlets. Cervical cancer prevention programmes have been implemented in many countries including Guinea, Uganda, South Africa, Zimbabwe and Tanzania; these initiatives must be scaled up. Well-equipped infrastructure and facilities for early cancer detection or management requiring surgery, chemotherapy and radiotherapy are very lacking in most countries. While there is an acute shortage of cancer specialists such as pathologists for diagnosis, oncologists for treatment and oncology nurses for care, some national universities, especially in South Africa, Nigeria, Kenya and Senegal, have started training programmes for health personnel specialists in various cancer domains. There is increasing political will to address cancer-related issues and challenges.

The WHO Regional Office for Africa (AFRO) is committed to public health actions designed to reduce cancer incidence and mortality and to improve quality of life of patients through the systematic implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment and palliative care. The WHO-AFRO Regional Director has made cancer prevention and control a priority for the Region and provided the Regional office with resources to tackle the problem. There have been:

- actions of *advocacy* to increase commitment, such as a roundtable held on August 2007 during the AFRO Regional committee to underline the best approaches to increase awareness and put cancer high on the national agenda;
- *statements of commitment* facilitated among member states including the adoption of resolutions and, a regional strategy for cancer control to be submitted to next regional committee in September 2008 for adoption by Member States;
- *normative guidance and technical support* for national programme development and implementation, such as a tool for key interventions in cancer prevention and control to be published soon and an integrated approach for non-communicable diseases that incorporates comprehensive health promotion components;
- at regional and country levels, many *specific interventions* have been implemented with AFRO's support including capacity-building, mobilisation and allocation of resources, collaboration and partnerships (with other UN agencies such as IAEA and IARC, and international NGOs including UICC and the American Cancer Society), strategic information and surveillance including STEPs and tobacco surveys; and research.

The future perspective for the WHO African Region is the adoption and implementation of a regional strategy for cancer control where prevention, early detection, treatment and cure of cancers are systematically implemented or scaled up and where all cancer patients receive the best possible care.

website: www.afro.who.int)

5.18 Testicular Cancer

Summary

- A rapid increase in the incidence of germ-cell testicular cancer has been reported, particularly in young white men
- Little is known about the etiology and the cause(s) of the observed increase in incidence of the disease. Exposure to sex hormones and hormone-like chemicals in utero and/or during puberty appears to be important to the occurrence and the progression of the disease
- Genetic susceptibility is likely to explain the uniformly low rate and lack of increase in black populations worldwide
- Epigenetic or other cellular changes may be responsible for the rapid decrease of the disease after age 35

During the last several decades, epidemiological studies conducted in various parts of the world have demonstrated a rapid increase in the incidence of germ-cell testicular cancer, predominantly in young men. Birth cohort analyses suggest that the observed long-term increasing trend of testicular cancer is real. While considerable efforts have been made in studying the etiology of testicular cancer, little is known about the etiology and the cause(s) of the observed increase in incidence of the disease. Nevertheless, the following descriptive epidemiological features of germ-cell testicular cancer as summarised by Zheng et al. [2] offer important clues for searching for the risk factors of germ-cell testicular cancer:

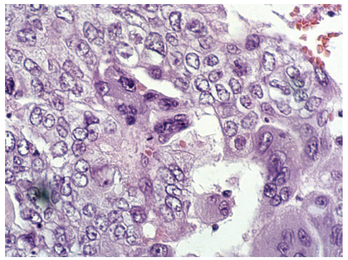


Fig. 5.18.1 *Testicular teratoma, Wellcome Images*

1. Different populations or different birth cohorts of the same population have wide differences in magnitude in the incidence of testicular cancer. For example, there is a fivefold difference in incidence rates between Denmark and Finland, with Denmark (along with Switzerland) having the highest reported incidence rate of germ-cell testicular cancer in the world. Danish men born during World War II, however, had lower-than-expected rates in most age groups [3]. These observations indicate that environmental exposures may be of significant importance in the occurrence and/or the progression of the disease.

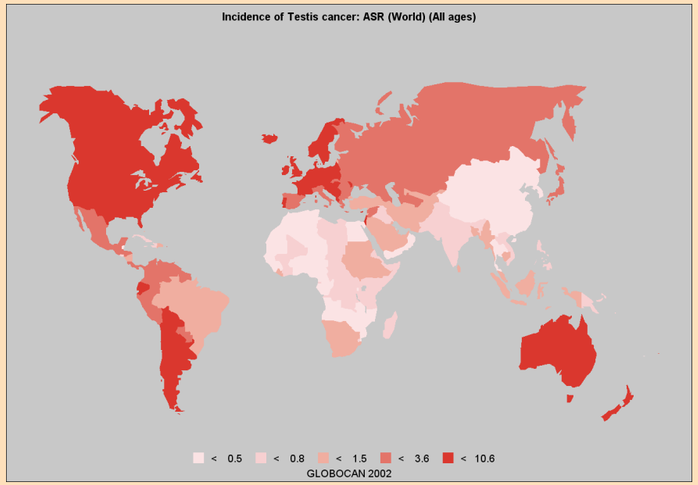
2. Different populations or different birth cohorts of the same population have very similar age-incidence patterns. Testicular cancer has a very small peak in the postnatal period (particularly for non-seminoma), followed by a rapid increase after puberty, and peak at around age 25 for non-seminoma and age 35 for seminoma. The vast majority of the cases of germ-cell testicular cancer are diagnosed between ages 15–45. The early onset of the disease, the rapid increase in rate after puberty and the peak at young age suggest that early-life exposure and male sex hormones are related to the occurrence and/or progression of germ-cell testicular cancer.

3. Black populations living in different parts of the world, whether in North America, Europe or Africa, have very low and similar incidence rates of germ-cell testicular cancer (<1/100 000 for the majority of the black populations). They also have not shown a long-term increase during the past decades as observed in the white populations. It is difficult to argue that blacks have universally had lower exposure to testicular cancer risk factors than whites. Rather, lower genetic susceptibility to environmental exposures may be responsible for the uniformly low rate and lack of increase in the black populations. A recent study by Zhang et al. [4] found that black mothers had a significantly lower ratio of sex hormones (estradiol/testosterone) in the first and the third trimesters; the authors suggested that this lower ratio might be responsible for the lower risk of germ-cell testicular cancer observed among black men.

Etiology

Analytical epidemiologic studies of risk factors for testicular cancer have thus far not provided convincing evidence to explain these descriptive features of germ-cell testicular cancers. The results linking major suspected risk factors (such as endogenous hormones and environmental hormone disruptors) to testicular cancer risk have been inconsistent, possibly due to small sample sizes in the majority of studies. Few studies so far have investigated the relationship between genetic susceptibility and gene-environment interaction in the risk of developing the disease. The following summarises the major suspected risk factors for germ-cell testicular cancer:

High levels of endogenous hormones during early pregnancy or adolescences. Henderson et al. [5] and Depue et al. [6] hypothesised that the major risk factor for testis cancer is a relative excess of certain hormones (in particular estrogen) during early pregnancy, perhaps at the time of differentiation of the testes. Several indices of early-life exposure to elevated levels of circulating maternal estrogens have been linked to testicular cancer risk, though the results have been inconsistent. These indices include bleeding, spotting, excessive nausea and vomiting during early pregnancy, neonatal jaundice, early birth order, preterm birth, low birth weight or abnormally high birth weight, high placenta weight, hypospadias, cryptorchidism and inguinal hernia of the subject, and dizygotic twins. High maternal age at pregnancy and high maternal body mass index at the time of conception with the index pregnancy have also been associated with the risk of testicular cancer in their sons.



World Map 5.18.1

The observed relationship between these prenatal exposure surrogates and testicular cancer risk has generally been considered to be due to a raised maternal level of available estrogens early in life. For example, the cause of severe nausea in pregnancy is considered to be due to the rapid rise of estrogen levels in the mother in the first 2 months of gestation. Higher risk of testicular cancer for early birth order is consistent with the fact that pregnancy estrogen concentrations are higher during the first pregnancy. Cryptorchidism is related to an excess of available maternal estrogen during early pregnancy. Thus, rather than as a cause of testicular cancer, cryptorchidism may simply share common risk factor(s) with testicular cancer [7]. Neonatal jaundice is also related to high estrogen levels among infants. Abnormally high birth weights are associated with testicular cancer risk since foetal growth was reported to be positively correlated with pregnancy estrogen levels in both blood and in urine. Pregnancy estrogen concentrations were also reported to be higher among older women. Dizygotic twin pregnancies have higher estrogen levels because dizygotic twins tend to have two placentas.

Moller [8] proposed a "carcinoma in situ model", according to which germ-cell testis cancer is a process initiated by causes acting very early in life, most probably before birth, and leading to carcinoma in situ (CIS). Adulthood exposures, whether male sex hormones or environmental exposures, would only influence the further progression of the existing CIS to invasive testis cancer or different types of germ-cell testis cancers. A rapid increase of testis cancer incidence after puberty indicates that male sex hormones may be responsible for the further progression of the existing CIS to invasive testis cancer. The relationship between severe acne at puberty and testicular cancer risk further supports the role of male sex hormones in the progression of the disease because severe acne at puberty is associated with increasing testosterone levels. Thus, prenatal exposure to excess estrogens (while subnormal androgen exposure has also been proposed as a risk factor) may play a major role in the development of the CIS, while adolescent exposure to excess male sex hormones may play a critical role for the progression of the CIS to invasive testicular cancer.

No study has systematically examined the relationships between prenatal exposures and various prenatal exposure surrogates at different critical periods of pregnancy. Several epidemiological studies actually do not support the estrogen hypothesis as recently reviewed by Zhang et al. [4]. Studies showed that both Chinese women and black women had significantly higher serum levels of estradiol and estriol during early gestation than US white women, but both Chinese men and black men have a much lower incidence rate of germ-cell testicular cancer than do US white men. Based on these results, Zhang et al. [4] suggested that increased testosterone levels during early pregnancy, rather than estrogen levels, are associated with a reduced risk of germ-cell testicular cancer. They considered that more critical is the ratio of estrogen to androgen; that is, a lower ratio of sex hormones (estrogens/androgens) is associated with a reduced risk of germ-cell testicular cancer. More studies clearly are needed to clarify the role of both the estrogen hypothesis and the androgen hypothesis in the risk of testicular cancer.

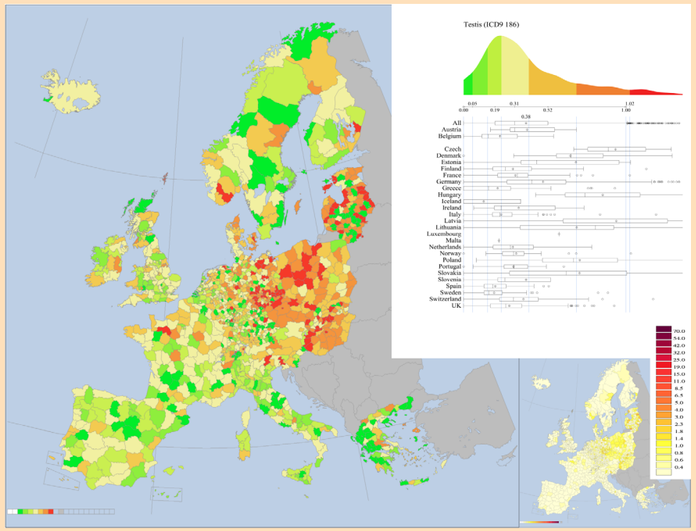
Environmental hormone disruptors. Although prenatal exposure to high levels of endogenous hormones and adolescent exposure to high levels of male sex hormones might be related to the risk of testicular cancer (the age-incidence pattern), this excess hormone hypothesis itself, however, cannot explain the increasing trend of testicular

cancer observed during the past decades (the secular incidence pattern). Based on recent laboratory studies in animal systems, investigators have suggested that environmental hormone disruptors may be risk factors for testicular cancer, and population-wide increasing exposure to estrogenic or other hormonally active (e.g. antiandrogenic) compounds may be at least in part responsible for the observed increasing trend of the disease [9,10]. Specifically, there is concern over the relationship between environmental exposure to organochlorines (e.g. polychlorinated biphenyls, organochlorine insecticides such as DDT and its analogues, and others), polybrominated diphenyl ethers (PBDEs) and the risk of testicular cancer.

While there has been considerable interest in the relationship between environmental endocrine disruptors and human testicular cancer, few epidemiological studies have directly examined these relationships. Thus, a relationship between environmental endocrine disruptors and increased risk of testicular cancer risk is mainly based on the following observations:

1. Experimental studies show that exposure to both endogenous and exogenous hormones produces testicular cancer and other male reproductive disorders.

2. Results from a pilot study support a potential relationship between environmental hormone disruptors and testicular cancer risk. In this small study, Hardell et al. [11] reported that the mothers of testicular cancer cases had significantly higher serum levels of PCBs, hexachlorobenzene (HCB), transnonachlordane (TNC), cisnonachlordane (CNC) and the sum of chlordanes than did the mothers of noncancerous controls. When using the median concentration for the controls as cut-off value, the OR was 3.8 (95% CI 1.4–10) for PCBs, 4.4 (1.7–12) for HCB, 4.1 (1.5–11) for TNC, 3.1 (1.2–7.8) for CNC and 1.9 (0.7–5.0) for sum of chlordanes.



European Map 5.18.1 *The main feature of the geographic distribution of testicular cancer mortality is the grouping of areas with high rates in the former communist countries - the eastern part of Germany, Poland, the Czech Republic, Slovakia, Hungary, and the three Baltic countries. The patchwork appearance of the remainder of the map simply reflects the wide random variation inherent in rates based on very small numbers of deaths [1].*

3. Men exposed in utero to diethylstilbestrol (DES) showed an increased risk of testicular cancer in some studies, and the combined estrogenic effects of environmental estrogens may exceed those of DES.

4. Pesticide applicators were reported to have an increased risk of testicular cancer, though the results are inconsistent.

5. While testicular cancer is increasing, other male reproductive disorders, such as cryptorchidism, hypospadias, reduced sperm count and quality, and infertility, are also increasing. These disorders are now collectively called testicular dysgenesis syndrome (TDS). TDS and testicular cancer may share a common risk factor—environmental hormones.

6. The hormone properties, carcinogenicity, tumour promotion activity and enzyme induction ability of these chemicals strongly support that exposure to environmental hormone disruptors may increase the risk of testicular cancer.

In summary, the hypothesis that environmental hormone disruptors are risk factors for testicular cancer is plausible based on animal data and limited human data. Organochlorines, for example, possess estrogenic and antiandrogenic activity, are known animal carcinogens and suspected human carcinogens, and have tumour promotion activity. Due to these properties, along with the continued widespread exposure to environmentally persistent organochlorine compounds and PBDEs among the general population, there exists a need to determine whether these compounds are risk factors for testicular cancer.

Family history and genetic susceptibility. It is estimated that about 2% of the cases of testicular cancer may be explained by family history of testicular cancer. As described previously, epidemiological studies have strongly suggested a role of genetic susceptibility in the risk of testicular cancer. While few studies have investigated the relationship between testicular cancer risk and genetic polymorphisms, it seems reasonable to assume that major genes that have been associated with either the regulation, metabolism or functional activities of endogenous and exogenous hormones (such as genes of the CYP family, the oxidative stress defense enzyme genes and the hormone receptor genes) should play a major role in the risk of occurrence and progression of testicular cancer.

In a study of estrogen receptor polymorphisms and risk of testicular cancer, for example, Heimdal et al. [12] found that the variant-B allele was somewhat more frequent in cancer patients who were firstborn compared to controls, although this was not statistically significant. They also found that the frequency of the variant B allele seemed to decrease in cancer patients born later in the sibship. This observation is consistent with the hypothesis that firstborn testicular cancer patients, who presumably are exposed to higher maternal estrogen levels, in some instances may have an ER variant that interacts differently with maternal estrogen than do later-born patients. Sexual differentiation to the male phenotype is dependent on activation of the androgen receptor by androgens during foetal development [13]. Testosterone is converted to dihydrotestosterone (DHT) and DHT binds to the AR to form a complex, which translocates to the nucleus and transactivates target genes [14]. It is conceivable that variant forms of the gene for AR affect the function and efficiency of its gene products, thus influencing the development and progression of testicular cancer. CYP1A1 genetic polymorphism may affect the relationship between endogenous hormones, environmental hormone disruptors and testicular cancer risk because AHH is 17-beta-estradiol hydroxylase, therefore involved in steroid hormone metabolism [15]. The enhanced CYP1A1 activity from exposure to environmental hormone disruptors could lead to increased activation of environmental carcinogens; thus increased testicular cancer risk. Studies of environmental hormone disruptors and breast cancer risk have reported a strong interaction between CYP1A1 m2 genetic polymorphisms, PCB exposures and risk of breast cancer [16].

Other suggested risk factors. Several factors, such as testicular trauma, viral exposure, unusual amounts of heat to the testis, vasectomy, EMF exposure, farming and farm-related exposures, maternal dietary intakes, maternal viral or bacterial infection before pregnancy, smoking and alcohol consumption during pregnancy, and immunologic reaction during foetal life have also been inconsistently associated with the risk of testicular cancer [17,18]. These factors, however, can hardly explain the observed age-incidence pattern and the reported increase in rates during the past decades. The reported effect due to these factors is also not great enough to explain the increase in incidence rates of testicular cancer among young men.

Similar risk profiles for seminoma and nonseminoma? Both seminoma and nonseminoma are considered to have a common cell of origin, the carcinoma in situ germ cell [19]. The similar secular trend for both seminoma and nonseminoma supports that these two types of testis cancer are likely to have similar risk profiles. Analytical epidemiological studies so far have not provided strong evidence demonstrating separate etiologies of seminoma and nonseminoma. Even if some differences exist in the risk factors for these two types of testis cancer as suggested by some of the studies [20], the major risk factors responsible for the time trend must be similar between seminoma and nonseminoma.

Prevention

The descriptive epidemiological features of testicular cancer as summarised previously suggest that environmental factors may play a major role on the occurrence and/or progression of testicular cancer, thus a large proportion of the disease is potentially preventable. However, since so little is known about the etiology of testicular cancer, it is not possible at this stage to develop effective preventive measures to reduce the disease. Greater efforts must be made to better understand the etiology of testicular cancer and to better understand the underlying causes for the observed increase of the disease during the past few decades. If indeed in-utero exposure to high levels of free estrogens is responsible for the occurrence of testicular cancer, modification of the factors that directly affect the secretion and metabolism of the estrogen of pregnancy might prove to be effective [21]. If indeed human exposure to environmental hormone disruptors increases the risk of development and progression of testicular cancer, greater effort needs to be made to reduce human exposure to these man-made environmental pollutants. While it is difficult to develop effective preventive measures to reduce disease incidence, testicular cancer could almost be eliminated as a cause of death worldwide if the political will, adequate finance, and the necessary training and logistics to deliver appropriate treatment were implemented [22].

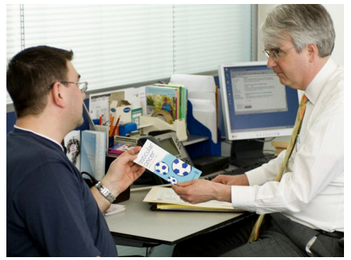


Fig. 5.18.2 *Discussion of testicular cancer between a young man and family doctor*

In summary, much of the etiology of testicular cancer remains unexplained, and hitherto unidentified risk factors remain to be identified. The question that must be answered is to what extent are endogenous hormones, environmental hormone disruptors, and genetic polymorphisms not only responsible for the observed age-incidence pattern, but also for the observed secular-incidence trend of testicular cancer. Unless major risk factors of testicular cancer are identified, no effective preventive measures can be developed to reduce the disease.

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BRIEF REPORT FROM THE WHO REGIONAL OFFICE FOR EUROPE (WHO EURO)

Cancer in the WHO European Region

Cancer was estimated to cause 19% of deaths and 11% of the disease burden (as measured by DALYs) in the WHO European Region in 2005. There were approximately 1.8 million deaths from cancer in the Region in 2005; leading causes of cancer death are lung, colorectal, stomach and breast, with the leading cancers for incidence burden being lung, colorectal, breast cancer and prostate.

Disease patterns cannot simply be generalised–overall cancer incidence and mortality rates vary at least two-fold between European countries, and differences are often greater for specific cancers. Across WHO European Region as a whole, death rates from cancer have been decreasing since late 1980s; however the picture is mixed and complex according to age, sex, type of cancer and country. Cancer incidence is rising for the Region as whole–trends largely reflect changes in the age structure of the population and its risk factor profile, which is in turn related to the success of primary prevention programmes. Irrespective of changes in risk, the demographic changes alone are projected to substantially increase cancer incidence in next few decades.

There are marked disparities within countries and between countries in cancer survival, which partly reflects success of the health system in early detection and effective care. There are some indications that this survival gap is narrowing, suggesting improvements in care in countries with previously poor survival.

Steps being taken by WHO Regional Office for Europe

WHO EURO promotes a comprehensive approach to cancer: prevention; early detection; diagnosis and treatment; palliative care. All countries, no matter what their resource level, can mount an effective response to cancer; only their prioritisation will differ. During 2008–09, WHO EURO is working in-depth with 8 countries in development or review of National Cancer Control Programmes, and at least another 10 countries on strategies for the prevention and control of Noncommunicable diseases (NCD) including cancer.

Primary prevention, particularly tobacco control, is key. Cancer shares common risk factors with other NCDs such as heart disease and stroke. EURO promotes an integrated approach to prevention across such diseases through the European Strategy on Prevention and Control of Noncommunicable Diseases, as well as through WHO strategies, frameworks and action plans for individual risk factors such as tobacco control, food and nutrition, alcohol, counteracting obesity, physical activity, environment and health. There are now 41 Member States of the WHO European Region that are parties to the Framework Convention for Tobacco Control (WHO FCTC), and a further 5 that are signatories. Regarding infectious agents, EURO works with countries and partners to strengthen immunisation in Europe, control sexually transmitted infections and develop policy advice, for example on Human Papilloma Virus (HPV) vaccination. By 2003, 43 Member States had included hepatitis B in their national immunisation programmes. In May 2007, WHO EURO held a meeting with policymakers from more than 40 countries in Europe on strengthening cervical cancer prevention in Europe, and is following up during 2008–09 with support to a number of countries in developing and strengthening cervical cancer prevention programmes. This work is underpinned by the broader work of the office to strengthen health systems in particular to improve quality assurance systems.

Good palliative care and access to morphine could significantly improve the lives of many. Working closely with its WHO Collaborating Centres and other partners, WHO EURO is promoting a public health approach to palliative care and the rational use of drugs for cancer treatment. A meeting of countries is planned for autumn 2008.

website: www.euro.who.int

5.19 Kidney Cancer

Summary

> Populations with a high incidence of kidney cancer include Central Europe and the black population in the USA

> Tobacco smoking is a recognised risk factor for kidney cancer, as are obesity and hypertension

> Apart from rare high-risk variants, susceptibility genes for kidney cancer are yet to be discovered

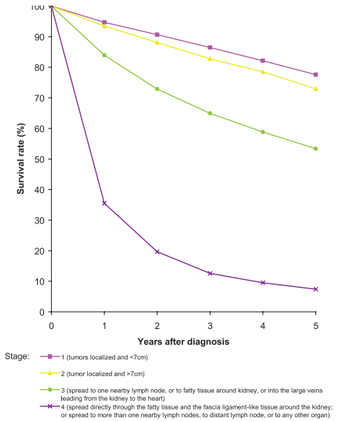


Fig. 5.19.1 *5-year relative survival rates (%) for kidney cancer cases diagnosed in 1990–94, in selected countries and by age at diagnosis (source: Eurocare-3 study)*
Relative survival rates were based on 474 000 kidney cancer cases diagnosed in Europe in 1990–94. The prognosis of patients with kidney cancer improved at younger ages of diagnosis, with the 5-year relative survival rates falling from 71% for patients diagnosed at 15–44 years old to 45% for patients diagnosed at 75 years or older. On average, Germany showed the highest survival rates, whereas Wales had the lowest rates, with greater difference between countries than for bladder cancer survival rates

Histological types

The vast majority of cancers which arise in the renal parenchyma are clear cell carcinomas.[2] Non-clear cell types include papillary, chromophobe, collecting duct and oncocytoma, although whether the epidemiology of these rarer types differs from that of clear cell has not been established. Finally, nephroblastoma (Wilms' tumour) occurs in children. The epidemiology of cancers of the renal pelvis differs markedly from that of the renal parenchyma, the former having histology similar to that of transitional cell bladder cancer.

Stage at diagnosis and survival

In the USA in 2003, 49% of cases of kidney cancer were diagnosed at stage 1, 10% at stage 2, 13% at stage 3, 18% at stage 4, and the stage was unknown in 10% of cases (2003 data from the National Cancer Data Base, NCDB).[3] The five-year relative survival after kidney cancer in the third version of the Eurocare study, comprising 47 000 kidney cancer cases diagnosed 1990–1994, is shown in Figure 5.19.1.[4] Overall, the 5-year relative survival rate kidney cancer was 56% in males and 58% in females. The prognosis of patients improved at younger ages of diagnosis, with the 5-year relative survival rates falling from 71% for patients diagnosed at 15–44 years old with kidney cancer to 45% for patients diagnosed at 75 years or older.

Incidence

Worldwide geographical variations in incidence rates (age-standardised for the world population) of kidney cancers in men and women respectively are shown in 5.19.2.[5] the highest rate was found for both sexes in

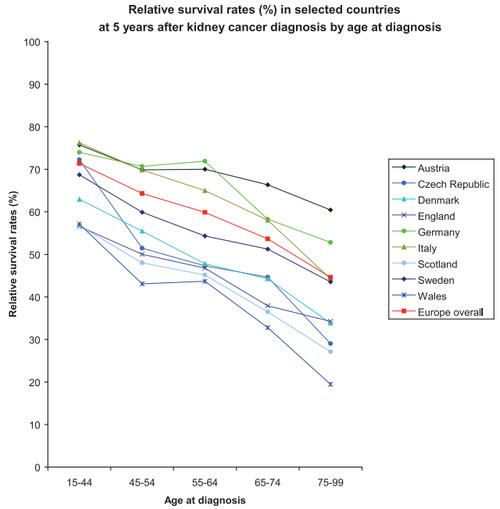


Fig. 5.19.2 *Observed survival rates (%) for kidney cancer cases diagnosed in 1998 in the USA (source: National Cancer DataBase). Important differences were found between the survival rates for different stages at diagnosis*

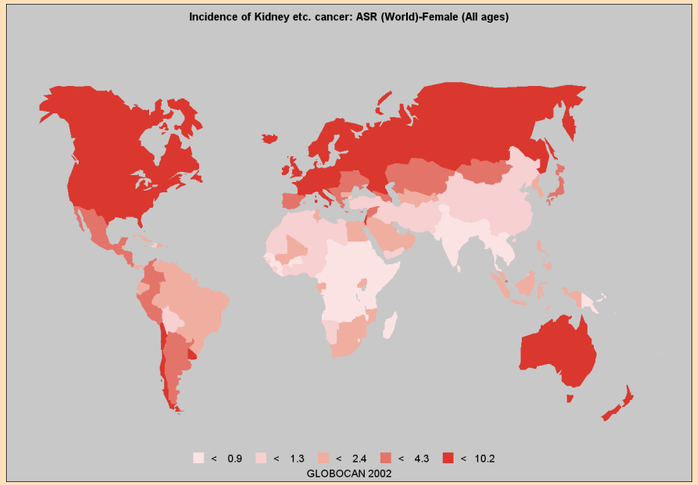
Czech Republic (21.1/100 000 in men and 10.2/100 000 in women). In men, other regions with high incidence rates included Estonia (17.3/100 000), Lithuania (14.7/100 000), Hungary (14.7/100 000), Slovakia (13.7/100 000), and Poland (13.5/100 000). Among females, the intermediate high incidence rates were found in Lithuania (8.4/100 000), Estonia (7.1/100 000), Austria (6.8/100 000), Slovakia (6.6/100 000) and Hungary (6.6/100 000). In both sexes, the lowest rates were found in Africa and Asia.

A sharp increase in the incidence of kidney cancer was observed in numerous registries. Some of the greatest increases were observed in the Czech Republic and among the black population in the USA.[6]

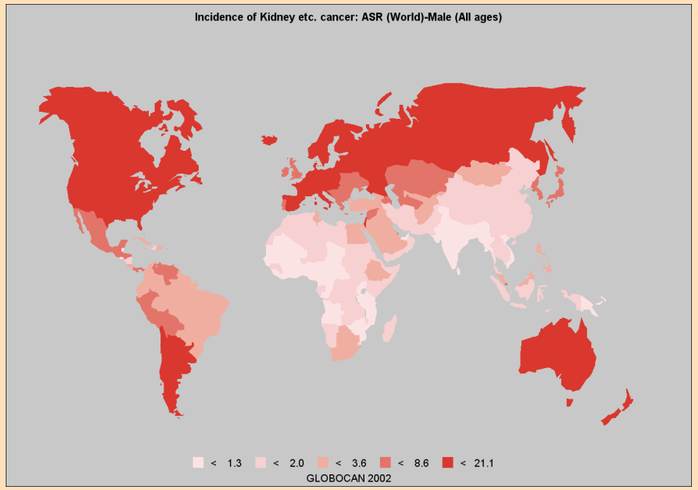
Regarding time trends for kidney cancer and using data reported in two volumes of the CI5 series from various cancer registries for the calendar periods 1983–1987[7] and 1993–1997 [8], a sharp increase in incidence was observed in numerous registries. Some of the greatest increases were observed in the Czech Republic and among the black population in the USA.[6] These increasing trends are unlikely to be explained by increasing detection of presymptomatic tumours, and are instead likely to reflect real increases in the numbers of new cases.[9]

Risk factors for kidney cancer

Cigarette smoking. Cigarette smoking has been consistently observed to be a risk factor for kidney cancer, with increased risks compared to never smokers in the order of 50%.[10,11] A number of studies have also demonstrated a dose-response relationship with increasing consumption, with risks of developing kidney cancer for heavy smokers ranging from 2.0 to 3.0 above that of people who have never smoked. The risk appears to decline with increasing years of smoking cessation. Population attributable risk estimates indicate that cigarette smoking, both past and present, is responsible for approximately 20% of kidney cancer cases among men and 10% of cases



World Map 5.19.1



World Map 5.19.2

among women.[12,13] Approximately half of this attributable risk is due to current smoking. The mechanism by which cigarette smoking increases the risk of kidney cancer has not been elucidated, although this clearly represents a major opportunity for prevention.

Obesity. A recent overview of the relationship between obesity and kidney cancer concluded that there was sufficient evidence to conclude that weight gain led to an increased risk of developing renal cancer.[14] The review was based on consistent evidence from four cohort and fifteen case–control studies that reported a steadily increasing risk with increasing weight gain, and indicated that the effects among men and women were similar. Approximately 25% of kidney cancer cases among both men and women are likely to be due to being overweight and obese.[15,16] The mechanism by which obesity causes kidney cancer is unclear, although hormonal changes such as increased levels of endogenous oestrogens might be responsible. Other correlates of obesity, such as hypertension and lack of physical exercise, have not been found to explain this relationship.

Medical conditions and treatment. A history of hypertension has also been consistently linked to kidney cancer.[17-22] The increase in risk appears to occur in a dose-response manner, with even moderately increased blood pressure resulting in an increased risk of kidney cancer. Several studies have tried to separate the effect of hypertension and a possible effect from diuretic and non-diuretic antihypertensive medications. Given the strong correlation between hypertension and the use of these drugs, this has been very difficult. However, evidence that reductions in blood pressure over time may lead to a decrease in kidney cancer risk would appear to indicate that the primary effect is with hypertension and is not treatment related.[17] It is also likely to account for a substantial proportion of cases. The attributable risk of reported hypertension or treatment with anti-hypertensive drugs has been estimated to be 21% overall, and 39% among women.[23]

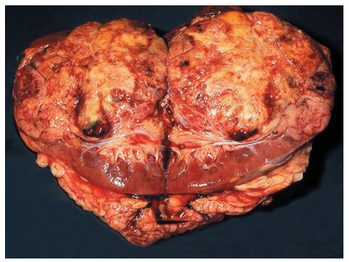
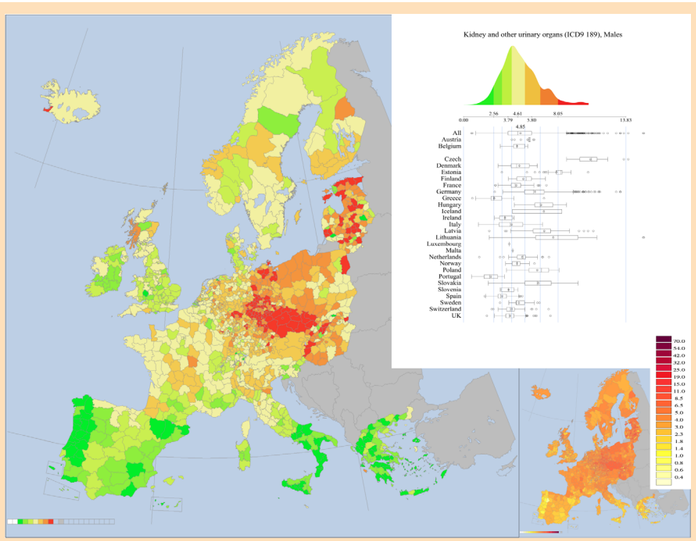


Fig. 5.19.3 *Surgical specimen of a bisected kidney showing a large renal cell carcinoma. Much of the kidney has been replaced by tumour tissue*



European Map 5.19.1 *The strongest feature of the geographic distribution of kidney cancer mortality in men is the strong gradient from the low rates in Portugal, Spain, southern Italy and Greece through rates generally close to the average in France, northern Italy, Switzerland, Slovenia, Belgium, The Netherlands and the United Kingdom and Ireland, to high rates in eastern Germany and Austria, the Czech Republic, and western parts of Poland, Slovakia and Hungary. Rates were also generally high in all three Baltic countries. Mortality rates in all the Nordic countries were generally close to the average [1]*

There is also strong evidence for a role of diabetes mellitus in the etiology of kidney cancer. Two large nationwide cohort studies in Sweden and Denmark both identified an increased risk of kidney cancer among inpatients with diabetes, in the order of 40% among men and 70% among women.[24,25] The risk appeared to be constant with follow-up and was restricted to type II diabetes.

Acquired cystic kidney disease, which occurs in end-stage renal disease, is associated with the development of kidney cancer, as are both kidney stones and kidney infections.[26]

Dietary factors. A recent IARC evaluation on the potential cancer preventative effect of diets high in fruits and vegetables reported that higher intake of both fruits and vegetables possibly reduce the risk of kidney cancer.[27] The amount of evidence from prospective cohort studies was, however, sparse, with only two studies reporting on fruit consumption and one on vegetable consumption. A more recent report from the European Prospective Investigation into Cancer and Nutrition (EPIC) reported no overall protective effect for high consumption of fruits and vegetables, although an increased risk at very low levels of consumption could not be ruled out.[28]

High protein consumption from meat and dairy products has been associated with chronic renal conditions that may predispose to kidney cancer, although the evidence is inconsistent.[29] The role of coffee and alcohol have also been studied extensively for kidney cancer, although no increase in risk with increased consumption of coffee or alcohol appears to exist.[30]

Occupational risk factors. Consistent and strong increases in risk with occupational exposures have not been detected for kidney cancer. Suggestive increases in risk have been observed for a variety of occupations with exposure to polycyclic aromatic hydrocarbons such as coke and coal oven workers, fire-fighters, and asphalt and tar workers.[31] Excess risks have also been reported for occupations with exposure to gasoline and other petroleum products such as oil refinery workers and gas station attendants, as well as with exposure to asbestos.[32]

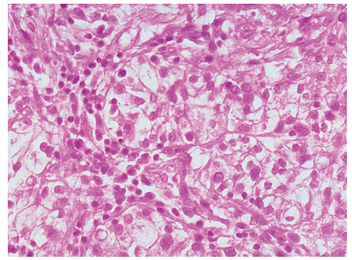
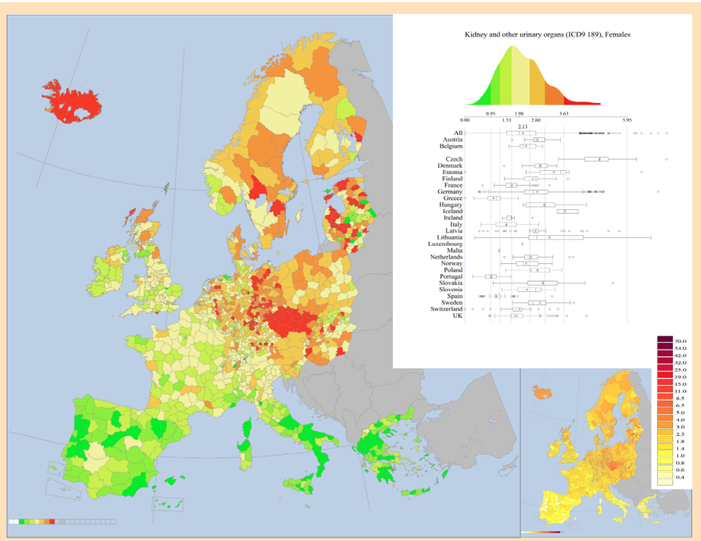


Fig. 5.19.4 *Clear cell carcinoma of the kidney showing a monomorphic proliferation of distinctive tumour cells, with an abundant clear, lipid-containing cytoplasm, arranged in a trabecular pattern*

Exposure to organic solvents, in particular to chlorinated aliphatic hydrocarbons, has also been suggested as a risk factor in occupations including dry-cleaning and printing. A report from a German series of individuals with kidney cancer that exposure to trichlorethylene was associated with a specific mutation pattern in the von Hippel-Lindau (VHL) tumour suppressor gene is of interest although requires confirmation.[33] Overall, the evidence for associations of specific occupational exposures with kidney cancer is still inconclusive.



European Map 5.19.2 *The map for females shows that both the between- and the within-country variability in mortality rates were closely similar to the patterns in males. There were generally low rates in Portugal, Spain, Italy and Greece and around average rates in Ireland, the southern parts of the UK, France, Belgium and Switzerland. High rates, as in males, occurred in northeast Germany, the Czech Republic, eastern Austria, and western Poland, Slovakia and Hungary, and in the Baltic countries. Many areas in the Nordic countries had above average rates in females but not in males [1].*

Family history and genetic risk factors. Several registry-based studies including the Swedish Family Cancer Database, deCODE Genetics, and the Utah database have reported an increased risk of renal cell carcinoma (RCC) for subjects with affected first-degree relatives, with a familial relative risk of 2–2.5.[34,35] The familial risk for kidney cancer appears to be greater between siblings as compared with that between parent and child, indicating the possible existence of recessive genetic effects. An elevated familial relative risk probably indicates a genetic component in cancer etiology, although a contribution due to shared environmental exposures within the family is also possible. The contribution of these two factors might be determined by twin studies, although the largest twin study to date has not been informa-

tive due to the lack of concordant twins with kidney cancer.[36]

One of the important genetic alterations identified in familial RCC is the aforementioned VHL syndrome, a rare autosomal dominant condition caused by the point mutations or deletions in *VHL* gene at chromosome 3p25.[37] Individuals with *VHL* alterations have an increased risk of developing benign or malignant tumours of the central nervous system, eye, inner ear and endocrine glands, in addition to the kidney. Furthermore, most sporadic clear cell cancers have somatic *VHL* inactivation. Several genes predisposing to non-clear cell RCC have also been characterised, including mutations in the *MET* oncogene and hereditary type 1 papillary RCC, and mutations in the *BHD* gene causing several histopathological subtypes of RCC.

Identifying rare genetic variants that result in a high risk of renal cancer is important for understanding the etiology of cancer and potentially identifying high risk groups among family members; however, such genes explain very little of the familial risk of renal cancer. It is likely that most of the genetic contribution will be due to multiple low- or moderate-risk variants that act in combination with each other or with environmental risk factors. Such genetic variants will not be detected in studies based on multiple cases in individual families, but instead will require large series of cases and controls and genotyping for hundreds of thousands of genetic variants across the genome. These studies are currently in progress.

Fig. 5.19.5 *Tobacco smoking is a recognised risk factor for kidney cancer*

Avoiding risks

The main known avoidable causes of kidney cancer include cigarette smoking, excess body weight and hypertension, which together are likely to account for up to 60% of all cases of these tumours. Primary prevention by reducing cigarette smoking, obesity and hypertension are, therefore, the clearest strategies for reducing the incidence of the disease. A substantial proportion of cases is also likely to be related to diabetes, although further information on whether this is an independent risk factor is required. It seems unlikely that these exposures can explain the very large disparities in incidence that occur between different populations, and further important causes of renal cancer are likely to exist. Ongoing studies into the genetic epidemiology of kidney cancer might provide new hypotheses for such exposures, and may also help lead to the identification of high-risk subgroups.

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5.20 Bladder Cancer

Summary

> Populations with a high incidence of bladder cancer include those of Mediterranean Europe and Egypt

> Survival improves with early age of onset

> Tobacco smoking is the most important risk factor for bladder cancer. Occupational exposure to aromatic amines and infection with *Schistosoma haematobium* are also recognised risk factors

> Gene variants of *GSTM1* and *NAT2* are involved in bladder cancer risk, interacting with smoking status for *NAT2*

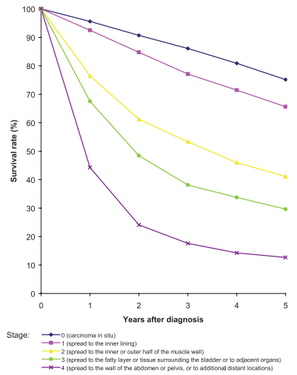


Fig. 5.20.1 *5-year relative survival rates (%) for bladder cancer cases diagnosed in 1990–94, in selected countries and by age at diagnosis (source: Eurocare-3 study). Relative survival rates were based on 104 000 bladder cancer cases diagnosed in Europe in 1990–94. The prognosis of patients with bladder cancer improved at younger ages of diagnosis, with the 5-year relative survival rates falling from 90% for patients diagnosed at 15–44 years old to 61% for patients diagnosed at 75 years or older. On average, Austria showed the highest survival rates, whereas Czech Republic had the lowest rates, with little difference between countries however*

Histological types

The most common type of bladder cancer is urothelial carcinoma, also called transitional cell epithelium[2], although the proportion of this histological type among all cases of bladder cancer varies between countries. For example, 92–99% of bladder cancer cases with available histology in North America, Europe and Australia are urothelial carcinoma, whereas the proportion is around 70–80% in Southeast Asia and substantially less than 50% in parts of Africa [3-7]. In general, urothelial carcinoma constitutes a slightly higher proportion of bladder cancer cases in males than in females. Other types of bladder carcinoma include squamous-cell carcinoma and adenocarcinoma. In Africa, squamous-cell carcinoma is the most common type of bladder cancer, resulting from *schistosoma hematobium* infection. Non-invasive urothelial tumours are often considered as bladder cancer in cancer registries. Non-invasive papillary carcinoma has a tendency to recur and to develop into invasive bladder carcinoma [2]. The variable degree to which such tumours are reported might substantially influence available descriptive data [8].

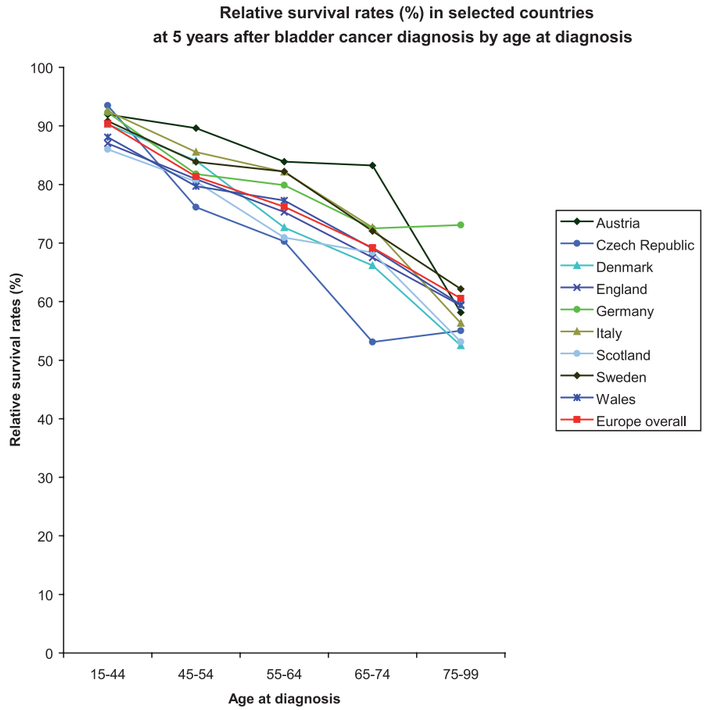


Fig. 5.20.2 *Observed survival rates (%) for bladder cancer cases diagnosed in 1998 in the USA (source: National Cancer DataBase).Important differences were found between the survival rates for different stages at diagnosis.*

Stage of diagnosis

Comprehensive data on stage of diagnosis include the US National Cancer Database (NCDB) and the Eindhoven cancer registry. In 2003, 47% of bladder cancer cases diagnosed in the USA were at stage 0, 22% at stage 1, 11% at stage 2, 5% at stage 3, and 6% at stage 4; for 8% the stage was not reported [9]. Bladder cancer data from the Eindhoven cancer registry showed a considerable shift towards lower stage at diagnosis between 1975 and 1989, mainly in favor of stage 0 [10]. This trend was less evident when invasive tumours were considered separately.

Relative survival rates compare the observed survival over a period of time to the expected survival based on background mortality rates. Figure 5.20.1 shows 5-year relative survival rates after bladder diagnosis for nine different European countries and by age at diagnosis, using data from the third version of the Eurocare study based on 104 000 bladder cancer cases diagnosed between 1990 and 1994 [11]. Overall, the 5-year relative survival rate after bladder cancer diagnosis was 72% in males and 67% in females. On average,

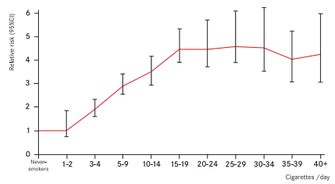
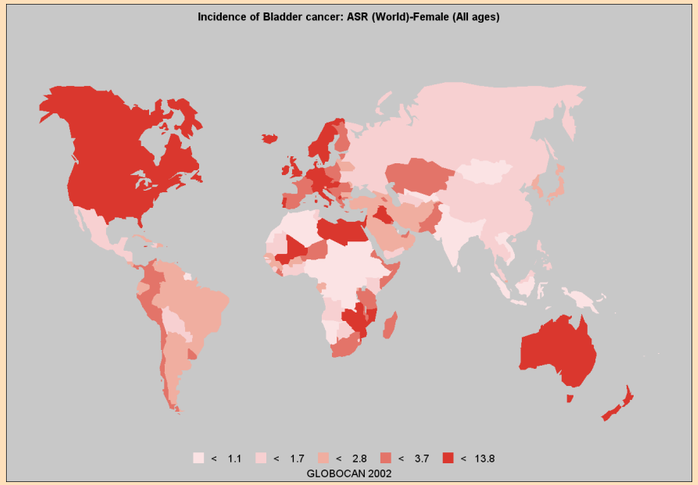
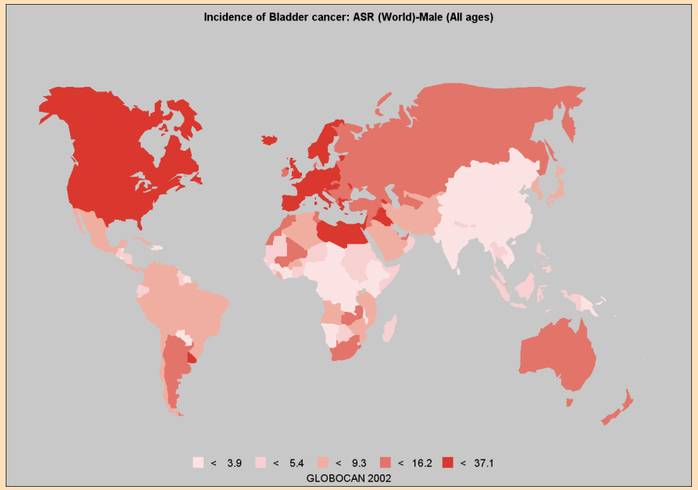


Fig. 5.19.3 *Risk of bladder cancer among men who smoke relative to never-smokers, according to daily cigarette consumption*



World Map 5.20.1



World Map 5.20.2

Austria showed the highest survival rates, whereas Wales had the lowest survival rates for bladder cancer.

In men, the highest rates of bladder cancer were found in Egypt (37.1/100 000), Spain (33.0/100 000), the Netherlands (32.6/100 000), and Italy (29.8/100 000). In women, the pattern is different: The highest rates were found in Zambia (13.8/100 000) and Mozambique (13.0/100 000), although these results were based on frequency data and might therefore not be reliable.

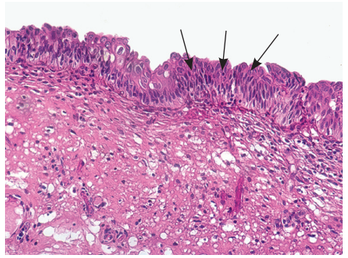


Fig. 5.19.4 *Carcinoma in situ of the bladder; the normal transitional epithelium has been replaced by a disorganized, poorly-differentiated cell layer (arrows)*

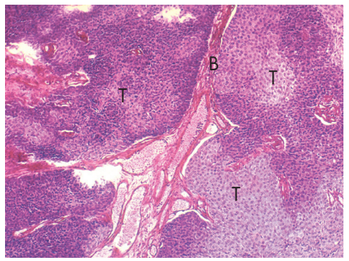
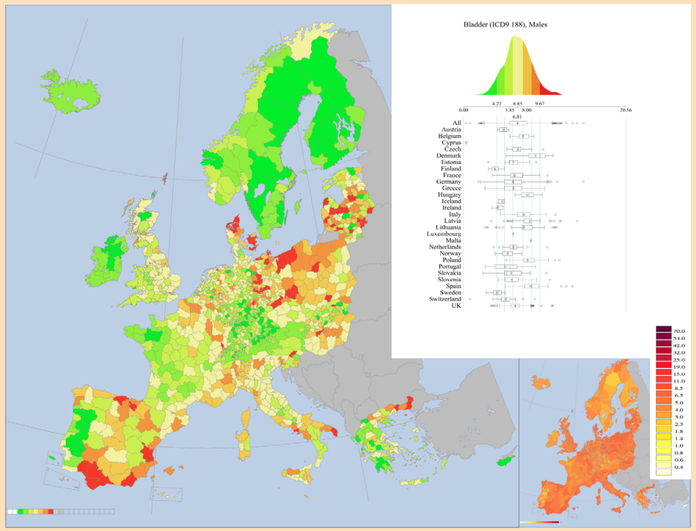


Fig. 5.19.5 *Transitional cell carcinoma of the bladder, moderately differentiated, with a papillary architecture. B = blood vessel, T = Tumour*



European Map 5.20.1 *An intriguing feature of the geographic map of bladder cancer in men is the high rates in coastal areas of Spain and parts of the Mediterranean coastlines of France (including Corsica) and Italy (including Sardinia and Sicily). There were high rates in other regions of Spain, northern Italy and northern Greece. Rates were high in Denmark and in the northern part of the former East Germany and Poland, and in Lithuania and Latvia. There were low rates throughout the Nordic Countries (other than Denmark), Ireland, the south of Germany, Austria and Switzerland.[1]*

Risk factors for bladder cancer

Tobacco use. The most important risk factor for bladder cancer is cigarette smoking, which is thought to account for approximately 66% of new cases in men and 30% of cases in women in industrialized populations [12,13]. Irrespective of the study design, most of the epidemiological studies found relative risks of 1.5–3.0 in smokers compared to non-smokers, as well as dose-response relationships considering both number of cigarettes smoked and duration of cigarette smoking [12,13]. Cigarette smoking seems to have the same effect in males and females, and in different races/ethnicities. A pooled analysis which combined nontransitional cell bladder cancer data from a number of studies found the same associations as for transitional cell carcinomas [14]. It is likely that smokers of black (air-cured) tobacco are at a higher risk than smokers of blond (flue-cured) tobacco [12], and this likely explains much of the higher incidence rates observed in Spain, Italy and Uruguay, where smoking of black tobacco was common in the past.

An immediate decrease in risk (around 40%) of bladder cancer is observed among both men and women who give up smoking, implying a late stage effect in the carcinogenic process, and the decrease in risk continues with time since cessation.

Much of the risk associated with smoking is likely to be due to aromatic amines present in cigarette smoke, including benzidine, 4-aminobiphenyl, naphthylamine and 4-chloro-o-toluidine.

Occupational risks. A high risk of bladder cancer has been reported among workers in industries that involve exposure to aromatic amines, in particular 2-naphthylamine, 4-aminobiphenyl and benzidine, including the rubber and dyestuff industries [15]. Working in aluminum production, auramine manufacture, coal gasification and magenta manufacture also significantly increases the risk of developing bladder cancer. Other occupations that might increase the risk of bladder cancer include leather workers, painters, hairdressers and barbers, coke production workers, and petroleum refining workers, possibly because of exposure to a variety of chemicals including polycyclic aromatic hydrocarbons, polychlorinated biphenyls, formaldehyde and solvents. The uncertainty surrounding these occupations is partly due to the difficulty of measuring past exposure to specific chemical agents.

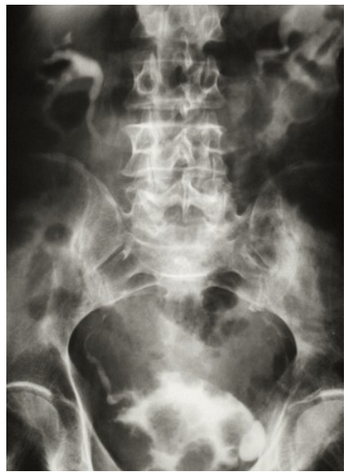
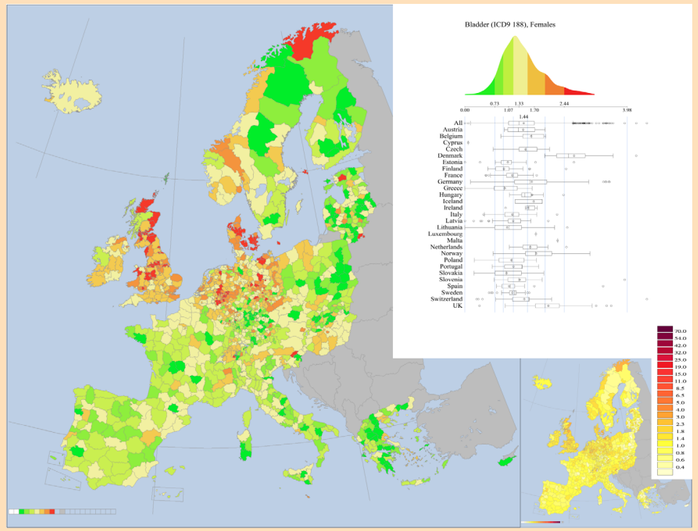


Fig. 5.19.6 *Bladder tumour*



European Map 5.20.2 *In women, rates were high in Denmark and northern Germany (as in males) but were also high in parts of the United Kingdom (especially Scotland) and The Netherlands. There were areas of low rates in the north of Europe except Norway: Sweden, Finland, the Baltic Countries and much of Poland; and in most of southern Europe: Portugal, Spain, France, Italy and Greece.*
In terms of explaining the geographic pattern in Europe, the high rates in men in Spain could well be associated with the prevalent habit of smoking black tobacco, which carries an excess risk of bladder cancer over Virginia cured tobacco. The high rates in Denmark are a reflection of the high incidence rates which have persisted there for decades. The pattern of high risk areas in men–but not women–in areas around the Mediterranean coast is interesting and may be related to differences in smoking habits between the sexes [1]

Dietary factors. Investigations into dietary factors have provided evidence of decreased risks associated with consumption of fruits but not with vegetables [16]. No consistent association has emerged between intake of related micronutrients and reduced risk of bladder cancer [17].

Concerning fluid consumption, an increased risk has been associated with high intake of tap water possibly due to exposure to the by-products of disinfection and arsenic [18]. Consumption of tea and alcohol are probably not associated with bladder cancer, although an increased risk with coffee consumption has been reported in some studies [19].

Familial history and genetic risk factors. First-degree relatives of bladder cancer patients have a 50–100% increased risk of developing the disease compared to the general population [17]. This relative risk is likely to interact with smoking habits, as the risk is elevated fivefold in smoking probands compared with nonsmokers [20].

The enzyme N-acetyl transferase 2 (NAT2) is involved in the detoxification of various bladder carcinogens including arylamines. The gene encoding NAT2 includes a dominant mutation

that results in slow metabolisation of arylamines and is associated with an increased risk of bladder cancer of around 40% [21]. This increased risk of developing bladder cancer appeared to be stronger in cigarette smokers (particularly black tobacco smokers) than non-smokers, and a joint effect between NAT2 slow acetylators and heavy smokers was observed, translating to a much higher risk of developing bladder cancer than exists in nonsmokers that do not possess the *NAT2* mutation. The GSTM1 null genotype also increases the risk of bladder cancer, although it has no interaction with smoking status [21].

Pharmacological-related risk factors

A consistent relationship has been observed between use of phenacetin-containing drugs and bladder cancer, with relative risks varying from 2.4-fold to over 6-fold [22]. Cyclophosphamide, an alkylating agent which has been used to treat both malignant and non-malignant diseases, has also been linked to bladder cancer. Studies based on cohorts of cancer patients indicate an approximately 5-fold increase in risk associated with cyclophosphamide therapy, with higher risks among heavily exposed subjects.

Infection

Infection with *Schistosoma haematobium* is prevalent throughout Africa and is associated with an increased risk of bladder cancer of approximately 2 to 4-fold [23,24]. Infection occurs via contact with water contaminated by the cercarial form (Figure 4). Eggs are eliminated with feces or urine and, under optimal conditions, the eggs hatch and release miracidia, which swim and penetrate specific snail intermediate hosts. The stages in the snail include two generations of sporocysts and the production of cercariae. Upon release from the snail, the infective cercariae swim, penetrate the skin of the human host and shed their forked tail, becoming schistosomulae. The schistosomulae migrate through several tissues and stages to their residence in the veins. Adult worms in humans reside in the mesenteric venules in various locations, which may be specific for each species. *S. haematobium* infection most often occurs in the venous plexus of the bladder, but it can also be found in the rectal venules. The females (7–20mm in length; males slightly smaller) deposit eggs in the small venules of the portal and perivesical systems. The eggs are moved progressively toward the lumen of the intestine (*S. mansoni* and *S. japonicum*) and of the bladder and ureter (*S. haematobium*), and are eliminated with feces or urine, completing the life cycle.

Bladder cancers associated with Schistosoma infection are mainly of the squamous cell type. The infection is responsible for an estimated 50% of bladder cancer cases in some parts of Africa, and about 3% of cases overall [25].

Avoiding risks

Regarding prevention, past changes in industrial processes have undoubtedly led to a decrease in some occupational exposures. Currently, avoidance of cigarette smoking is the most effective public health measure against bladder cancer. Approximately 60% of bladder cancer cases are due to smoking, at least half of which could be prevented by smoking cessation among current smokers. Prevention of Schistosoma infection through avoidance of contaminated water is important in endemic areas. No effective screening approach is available for bladder cancer.

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5.21 Prostate Cancer

Summary

> Prostate cancer is very common, and while the incident rate is rising quickly, in many countries the mortality rate has started to fall

> While aggressive testing with Prostate specific antigen (PSA) has contributed to this decline in mortality, it does not explain all the effect

> The etiology of prostate cancer remains obscure. Tobacco smoking and alcohol consumption are not associated with prostate cancer risk. There is weak evidence of an association with certain dietary practices although the attributable fraction is small

> Chemoprevention studies have been conducted using finasteride, and a major randomised trial of Selenium and Vitamin E is on-going

> Despite many large prostate cancer families, with cases spreading over many generations, there has not been a major gene found for this disease

Urological cancers comprise approximately one third of all cancers diagnosed in men worldwide, and prostate cancer is the commonest of these. The global burden of prostate cancer rose from 200 000 new cases each year in 1975 to reach an estimated 700 000 new cases in 2002. In Europe, it was estimated that in 2006 Prostate Cancer was the fourth commonest form of cancer diagnosed in men, with 345 900 new cases in 2006 and 87 400 deaths recorded [2].

Figure 5.21.1 presents the 20 highest and lowest age-standardised prostate cancer incidence rates (all ages) for the period 1998–2002 among registries with the highest quality data and over one million person-years of observation (to ensure stability of the rates) [3]. The highest rates are from populations in the United States, especially among black population groups, Canada, Switzerland and Austria. The lowest rates are recorded from a variety of populations in Italy and Spain, and Korea, China and India (Figure 5.21.1).

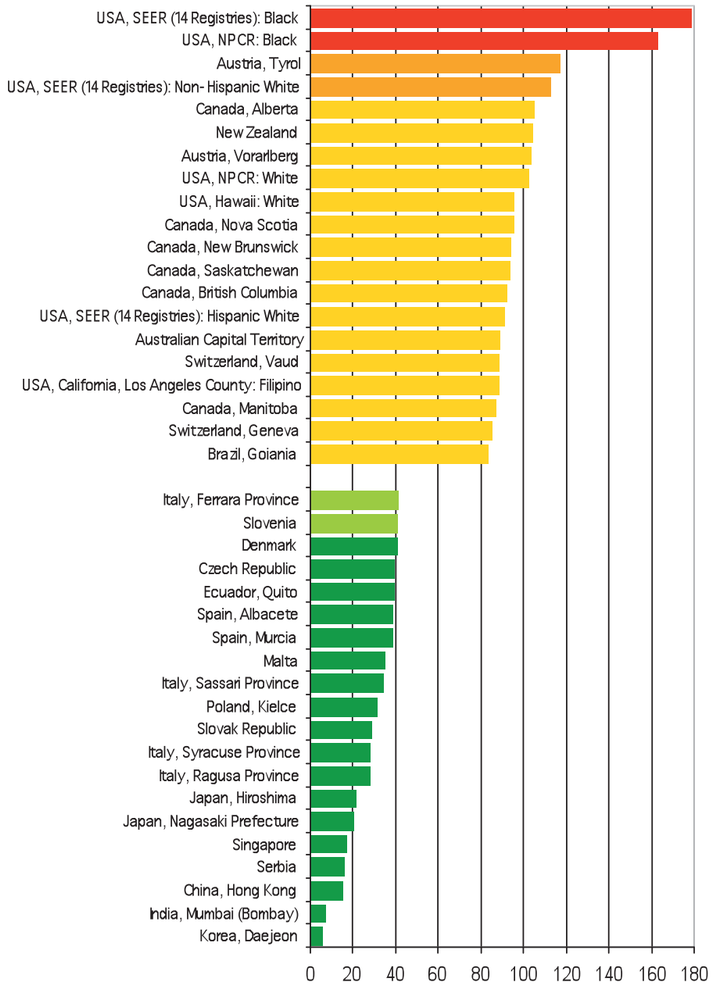


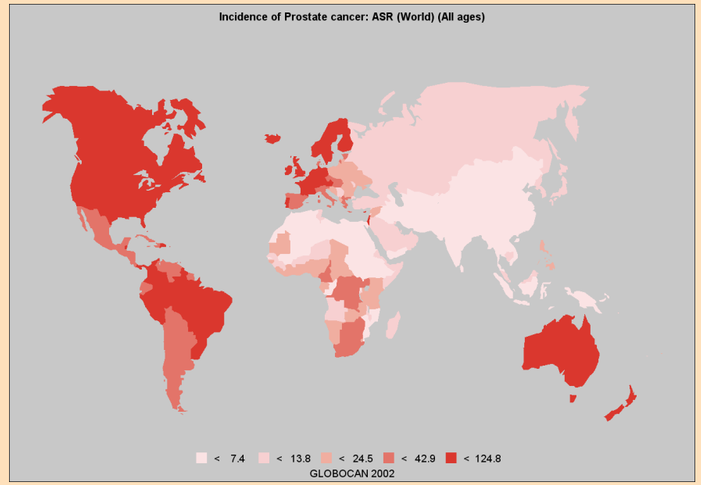
Fig. 5.21.1 *The 20 highest and lowest age-standardised incidence rates (all ages) for the period 1998–2002, for prostate cancer among registries with the highest quality data and over one million person-years of observation (to ensure stability of the rates)*

Long-term series confirm that the (all-ages) mortality rate from prostate cancer has been rising steadily in Ireland (1926–2004) (Figure 5.21.2) and Scotland (1911–2004) (Figure 5.21.3). It is notable that the increased mortality rate is much less in men in middle age (35–64) in Scotland.

Comparisons between trends in incidence and mortality in countries where both are available demonstrate a tendency for large increases in incidence accompanied by little change, and perhaps subsequent declines in mortality rates (Figure 5.21.4).

The Nordic countries (Denmark, Finland, Sweden and Norway) provide some important clues to explain this situation. Incidence rates were increasing and similar in the Nordic countries during the 1980s. Around 1990, a more rapid incidence increase began in all Nordic countries except Denmark, where an increase was seen 5 years later. In 2001, incidence rates in Denmark were half of those seen in the other Nordic countries, but mortality rates varied only marginally among countries. Mean annual declines in prostate cancer mortality of 1.9% and 1.8% were observed from 1996 to 2004 in Finland and Norway, respectively. During the same period, mortality rates levelled off in Iceland and Sweden but continued to increase in Denmark [4].

The rapid increase in incidence during the early 1990s coincided with the introduction of the prostate specific antigen (PSA) test and conveys little information about the occurrence of potentially lethal disease. Mortality rates, however, have recently stabilised or declined in countries where PSA testing and curative treatment have been commonly practiced since the late 1980s. Although other explanatory factors may be in operation, these trends are consistent with a moderate effect of increased curative treatment of early diagnosed prostate cancer and improved treatment of more advanced disease [4].



World Map 5.21.1

In order to quantify the plausible contribution of PSA screening to the nearly 30% decline in the United States prostate cancer mortality rate observed during the 1990s, two mathematical modelling teams independently projected disease mortality in the absence and presence of PSA screening using the same data source, the Surveillance, Epidemiology and End Results (SEER) registry [5]. The teams projected similar mortality increases in the absence of screening and decreases in the presence of screening after 1985. By 2000, the models projected that 45% (Fred Hutchinson Cancer Research Center) to 70% (University of Michigan) of the observed decline in prostate cancer mortality could be plausibly attributed to the stage shift induced by screening. While PSA screening may account for much, but not all, of the observed drop in prostate cancer mortality, other factors, such as changing treatment practices, may also have played a role in improving prostate cancer outcomes [5].

Etiology and genetics

The etiology of prostate cancer remains shrouded in mystery [6]. An IARC Monograph Working Group found no association with Tobacco Smoking [7], and this was confirmed subsequently [8]. Another IARC Monograph Working Group found no association with Alcohol Consumption [9], and this too was confirmed subsequently [10].

There appears to be little association with macronutrient intake and prostate cancer risk. Dietary fat and meat as potential risk factors for prostate cancer have been the focus of many

epidemiologic investigations, and findings from recent studies in particular have been inconsistent. Analysis of the information in the Multiethnic Cohort Study found that intake of different types of fat (total, saturated, monounsaturated or polyunsaturated), n-6 fatty acid, cholesterol, various meats and fats from meat showed no association with overall prostate cancer risk or with non-localised or high-grade prostate cancer. There was little evidence of any relation of fat and meat intake with prostate cancer risk within any of the 4 racial/ethnic groups (African Americans, Japanese Americans, Latinos and whites). The overall findings from this large cohort study of ethnically diverse populations gives no indication that intake of fat and meat substantially affects prostate cancer risk [11].

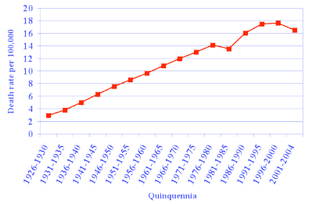


Fig. 5.21.2 *Cancer of the Prostate in Men in Ireland, 1926–2004*
Annual, average age-standardised death rates per 100 000 All-ages, age-standardised mortality rate from prostate cancer per 100 000 in Ireland (1926–2004)

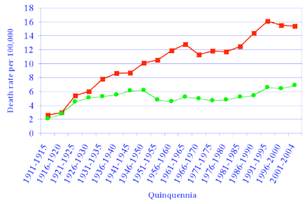
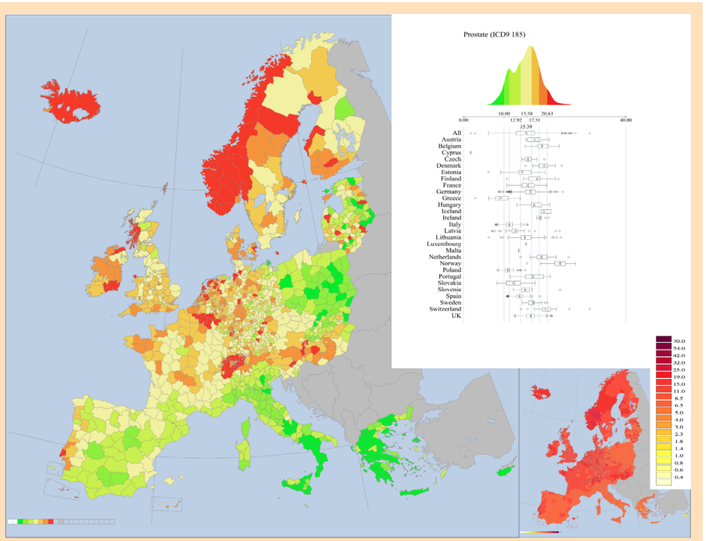


Fig. 5.21.3 *Cancer of the Prostate in Men in Scotland, 1911–2004*
Annual, average age-standardised death rates per 100 000 All-ages, age-standardised mortality rate, and truncated (35–64) rate, from Prostate Cancer per 100 000 in Scotland (1911–2004)



European Map 5.21.1 *High mortality rates from prostate cancer are apparent in Iceland, Norway, much of Sweden, southern Finland and Denmark; there were also higher-than-average rates in The Netherlands, Belgium and northern France, and Ireland.*
There was also a band of high rates from Switzerland eastwards into Austria and western Hungary. Low rates are notable throughout Poland, Greece and Italy, and much of Spain.[1]

Omega-3 fatty acids are purported to reduce the risk of cancer although studies have reported mixed results. A meta-analysis of 38 articles from prospective epidemiological studies investigated the risk of cancer with intake of omega-3 fatty acids. For prostate cancer, there was no evidence of association. Dietary supplementation with omega-3 fatty acids is unlikely to prevent cancer [12].

There are some potential relationships which still need to be clarified. Inverse associations with prostate cancer have been observed for allium vegetable consumption and weak inverse associations for palmitoleic acid, fatty acid, 20:5 n-6 and for oleic acid [13]. Diets rich in olive oil (a source of oleic acid) and allium vegetables might reduce the risk of prostate cancer; this is consistent with low rates in many parts of southern Italy (Figure 5.21.2).

Calcium and dairy foods in relation to prostate cancer were examined in the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study (1995/1996–2001) [14]. During up to 6 years of follow-up (n=293 888), the authors identified 10 180 total prostate cancer cases (8754 non-advanced, 1426 advanced and 178 fatal cases). Total and supplemental calcium were unrelated to total and non-advanced prostate cancer. These findings do not provide consistent support for the hypothesis that calcium and dairy foods increase prostate cancer risk.

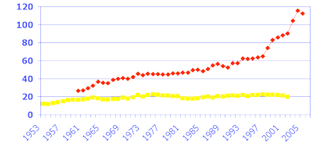
Several studies have reported an inverse association between tomato and/or lycopene intake and the risk of some types of cancer, prompting two petitions to the US Food and Drug Administration (FDA) for qualified health claims regarding tomatoes, lycopene, and the risk reduction for some forms of cancer, notably prostate cancer. The FDA review found no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial or pancreatic cancer. The FDA also found no credible evidence for an association between tomato consumption and a reduced risk of lung, colorectal, breast, cervical or endometrial cancer. The FDA found very limited evidence to support an association between tomato consumption and reduced risks of prostate, ovarian, gastric and pancreatic cancers [15].

Statins are commonly used cholesterol-lowering drugs that have proapoptotic and antimetastatic activities that could affect cancer risk or progression. Results from previous epidemiologic studies of the association between statin use and cancer have been inconsistent. Platz and co-workers (2006) investigated the association of statin use with total and advanced prostate cancer, the latter being the most important endpoint to prevent in an ongoing prospective cohort study of 34 989 US male health professionals. Use of statin drugs was not associated with risk of prostate cancer overall but was associated with a reduced risk of advanced (especially metastatic or fatal) prostate cancer [16].

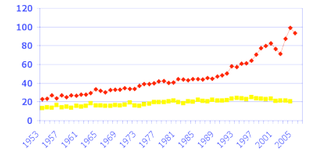
Some recent epidemiologic studies have failed to confirm positive associations between insulin-like growth factor-I (IGF-I) and the risk of prostate cancer observed in earlier studies, but have reported suggestive evidence for a positive association between IGF-binding protein-3 (IGFBP-3) and prostate cancer risk, a result contradicting the earlier assumption that high levels of IGFBP-3 would be protective against prostate cancer. The association between IGF-I and IGFBP-3 and prostate cancer risk was determined by measuring the two peptides in plasma samples collected at baseline in a prospective cohort study of 17 049 men. The risk of prostate cancer was not associated with baseline levels of IGF-I or the molar ratio IGF-I/IGFBP-3 (all odds ratios 0.82–1.08; P(trend) ≥0.2), whereas the risk increased with baseline levels of IGFBP-3 (P(trend) = 0.008), the hazard ratio (HR) associated with a doubling of the concentration of IGFBP-3 being 1.70 (95% CI 1.15–2.52). The HR for quartile 4 relative to quartile 1 of IGFBP-3 was 1.49 (95% CI 1.11–2.00). The HRs did not differ by tumour aggressiveness or age at onset (all Ps ≥0.4). High levels of IGFBP-3 but not IGF-I were associated with an increased risk of prostate cancer [17].

Attention has recently focussed on the metabolic syndrome, characterised by insulin insensitivity, central obesity dyslipidemia and hypertension, on the risk of prostate cancer. It is recognised as a risk factor for cardiovascular disease in men; by the time metabolic syndrome is diagnosed, however, most men already have entrenched cardiovascular disease [18]. One third of men with type 2 diabetes mellitus are now recognised as testosterone deficient. Emerging evidence suggests that testosterone therapy may be able to reverse some aspects of metabolic syndrome [18], although the impact of such a strategy on prostate cancer risk remains an open question.

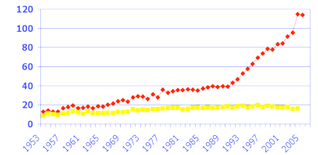
Endogenous androgens have long been suspected as being involved in the etiology of prostate cancer, although epidemiologic studies have failed to support the hypothesis that circulating androgens are positively associated with prostate cancer risk. Some recent studies have even suggested that high testosterone levels might be protective particularly against aggressive cancer. In a large Australian study, high levels of testosterone and adrenal androgens have been associated with reduced risk of aggressive prostate cancer but not with non-aggressive disease [19].



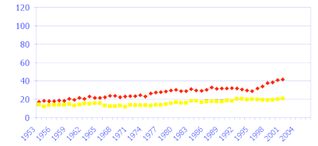
Incidence and Mortality from Prostate Cancer in Sweden, 1953-



Incidence and Mortality from Prostate Cancer in Finland, 1953-



Incidence and Mortality from Prostate Cancer in Norway, 1953-



Incidence and Mortality from Prostate Cancer in Denmark, 1953-

Fig. 5.21.4 *Trends in incidence and mortality in Norway, Denmark, Sweden, Finland and Scotland from mid 1950s to present*

Despite the large number of families with prostate cancer in brothers and across multiple generations, there is no gene which has been identified for prostate cancer with similar significance to those genes (BRCA1 and BRCA2) discovered some years ago for breast cancer. However, the search goes on and there have been some very interesting developments reported recently [20-22].

Prevention of prostate cancer

The dramatic international variation in prostate cancer incidence and mortality rates suggests that changeable environmental factors exert an influence [23]. This has prompted a search for ways to prevent the disease. Epidemiologic studies have reported variations in the strength and consistency of the evidence that dietary factors such as the carotenoid lycopene, selenium, vitamin E and high intake of fat have roles in prostate cancer risk. Impairment of androgen synthesis lowers the risk of prostate cancer. 5-alpha-reductase inhibitors have been shown to decrease prostate size by decreasing androgenic stimulation to the prostate. Other promising but less developed interventions include vitamin D supplements and modification of diet. Any manipulation to decrease one's risk of prostate cancer will by necessity have to be given to a large proportion of men who would never develop prostate cancer even without the intervention. To be acceptable, a successful preventive intervention should have few or no side effects; some additional benefits would be useful. All potential preventive interventions will need to be rigorously evaluated before they can be advocated for prostate cancer prevention [23].

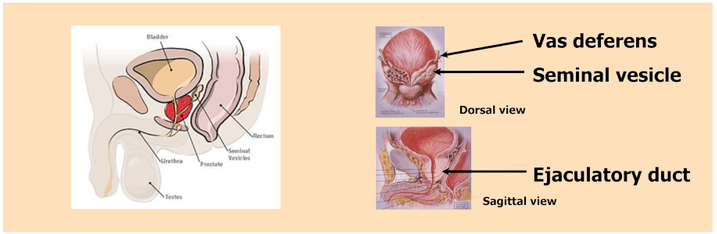


Fig. 5.21.5 *Male Urological Anatomy*

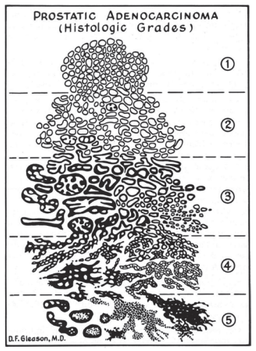


Fig. 5.21.6 *Dr. Donald F Gleason has provided a conceptual diagram (oversimplified) to show the continuum of deteriorating cancer cell architecture, and the four dividing lines along this continuum which he discovered are able to identify patients with significantly different prognosis derived from a study which included 2900 patients. http://www.phoenix5.org/Infolink/GleasonGrading.html*

Prevention of prostate cancer would have a major impact on disease-associated cost, morbidity and mortality for a large segment of the population. A major advance in prevention of prostate cancer came in 2003 with the publication of the Prostate Cancer Prevention Trial [24] which demonstrated that use of finasteride is associated with a 25% reduction in the 7-year period prevalence of prostate cancer in men over age 55 years with normal digital rectal exam and initial prostate specific antigen <3.0 ng/ml. Use of finasteride was associated with a slightly higher risk of Gleason sum 7–10 tumours, some sexual side effects, and fewer urinary symptoms.

A substantial body of new molecular evidence supports the existing body of clinical and epidemiological data leading to testing of vitamin E and selenium as preventative agents in men at risk for prostate cancer [25]. A large chemoprevention trial has been organised. SELECT is a randomised, prospective, double-blind study designed to determine if selenium and vitamin E can reduce the risk of prostate cancer among healthy men. Preclinical, epidemiologic and Phase III data suggest that both selenium and vitamin E have potential efficacy in prostate cancer prevention [26]. The experience of the Prostate Cancer Prevention Trial and the rapid accrual of SELECT during its first year demonstrate the interest and dedication of healthy men to long-term studies of cancer prevention. A total of 32 400 men are planned to be randomised in SELECT; enrolment began in 2001 with final results anticipated in 2013 [26].

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5.22 Thyroid Cancer

Summary

> Ionizing radiation and history of benign thyroid diseases are the best-established risk factors for thyroid cancer

> Iodine deficiency has been associated with follicular thyroid cancer

> A strong genetic component has been shown for medullary carcinoma, alone or as a part of multiple endocrine neoplasia (MEN) syndrome. The APC gene has been associated with papillary carcinoma

Fig. 5.22.1 *Composite artwork illustrating the controlling role of the tyroid gland in the body*

In most areas of the world, the incidence of thyroid cancer among women is in the range 2–5/100 000; that in men is 1–2/100 000. High-risk areas (incidence >5/100 000 in women) include Central America, Japan and the Pacific islands. International comparisons, however, are complicated by possible differences in diagnostic procedures. The most common thyroid neoplasm (50–80% of the total) is papillary carcinoma, followed by follicular carcinoma (10–40%) and medullary carcinoma (5–15%).

Survival from thyroid cancer is very good (over 85% five-year survival rate in Europe and North America), resulting in low mortality rates (below 1.2/100 000 in women and 0.6/100 000 in men in most areas of the world).

In most countries, incidence rates have been stable or have been slowly increasing (<1%/year) during the last decades; mortality rates have steadily declined, likely because of improved treatment.

Ionizing radiation is the main established risk factor for thyroid cancer [2]. The carcinogenic effect seems greater for exposure before age 5 than subsequently. The pooled analysis of studies of individuals irradiated in childhood for medical conditions and atomic bomb survivors resulted in a summary excess relative risk of 7.7 (95% CI 2.1–29) per Gy, and an excess absolute risk of 4.4 (95% CI 1.9–10) per 10 000 person-years Gy. Several studies have been published on adults exposed to ^{131}I for medical purposes. Although those studies suggest an increased risk, their interpretation is made complex by the fact that these patients were treated because of thyroid diseases. ^{131}I was the main exposure resulting from the accident of the Chernobyl nuclear reactor in 1986; since then, an increased incidence of thyroid cancer has been reported among children living in the contaminated areas of Belarus and Ukraine. Iodine supplementation in the immediate period following the Chernobyl accident has been shown to protect against thyroid cancer [3]. Studies of occupational exposure to low-level ionizing radiation, typically in the nuclear industry, have failed to show an increased in mortality from thyroid cancer.

An association between thyroid cancer and a history of benign thyroid diseases has been observed in most studies, although the strengths of these associations have varied across studies. Because thyroid cancer incidence rates in women are consistently 2–3 times higher than those in men, some studies in various geographic areas have focused on women in an attempt to identify hormonal factors that might explain this excess. However, findings related to menstrual and reproductive factors as well as to exogenous hormone use have been inconsistent, as have findings related to diet and to anthropometric and lifestyle factors.

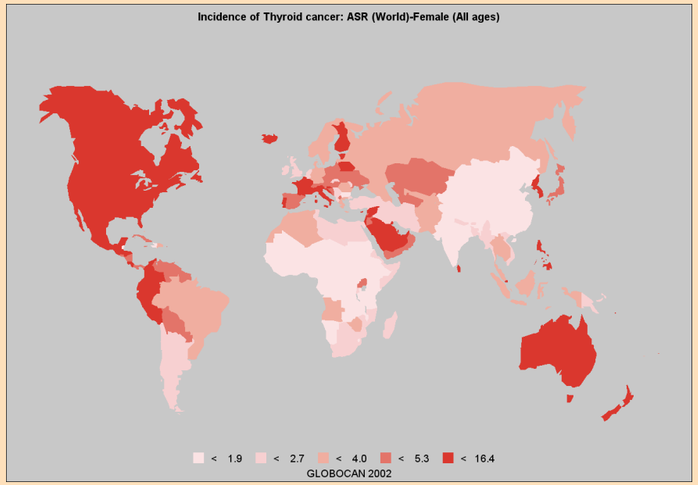
In a pooled analyses, goiter and benign nodules/adenomas were shown to be the strongest risk factors for thyroid cancer apart from radiation in childhood. In women, the pooled odds ratios (OR) were 5.9 for goiter and 38.3 for benign nodules/adenomas. Elevated risks were observed for men and women and in relation to both major histologic types (papillary/follicular). No significant heterogeneity was seen across geographic areas or across studies. The excess risk was greatest within 2–4 years prior to thyroid cancer diagnosis, but an elevated OR was present 10 years or more before cancer. Prior hyperthyroidism was related to a small, statistically non-significant increase that was reduced after allowance for a history of goiter. A history of hypothyroidism was not associated with cancer risk [4].

Elevated levels of thyroid-stimulating hormones are associated with thyroid growth and possibly thyroid cancer. The evidence of an association between iodine deficiency (and presence of endemic goiter) and thyroid cancer is equivocal: studies from central and southern Europe support such an association, which was not confirmed in studies from northern Europe and North America. It is possible that iodine deficiency increases the risk of follicular thyroid cancer, while the papillary type is linked to iodine-rich diet.

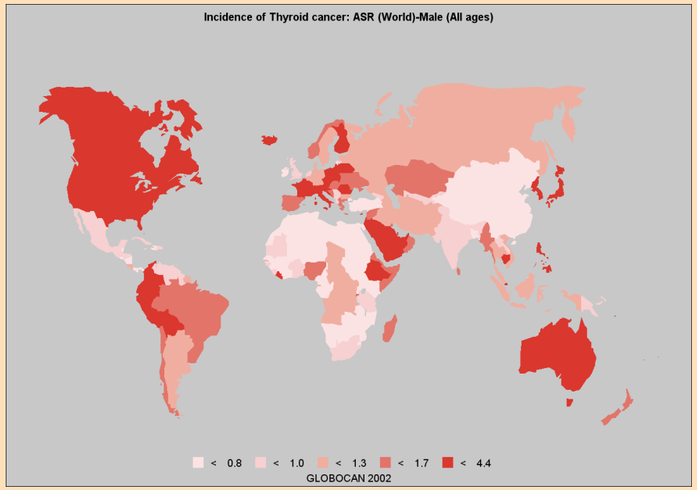
Among other risk factors considered, pooled analyses have focussed only on fish/seafood [5] and cruciferous and other vegetables [6]. Fish was not associated with thyroid cancer risk in all studies combined, but there was a suggestion of reduced risk in endemic goiter areas. It was reassuring to note that high levels of fish consumption did not appreciably increase risk in iodine-rich areas, and fish consumption was inversely related to thyroid cancer risk in endemic goiter areas. Cruciferous vegetables, which contain goitrogenic substances as well as several constituents which can inhibit carcinogenesis, were weakly and non-significantly related to reduced risk of thyroid cancer.

A strong genetic component has been shown for medullary carcinoma: about 20% of these neoplasms are associated with an autosomal dominant gene, with penetrance close to 100% [7]. It can also be associated with other endocrine neoplasms within the multiple endocrine neoplasia syndromes (MEN type 2). These include medullary thyroid carcinoma and hyperparathyroidism (MEN2A), resulting from mutation in the *ret* proto-oncogene, or mucosal neuromas of the lip and gastro intestinal tract (MEN 2B, [2]). Familial factors play a role in papillary carcinoma, too. Among the genes associated with papillary thyroid cancer are the *ret* and the APC gene.

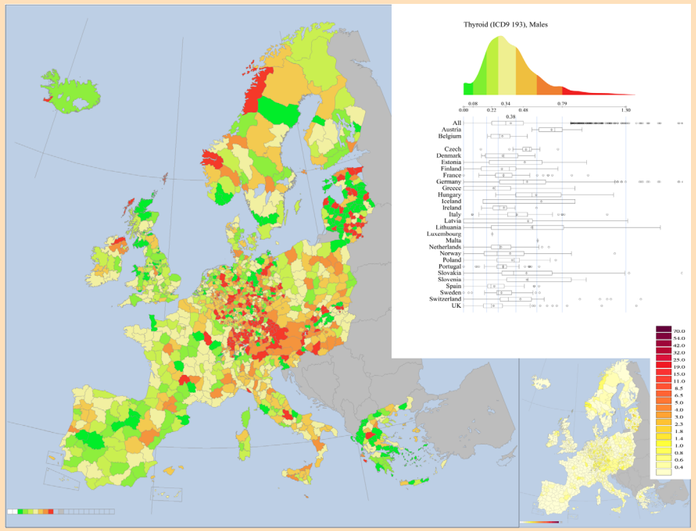
The prospects for prevention of thyroid cancer are made complex by the limited understanding of its etiology, with the exception of relatively rare high-risk conditions, such as childhood exposure to ionizing radiation and high-risk families.



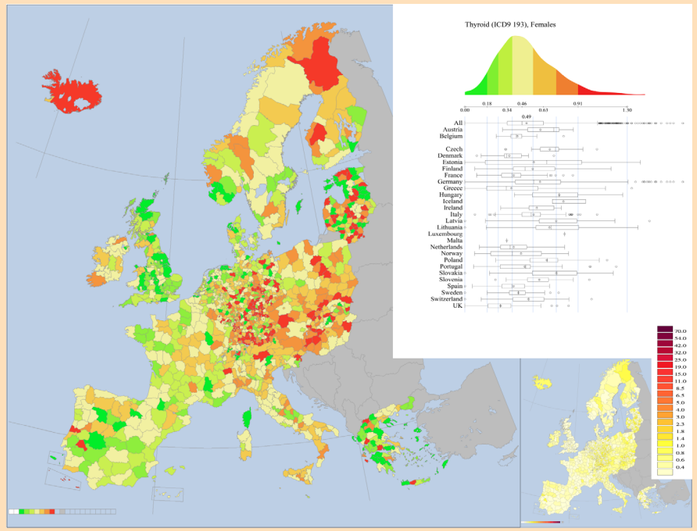
World Map 5.22.1



World Map 5.22.2



European Map 5.22.1 *In men, there appears to be an aggregation of high rates in the centre of Europe - the neighbouring countries of Austria, central and southern Germany, Switzerland and the west of the Czech Republic. There were generally low rates in the United Kingdom, Spain, Portugal, France and Greece [1].*



European Map 5.22.2 *In females, there was the same pattern of generally higher rates in Austria and adjacent countries, and mostly lower-than-average rates in much of western Europe. However, it must be kept in mind that all these mortality rates were very low in absolute terms [1].*

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5.23 Tumours of the Nervous System

Summary

> Tumours of the nervous system account for less than 2% of all malignancies (about 175 000 cases per year worldwide); the incidence does not vary markedly between regions or populations

> The incidence of these tumours tended to increase in most cancer registration areas over the last few decades, most probably because of better reporting by cancer registries and improvement in non-invasive imaging technologies

> Etiology is largely unknown; the only unequivocal cause is therapeutic irradiation, but occurrence in these circumstances is very rare

> The nervous system is frequently involved in inherited tumour syndromes, including neurofibromatosis (NF1/NF2 germline mutations), von Hippel-Lindau disease (VHL), tuberous sclerosis (TSC1/TSC2) and Li-Fraumeni syndrome (p53)

> Glioblastomas are the most common brain tumours and mainly affect adults. These tumours are surgically incurable and largely resistant to radiation and chemotherapy; only 3% of patients survive longer than 3 years

> Embryonal tumours, including cerebellar medulloblastomas, retinoblastomas and peripheral neuroblastoma, predominantly afflict children, ranking second after leukaemia as the most common types of paediatric cancer

Over 90% of nervous system tumours arise from the brain, the cranial nerves and the cranial meninges. On clinical grounds, benign tumours may be as dangerous as malignant tumours when they grow in the cranium or, in the base of the skull, or in the vertebrae and compress the surrounding nervous tissues.

Gliomas arise from the glial cells and are classified pathologically as astrocytomas (low-grade) and glioblastomas (high-grade). They represent 40–60% of primary tumours of the brain, are predominantly malignant, and are more common in men. Meningiomas arise from the cranial meninges and represent 20–35% of brain neoplasms, while schwannomas (or neurilemomas) arise from the Schwann cells of the nerve sheath (mainly of the eighth cranial (acoustic) nerve) and represent 5–10% of all brain neoplasms. These two latter types are mainly benign. Rare types of nervous system neoplasms include pituitary adenomas, childhood primary neuroectodermal tumours (also called medulloblastoma) and tumours of the spine and the peripheral nerves.

Although not very frequent, brain tumours contribute significantly to morbidity, often affect children and overall have a poor prognosis. Due to marked resistance to radiation and chemotherapy, the prognosis for patients with glioblastomas is very poor. The majority of patients die within 9–12 months, and fewer than 3% survive more than 3 years.

Epidemiology

Data on the descriptive epidemiology of nervous system tumours are difficult to interpret, because many studies include both benign and malignant tumours.

The age distribution of brain tumours is bimodal, with a peak incidence in children and a second larger peak in adults aged 45–70. In most developed countries, brain tumours are the 12th most frequent cause of cancer-related mortality in men.

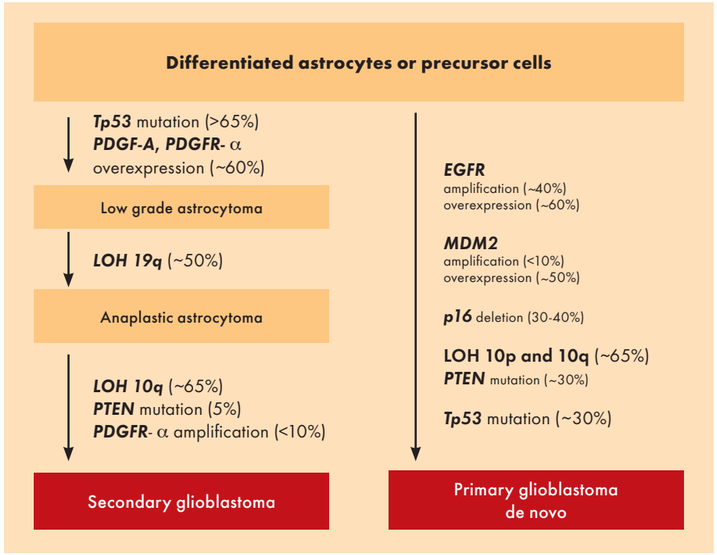


Fig. 5.23.1 *Genetic pathways in the evolution of primary and secondary glioblastoma*

The incidence of brain tumours is slightly higher in men than in women; the male:female ratio is approximately 1.3 for gliomas and 0.6 for meningiomas. There is a geographical variability in the incidence of brain neoplasms: rates in men are 6 to 8/100 000 in most countries from the Americas, Europe and Oceania, and in the range of 2 to 3/100 000 in Africa and Asia. In the USA, rates of gliomas are 30–50% higher in Whites than in other ethnic groups, while rates of meningiomas are slightly higher in Blacks.

During the last decades, incidence and mortality from brain tumours have increased in most developed countries, mainly in the older age groups [2]. The increase in the incidence was confined to the late 1970s and early 1980s and coincided with the introduction of improved diagnostic methods [3]. After 1983 and more recently during the period of increasing prevalence of mobile phone users, the incidence has remained relatively stable for both men and women. Analysis of temporary trends in introduction of medical technologies and improved diagnosis of brain tumours shows that most if not all of the increase is attributable to (i) the introduction of high-resolution neuroimaging (e.g. CT Scan, Magnetic Resonance Imaging, PET Scan) in the last decades; (ii) variations in diagnostic and reporting procedures; and (iii) the brain as a frequent site of metastases, principally from breast and lung cancer, because with more primitive imaging modalities, brain metastases may have been misclassified as primary brain

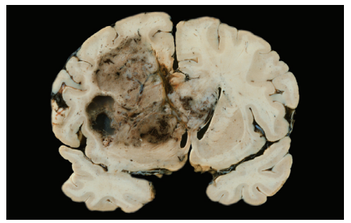
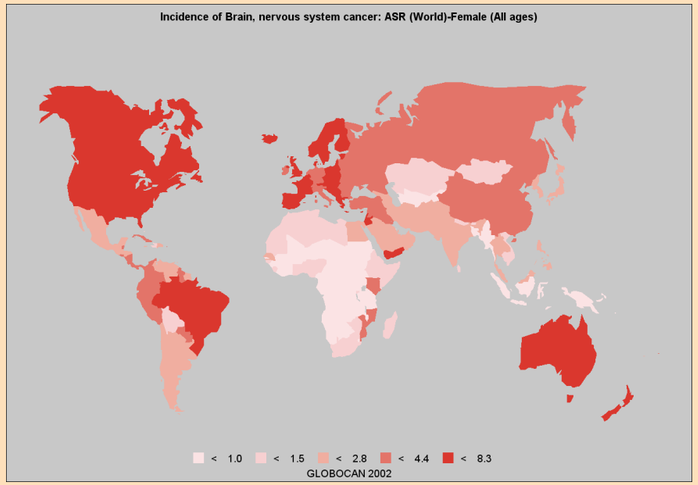
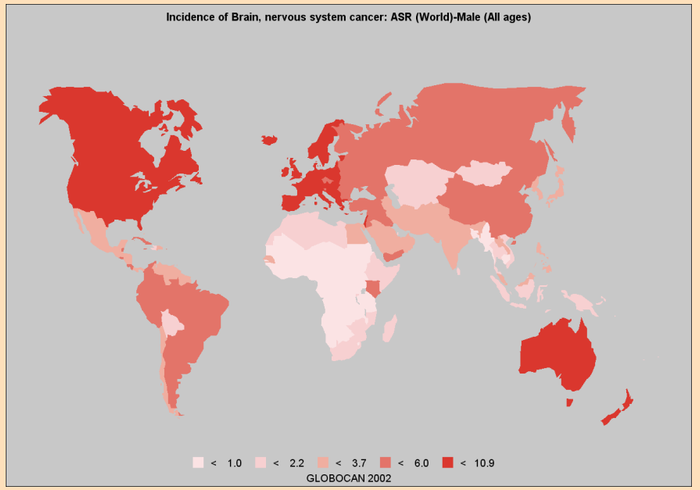


Fig. 5.23.2 *A large glioblastoma multiforme in the left frontal lobe, extending into the corpus callosum and the contralateral white matter*



World Map 5.23.1

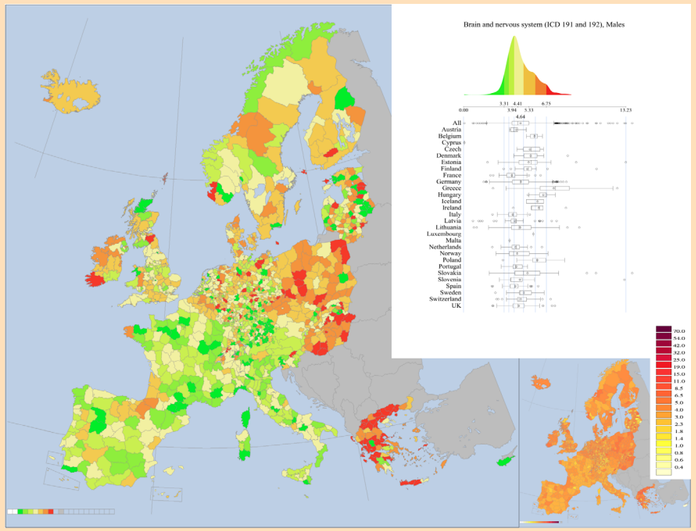


World Map 5.23.2

tumours. The likelihood for these three reasons being at the source of the recent increase in brain tumours incidence is reinforced by stable or even slight decreases in mortality from brain tumours (e.g. in the USA, [4]), which underlines that a large proportion of additional brain tumours found thanks to new imaging technologies are not as deadly and are probably more curable than brain tumours diagnosed in the past.

Geographical variation in incidence is less than for most other human neoplasms, but incidence tends to be higher in more developed countries.

The incidence of gliomas tends to be higher among people from high socioeconomic groups. Association of higher socioeconomic status with central nervous system tumours and greater access to imaging technologies in more affluent economic strata partly explain why the incidence of these tumours is greater in high than in medium- and low-resource countries, and within countries is also greater in upper socio-economic classes.



European Map 5.23.1 *In men, mortality rates from cancers of the brain and central nervous system were generally low in the south and west of Europe, including Portugal, Spain, France, Italy, Switzerland, Austria and southern Germany. Rates were noticeably higher-than-average in most of Greece, Hungary, the Czech Republic, Slovakia and Poland, and in parts of northern Germany and Belgium [1].*

Tumour (WHO Grade)	Typical location	Age at clinical manifestation (% of cases)			Five-year survival (% of patients)	Genetic alterations
		0–20 yrs	20–45 yrs	>45 yrs		
Pilocytic astrocytoma (Grade I)	Cerebellum, optic nerve	74	20	6	>85	*NF1* (neurofibromatosis cases)
Low grade diffuse astrocytoma (Grade II)	Cerebral hemispheres	10	61	29	>50	*p53* mutation
Glioblastoma (Grade IV)	Cerebral hemispheres	3	25	72	<3	*EGFR* amplification, *PTEN* mutation, p16 deletion, LOH chromosome10
Oligodendroglioma (Grade II/III)	Cerebral hemispheres	8	46	46	>50	LOH 1p, 19q
Ependymoma (Grade II)	Ventricles, spinal cord	37	38	25	<30	*NF1* (spinal tumours)
Medulloblastoma (Grade IV)	Cerebellum	74	23	3	>50	Isochromosome 17, *MYC* amplification, *PTCH*, beta-catenin
Neuroblastoma (Grade IV)	Abdomen	>95			>90 (<1 yr old) 20-50 (>1 yr)	LOH 1p, 11q, *MYCN* amplification, trisomy 17q

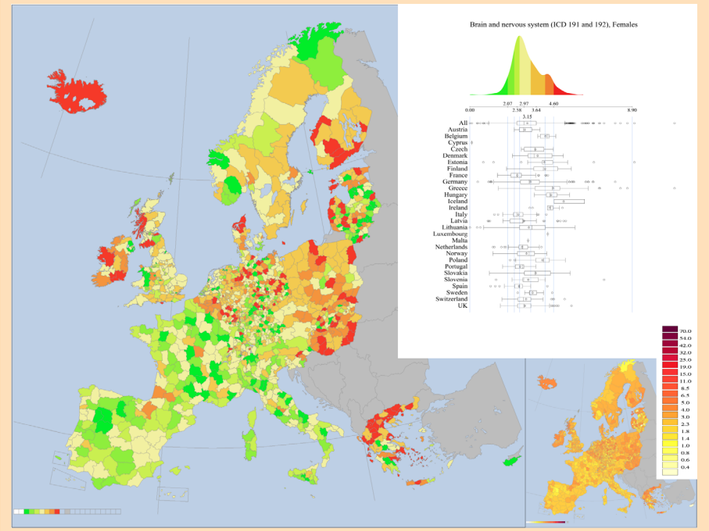
Table 5.23.1 *Summary of epidemiological data on intracranial tumours*

Etiology

During the last few decades, incidence and mortality from brain tumours have increased in most developed countries. However, differences in the descriptive epidemiology of brain cancer, including time trends, can be partially due to variations in diagnostic and reporting procedures.

Ionizing radiation is the only established non-genetic risk factor for brain tumours [2]. It causes all three major types of central nervous system tumours, but the association is stronger for meningioma and schwannoma than for glioma. The evidence comes mainly from studies of atomic bomb survivors and of patients given X-ray therapy in the head and neck region. Head trauma has been suggested as a risk factor for meningioma, and acoustic trauma (as in the case of jobs with exposure to loud noise) as a risk factor for acoustic schwannoma. N-nitroso compounds, in particular nitrosoureas, are potent experimental brain carcinogens, and are part of tobacco smoke. The evidence of an etiological role of tobacco smoking, either active or passive (i.e. childhood exposure to tobacco smoke) in humans is inconclusive [5]. Several other lifestyle, environmental (e.g. occupational exposures, use of pesticides) and medical (e.g. allergic conditions) factors have been suggested to play an etiological role in brain cancer, but the evidence is not sufficient to draw a conclusion.

Some studies have suggested an increased incidence of central nervous system tumours associated with certain occupations, including farming, fire-fighting, metalworking and the rubber and petrochemical industries, and with those who work as anatomists, pathologists and embalmers, but most of these reports have not been confirmed and causative agents have not been identified. Suggestions that radio-frequency radiation generated by mobile phones and microwave telecommunications may play a role in the etiology of malignant gliomas remain to be substantiated.



European Map 5.23.2 *The map for women shows both that the between- and within-country variability in the rates were very closely similar to those in males [1]*

The very limited knowledge about the etiology of tumours of the central nervous system offers scarce resources for an effective preventive strategy.

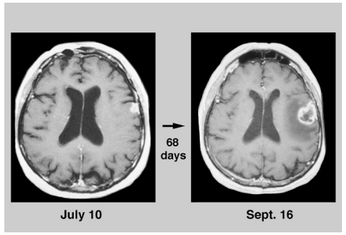


Fig. 5.23.3 *An MRI scan of a primary glioblastoma in a 79-year-old patient. A small cortical lesion rapidly developed into a full-blown glioblastoma with perifocal oedema and central necrosis*

Pathology and genetics

The WHO classification of tumours of the nervous system contains more than 50 clinico-pathological entities with a great variation in

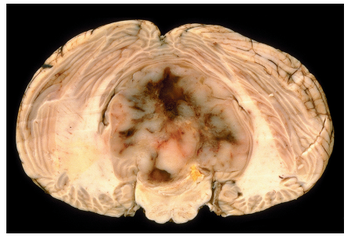


Fig. 5.23.4 *Macroscopic image of a medulloblastoma of the cerebellar vermis, compressing the brainstem*

Syndrome	Gene	Chromosome	Nervous system	Skin	Other tissues
Neurofibromatosis 1	*NF1*	17q11	Neurofibromas, MPNST, optic nerve gliomas, astrocytomas	Café-au-lait spots axillary freckling,	Iris hamartomas, osseous lesions, phaeochromocytoma, leukaemia
Neurofibromatosis 2	*NF2*	22q12	Bilateral vestibular schwannomas, peripheral schwannomas, meningiomas, meningioangiomatosis, spinal ependymomas, astrocytomas, micro-hamartomas, cerebral calcifications	-	Posterior lens opacities, retinal hamartoma
von Hippel-Lindau	*VHL*	3p25	Haemangioblastomas	-	Retinal haemangioblastomas renal cell carcinoma,
Tuberous sclerosis	*TSC1 TSC2*	9q34 16p13	Subependymal giant cell astrocytoma, cortical tubers	Cutaneous angiofibroma ("adenoma sebaceum") peau de chagrin, subungual fibromas	Cardiac rhabdomyomas, adenomatous polyps of the duodenum and the small intestine, cysts of the lung and kidney, lymphangioleiomyomatosis, renal, angiomyolipoma
Li-Fraumeni	*p53*	17p13	Astrocytomas, glioblastomas, medulloblastomas	-	Breast carcinoma, bone and soft tissue sarcomas, adrenocortical carcinoma, leukaemia
Cowden	*PTEN (MMAC1)*	10q23	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos), megalencephaly	Multiple trichilemmomas, fibromas	Hamartomatous polyps of the colon, thyroid neoplasms, breast carcinoma
Turcot	*APC*	5q21	Medulloblastoma	-	Colorectal cancer
	hMLH1	3p21	Glioblastoma	Café-au-lait spots	Colorectal cancer
	hPSM2	7p22			
Naevoid basal cell carcinoma syndrome (Gorlin)	*PTCH*	9q31	Medulloblastoma	Multiple basal palmar and plantar pits	Jaw cysts, ovarian fibromas, skeletal abnormalities

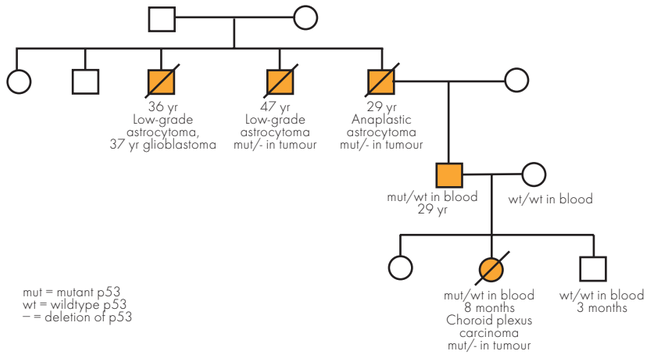
Table 5.23.2 *Major familial tumour syndromes involving the nervous system*

biological behaviour, response to therapy and clinical out-come [6]. The most frequent ones are listed in Table 5.23.1

Many genetic alterations involved in the development of nervous tissue tumours have been identified and are summarised in Table 5.23.2. Precise knowledge of these genetic lesions and may lead to novel therapeutic approaches, including gene therapy.

Cancer of the eye

Neoplasms of the eye are rare; the incidence is below 1/100 000 in all regions of the world, with the exception of Central and Southern Africa. The main histological types are squamous cell cancer arising from the conjunctiva; retinoblastoma, which arises in children and is relatively common in Africa; and uveal melanoma, which is the main adult type outside of Africa. Solar radiation and solar elastosis are causes of conjunctiva carcinoma [7]; the role of sun exposure in uveal melanoma is controversial. For instance, in populations where a sustained increase in cutaneous melanoma incidence is observed since several decades, the incidence of uveal melanoma remains quite constant. About 50% of cases of retinoblastoma are caused by an inherited mutation in the Rb gene.



Orange shading = carrier of CGG>TGG mutation in the p53 gene (resulting in a change of amino acid from arginine to tryptophan).

Fig. 5.23.5 *Pedigree of a family with Li-Fraumeni syndrome, caused by a germline mutation in codon 248 of the p53 tumour suppressor gene. Blood samples of affected family members have a mutation in one allele. In tumours, the second allele is usually deleted. This family shows a remarkable clustering of brain tumours*

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CANCER INSTITUTE PROFILE:
Centro Nacional de Investigaciones Oncologicas
(Spanish National Cancer Research Centre)

The Centro Nacional de Investigaciones Oncologicas (CNIO), located in Madrid, Spain, is fully dedicated to basic, translational and applied cancer research. Basic cancer research focuses on the molecular mechanisms of how genetic (oncogenes and tumour suppressors) and epigenetic events contribute to malignant transformation with special emphasis in the areas of genetic stability and proliferative signalling. Translational research is represented by the Molecular Pathology Programme that focuses primarily on lymphoma, lung, pancreas, bladder and melanoma, and the Human Cancer Genetics programme dedicated to studying inherited breast and endocrine tumours as well as the genetic epidemiology of bladder cancer. Bioinformatics and structural biology are also actively represented at the CNIO. Finally, we have seven research groups (four in biology and three in medicinal chemistry) fully dedicated to target-based drug discovery. A new programme on Cancer Cell Biology will be implemented during 2008. The CNIO also has eleven support units covering a wide range of technologies as well as a large barrier facility to house one of the largest collections in Europe of genetically engineered strains of mice. Scientific productivity at the CNIO for 2006–07 consists of 300 publications, of which 166 were generated at the CNIO and 134 were collaborations with other institutes. The average impact factor of these publications was 7.78 implying a total impact factor of 2335 (1397 for the publications generated at the CNIO).

website: www.cnio.es

5.24 Lymphoma

Summary

> Hodgkin lymphoma occurs mainly in young adulthood and then at old age. The main known cause of this disease is infection with Epstein-Barr virus.

> Non-Hodgkin lymphomas are a heterogeneous group of neoplasms with different causes and clinical behaviour. Their incidence has risen in recent decades but the increase has stopped since 2000: the causes of this trend are not known.

> Severe immunodeficiency, such as that occurring in AIDS patients, leads to non-Hodgkin lymphoma. Less severe forms of the immunological function alteration are likely to contribute to the burden of this disease.

> Several environmental factors, such as pesticides, have been suspected to cause lymphoma, but a causal link has not been confirmed.

The term lymphoma encompasses a diverse group of neoplasms which originate from the cells of the lymphopoietic system. Traditionally, two main groups of lymphomas have been distinguished including Hodgkin lymphoma (HL), characterised by large polynuclear cells named after Reed and Sternberg, and a diverse group of other neoplasms, defined as non-Hodgkin lymphoma (NHL). The complexity of lymphomas is reflected by the various classifications that have been used to separate different subtypes. The most recent World Health Organisation classification system [2] represents an effort to reach a consensus to allocate all lymphoma cases into clear categories. Neoplasms are divided between B and T cell lymphocytes, with over 20 different clinicopathological entities. Importantly, this classification incorporates all lymphoproliferative diseases, including multiple myeloma, B-cell acute lymphoblastic leukaemia, Burkitt lymphoma and HL.

Hodgkin lymphoma

The incidence of HL varies from low-incidence populations, with rates lower than 1/100 000, including areas of Southern and Eastern Asia and of Sub-Saharan Africa, to high-incidence populations, with rates in the order of 3/100 000 found in the USA and some European countries, as well as in Israeli Jews [3]. The incidence in men is consistently higher than in women, with a ratio of between 1.5 and 2. The incidence has been relatively stable over time and may even be declining. The age of onset of HL shows a bimodal distribution in high-resource populations, with a first peak between age 15 and 35 and a second peak after the age of 60. In low-resource countries the first peak tends to be observed during childhood. This bimodal distribution suggests that the HL includes at least two different entities.

Viral infections play an important role in the etiology of HL [4]. Its onset may be related to decreased or delayed exposure to infectious agents during childhood, as indicated by its association with having fewer siblings, living in single-family houses, and early birth order.

Infection with Epstein-Barr virus (EBV) is associated with the majority of HL cases. EBV is ubiquitous throughout the world, with 80–100% of individuals being infected by age 30 [5]. In low-resource countries infection occurs earlier in life, whereas in high-resource countries infection is often delayed until adolescence. The EBV genome is present in about 50% of the lymphoma cells of cases, and another EBV-related condition, infectious mononucleosis, is associated with a moderately elevated risk of development of HL. Sero-epidemiological studies indicate that patients with HL can be distinguished by an altered antibody profile to EBV.

A type 2 immune environment (predominance of Th2 cytokines and chemokines, and in particular of interleukin 13) is present in HL, but its etiological role is unclear. Patients suffering from immunodeficiences or autoimmune diseases are at increased risk of HL. A link between HL and lifestyle and environmental (e.g. occupation) factors has not been established. HL patients have an increased familial risk of HL and NHL, but this evidence is not supported by the identification of genetic variants at increased risk.

Non-Hodgkin lymphoma

The incidence of NHL is higher than the incidence of HL. Rates of over 10/100 000 are reported from the USA, Australia, Western Europe, and from Israel and the West Asia, while low rates of less than 5/100 000 are reported in Southern and Eastern Asia and parts of Africa [3]. Men have a 1.5–2 fold higher incidence than women. There is a strong geographical variation for some lymphoma subgroups. For example, Burkitt lymphoma is common among children in eastern Africa, and rates of adult T-cell leukaemia/lymphoma are increased in southern Japan and parts of Africa. The trend by age of NHL, on the other hand, shows a steady increase with age in most populations. Exceptions are the populations in which a specific type of lymphoma predominates, such as Burkitt lymphoma in children.

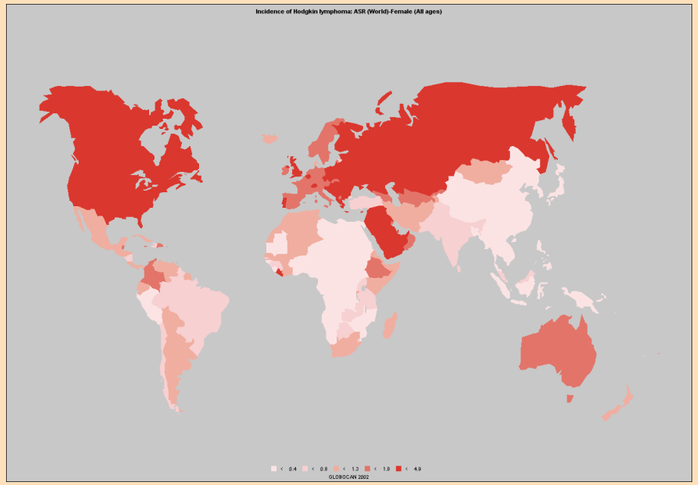
An increase in the incidence of NHL was observed in most high-resource countries until the end of the 20th century. The rate of increase was approximately 4% per year in most populations. In the last few years, however, this increase has levelled off. The reasons for the increase in NHL incidence have been widely discussed, and it is possible that improvement in diagnostic procedures during the 1980s and 1990s explains part of it, in particular in the elderly. However, it is now accepted that the trend also reflected a real increase in the number of cases, the causes of which are not known.

Fig. 5.24.1 *Classical Hodgkin lymphoma. Spleen*

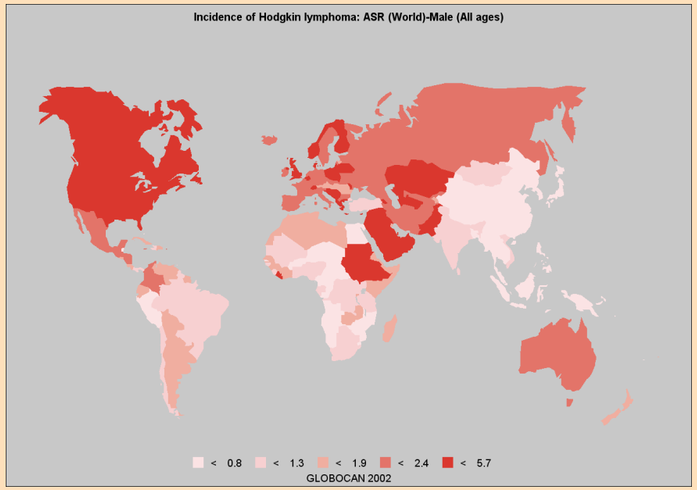
The current knowledge of potential risk factors for NHL is limited [6]. However, there is strong evidence that altered immunological function, either immunostimulation or immuno-suppression, entails an increased risk of NHL. For example, immunosuppressed renal transplant patients have a risk 30 times higher for developing NHL compared to the general population. Lymphomas that develop in immunosuppressed patients share common characteristics. They are generally high-grade B-cell lymphomas and are more likely to be extranodal and of worse prognosis. Lymphomas have also been reported for a variety of other conditions which are either auto-immune in nature, or require immunosuppressive treatment, including Sjögren syndrome and systemic lupus erithematosous.

Infectious agents associated with lymphoma include HIVuman T-cell lymphotropic virus 1 EBV and HCV. Human T-cell lymphotropic virus-2 and human herpes viruses 6 and 8 have also been linked to the development of NHL. In addition, infection with *Helicobacter pylori* is a risk factor for gastric lymphoma.

EBV is particularly prominent in lymphomas developing in immunosuppressed patients, and also in Burkitt lymphomas. The relationship with other forms of lymphoma is, however, unclear. Regarding HIV, NHL is 60 times more frequent among patients with AIDS than in the general population[7]. About 3% of patients with AIDS developed NHL, which represents a small contribution to the overall incidence of NHL, except in populations with a high HIV prevalence such as regions of sub-Saharan Africa. AIDS-related lymphomas tend to be high-grade B-cell lymphomas.



World Map 5.24.1



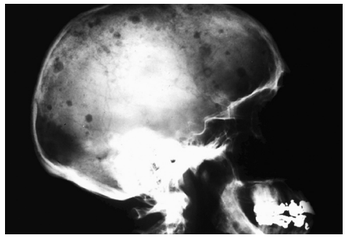
World Map 5.24.2

Human T-cell lymphotropic virus-1, and possibly human T-cell lymphotropic virus-2, appear to be associated with the rare adult T-cell leukaemia/lymphoma, a disease entity with strong geographical clustering in Japan, the Caribbean and parts of Africa. Transmission of the human T-cell lymphotropic virus is similar to that of HIV, involving vertical (mother-to-child) transmission, sexual contact or blood transfusion.

A familial aggregation is present for lymphoma: the risk of the disease among first-degree relatives of cases has been reported in the order of 1.5–4. However, the risk seems higher for siblings of the same sex, suggesting a role of shared environmental factors rather than genetics. Highly penetrant genetic predisposition to lymphomas is not very common but includes ataxia telangiectasia, Wiskott-Aldrich syndrome and hypogammaglobulinemia. Approximately 25% of the patients with rare forms of genetic immunodeficiency will develop a lymphoma.

The increasing recreational exposure to ultraviolet radiation in some populations and the decrease in the atmospheric ozone layer have been related to the observed increase in the incidence of NHL, but this hypothesis has not been supported by analytical studies, which, if anything, showed a decreased risk of lymphoma for high UV exposure [8].

Exposure to pesticides has been associated with NHL risk in studies conducted both on manufacturing workers and applicators in agriculture [9]. The results, however, are not very compelling, with the possible exception of phenoxy herbicides and chlorophenols. This effect might be due to contamination with dioxin. Farming as an occupation has also been weakly associated with lymphoma risk. Organic solvents represent another group of chemicals whose association with lymphoma risk has been widely investigated, without conclusive findings.



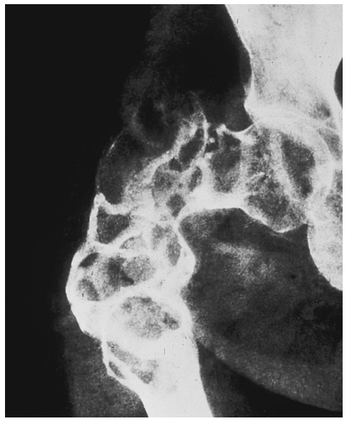
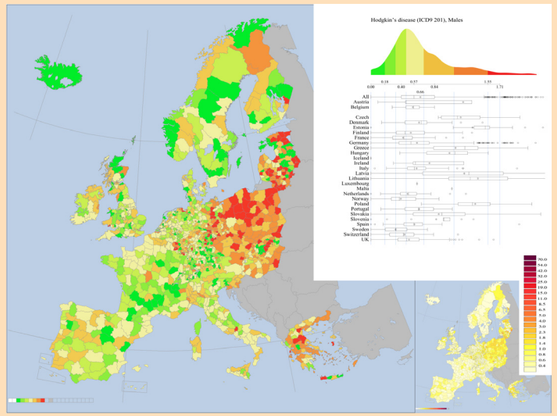
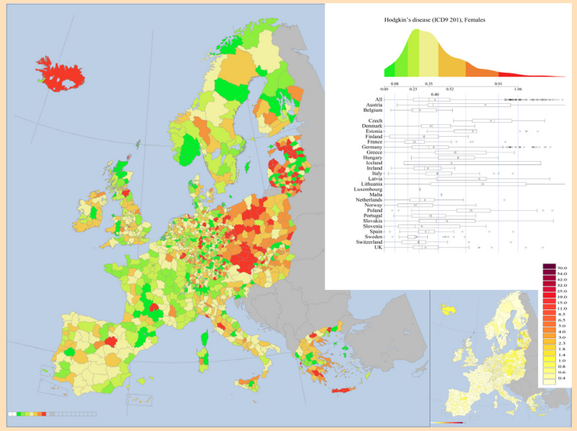


Fig. 5.24.2 *Radiographs of (A) skull and (B) femoral head demonstrate multiple lytic bone lesions*



European Map 5.24.1 *In men, the highest national mortality rates from Hodgkin Lymphoma were in Lithuania (1.4), Poland (1.4), Estonia (1.3), Latvia (1.2), Austria (1.2), the Czech Republic (1.2) and Greece (1.1). The lowest national rates were recorded in Sweden (0.3), Norway (0.4), France (0.4) and Switzerland (0.4). No deaths were recorded from this cause among males in Iceland during this period [1].*



European Map 5.24.2 *In females, the highest mortality rates from Hodgkin Lymphoma were in the Czech Republic (0.8), Austria (0.8), Lithuania (0.8), Latvia (0.8), Estonia (0.7) and Poland (0.7). Rates in most of the other countries were 0.2 to 0.4 per 100 000 [1].*

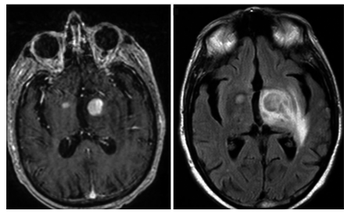
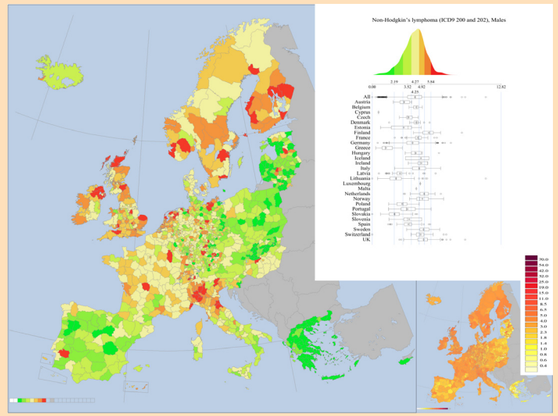
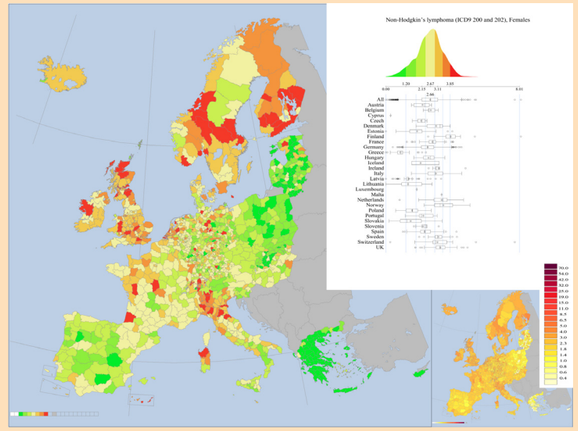


Fig. 5.24.3 *Nuclear magnetic resonance imaging (MRI) of CNS DLBCL. T1 after gadolinium injection (A) and fluid attenuated inversion recovery (FLAIR) sequences (B). There are two enhancing mass lesions in the basal ganglia.*



European Map 5.24.3 *In men, there were high regional mortality rates from Non-Hodgkin Lymphoma in the south of Norway, Sweden and Finland, in the United Kingdom and in northern Italy. There were aggregations of low rates in the Baltic Countries, much of central Europe including Austria, and southern Italy, Spain, Portugal and Greece [1].*



European Map 5.24.4 *The broad geographical pattern of the variability in mortality rates from Non-Hodgkin Lymphoma in women was very closely similar to that for men, with high regional rates in parts of Norway, Sweden and Finland, in the United Kingdom, and northern, but not southern, Italy. There were aggregations of low rates in central and southern Europe [1].*

PRECURSOR LYMPHOID NEOPLASMS	
B lymphoblastic leukaemia/lymphoma	
B lymphoblastic leukaemia/lymphoma, NOS	9811/3
B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities	
B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*	9812/3
B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL* rearranged	9813/3
B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1(ETV6-RUNX1)*	9814/3
B lymphoblastic leukaemia/lymphoma with hyperdiploidy	9815/3
B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)	9816/3
B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*	9817/3
B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1(TCF3-PBX1)*	9818/3
T lymphoblastic leukaemia/lymphoma	9837/3
MATURE B-CELL NEOPLASMS – The most important types are:	
Chronic lymphocytic leukaemia/ small lymphocytic lymphoma	9823/3
Hairy cell leukaemia	9940/3
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Nodal marginal zone lymphoma	9699/3
Follicular lymphoma	9690/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma (DLBCL), NOS	9680/3
Burkitt lymphoma	9687/3
MATURE T-CELL AND NK-CELL NEOPLASMS	
T-cell prolymphocytic leukaemia	9834/3
T-cell large granular lymphocytic leukaemia	9831/3
Chronic lymphoproliferative disorder of NK-cells	9831/3
Aggressive NK cell leukaemia	9948/3
Systemic EBV positive T-cell lymphoproliferative disease of childhood	9724/3
Hydroa vacciniforme-like lymphoma	9725/3
Adult T-cell leukaemia/lymphoma	9827/3
Extranodal NK/T cell lymphoma, nasal type	9719/3
Enteropathy-associated T-cell lymphoma	9717/3
Hepatosplenic T-cell lymphoma	9716/3
Subcutaneous panniculitis-like	
T-cell lymphoma	9708/3
Mycosis fungoides	9700/3
Sézary syndrome	9701/3
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	
Lymphomatoid papulosis	9718/1
Primary cutaneous anaplastic large cell lymphoma	9718/3
Primary cutaneous gamma-delta T-cell lymphoma	9726/3
Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma	9709/3
Primary cutaneous CD4 positive small/medium T-cell lymphoma	9709/3
Peripheral T-cell lymphoma, NOS	9702/3
Angioimmunoblastic T-cell lymphoma	9705/3
Anaplastic large cell lymphoma, *ALK* positive	9714/3
Anaplastic large cell lymphoma, ALK negative	9702/3
HODGKIN LYMPHOMA	
Nodular sclerosis classical	
Hodgkin lymphoma	9663/3
Lymphocyte-rich classical	
Hodgkin lymphoma	9651/3
Mixed cellularity classical	
Hodgkin lymphoma	9652/3
Lymphocyte-depleted classical	
Hodgkin lymphoma	9653/3

Table 5.24.1 *WHO Classification of Tumours*

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5.25 Leukaemias

Summary

> Recognised risk factors for leukaemias are ionizing radiation, alkylating agents used in chemotherapy, and occupational benzene exposure. However, the etiology of most leukaemias is not known. Familial clustering is seen in 5% of cases of chronic lymphoblastic leukaemia

> Chronic myeloid leukaemia was one of the first cancers to be linked to an acquired genetic abnormality, translocation (9;22), known as the Philadelphia chromosome

> Due to differing access to treatment, there is considerable global variation in survival. Among men in the USA and Western Europe, 5-year survival is at 43%; in Eastern Europe, 29%; Japan, 25%; India, 19%; South America, 24%; Thailand, 15%; and in sub-Saharan Africa, 14%

> In recent decades, there has been considerable progress in the development of treatments for leukaemia. In areas with good access to these treatments, 5-year survival in children has reached 80%

Leukaemias arise in one of the types of white blood cells. They may arise in lymphoblasts, which are lymphoid cells in the early stage of development, resulting in a rapid-onset illness termed acute lymphoblastic leukaemia. Alternatively, when the neoplasm involves mature cells, it is termed chronic lymphocytic leukaemia and is usually more indolent. In the WHO classification, chronic lymphocytic leukaemia is part of NHL [2]. Leukaemias may also be granulocytic in origin, occurring in either young myeloblastic cells resulting in acute myeloid leukaemia, or in the mature granulocytes resulting in chronic myeloid leukaemia. There also exist several rarer varieties including monocytic and hairy cell leukaemias.

Epidemiology

Acute lymphoblastic leukaemia is the most common childhood cancer, while over 80% of lymphoid leukaemias occurring in adulthood are chronic lymphocytic leukaemia. Incidence rates for chronic lymphocytic leukaemia are difficult to interpret because it is often diagnosed incidentally or in the course of evaluating other conditions. Differences in medical care may therefore substantially bias incidence data. Bearing this possible ascertainment bias in mind, the highest rates of lymphoid leukaemias are observed in areas of Canada, the USA, Western Europe and Oceania, and the lowest are in South America, the Caribbean, Asia and Africa. Rates tend to be lower in females although the ratio is usually less than 2. Some increases in leukaemia over time have been reported, although the extent to which these represent real increases in incidence is unclear. Some increasing incidence trends have been reported for both chronic and acute myeloid leukaemia, although these are not consistent and may simply reflect changes in clinical practice.

Etiology

Although the cause of most leukaemias is not known, there is consistent evidence for three factors, namely ionizing radiation, alkylating agents used in chemotherapy, and occupational benzene exposure [3]. Leukaemia was the first cancer to be linked to ionizing radiation after the atomic bombings in Hiroshima and Nagasaki. Excess incidences have been observed for acute lymphoblastic leukaemia, acute myeloid leukaemia and chronic myeloid leukaemia, but not for chronic lymphocytic leukaemia. Cohorts of patients who have received radiotherapy for both malignant and non-malignant conditions have also been found to be at an increased risk of leukaemia, usually myeloid. Whether there is any increased risk of leukaemia from other sources, including low-level diagnostic radiation, occupational exposure in the nuclear industry for workers and their offspring, or nuclear test explosions, is more contentious. Part of the problem lies in extrapolating from high acute doses experienced in particular circumstances like atomic bombing, to small or chronic exposures in other instances. There is no consistent evidence that exposure to electromagnetic fields is associated with leukaemia risk (see Chapter 2.12).

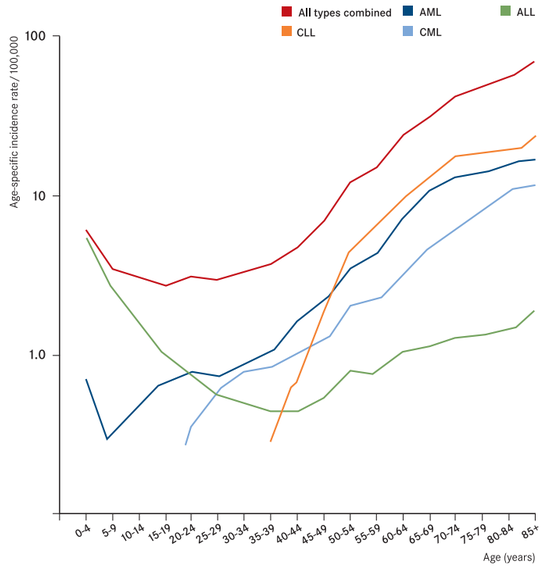
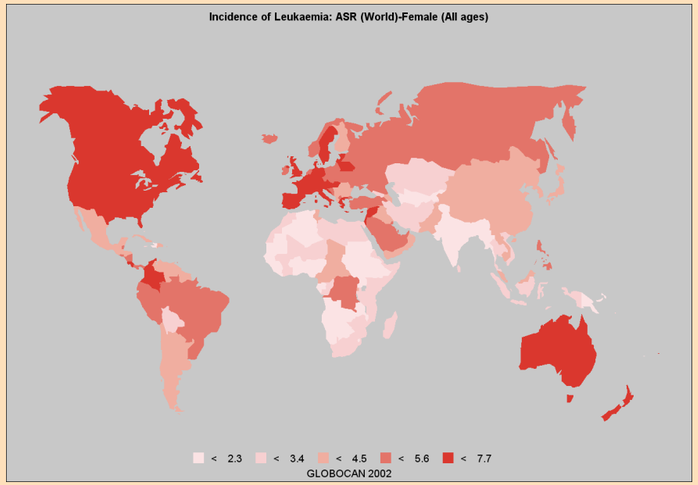


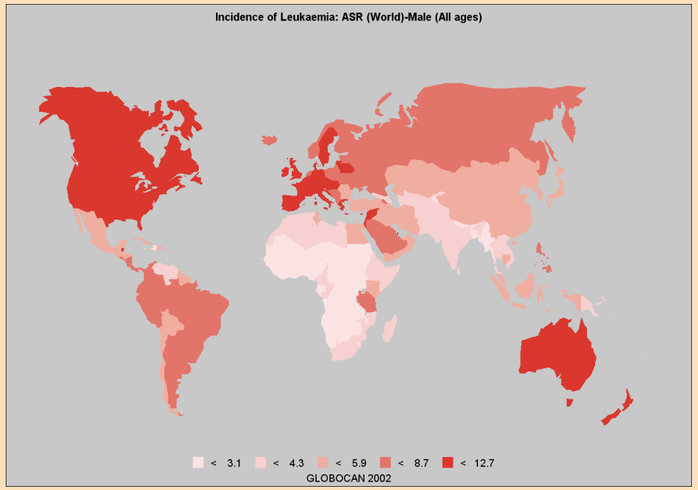
Fig. 5.25.1 *Age-specific incidence rates in the USA of leukaemia overall and of different subtypes. AML = acute myeloid leukaemia, ALL = acute lymphoblastic leukaemia, CLL = chronic lymphocytic leukaemia, CML = chronic myelogenous leukaemia. Note the high incidence of ALL in children*

Some leukaemias are also related to, or induced by therapy for a prior malignancy, most notably Hodgkin Lymphoma. Such patients have a 20–40 fold increased risk of leukaemia, most of which are acute myeloid leukaemia. The risk appears to be related to chemotherapy including alkylating agents (the majority being combination therapy with MOPP (mustargen, oncovin (vincristine), procarbazine, prednisone)). The effect is greater when patients are treated with both chemotherapy and radiotherapy, although whether an independent effect exists for radiotherapy is unclear. Other chemotherapy regimes which appear to be associated with acute myeloid leukaemia are those which contain the epipodophyllotoxin drugs teniposide and etoposide.

Occupational benzene exposure is also a recognized cause of leukaemia, in particular for acute myeloid leukaemia. An increased risk of between 3- and 5-fold has been observed in several occupational cohorts of workers following exposure to high levels of benzene, as has occurred in the past in shoe manufacturing, rubber manufacturing and printing. This type of leukaemia is fre-



World Map 5.25.1



World Map 5.25.2

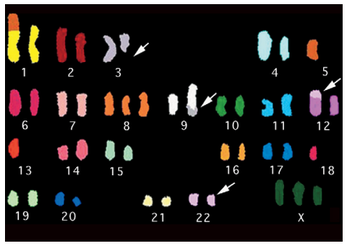


Fig. 5.25.2 *Spectral karyotyping of a chronic myeloid leukaemia case reveals a variant Philadelphia chromosome involving translocations between chromosomes 3, 9, 12 and 22. Secondary changes involving chromosomes 1, 5, 8, 18 and X are also seen, indicating advanced disease*

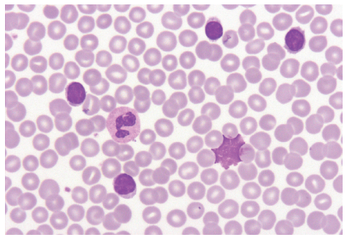
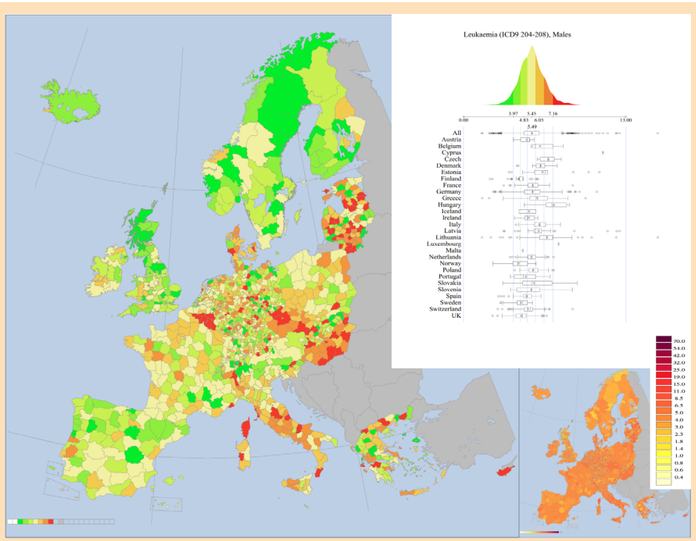


Fig. 5.25.3 *CLL in the peripheral blood. The CLL lymphocytes are small, round, with distinct clumped chromatin. Smudge cells are commonly seen*



European Map 5.25.1 *In men, the features of the geographic distribution of leukaemia mortality are the generally low rates in the Nordic countries and most of the United Kingdom and Ireland, and the areas of above-average rates in parts of the Baltic countries (particularly Lithuania), the Czech Republic and Hungary, southern Belgium and Luxembourg, and central and northern Italy [1].*

quently preceded by aplastic anemia. The role of low-dose exposure remains unclear. Tobacco smoking is a cause of acute myeloid leukaemia, possibly because of the relatively high levels of benzene present in the smoke.

Detection

Myelogenous leukaemias are characterised by an increase in the number of myeloid cells in bone marrow and blood, with resulting anemia, leukopenia and thrombocytopenia. At presentation, fatigue, night sweats, weight loss, and splenomegaly may be seen in both chronic and acute myeloid leukaemia. Patients with acute disease may also present with bruising or hemorrhage and have an increased risk of infection, with spleen and liver enlargement seen more rarely.

In high-resource settings, the majority of patients with chronic lymphoblastic leukaemia are diagnosed incidentally when a complete blood count obtained for other purposes is found to contain an elevated absolute lymphocyte count (>5000/μl). If not diagnosed incidentally, the most common symptoms are lymph node swelling with recurring infections; other abnormalities include enlarged spleen or liver, anaemia or thrombocytopenia, severe night sweats, and weight loss [4]. Patients with acute lymphoblastic leukaemia experience more rapid onset of these symptoms and may also exhibit bruising, bleeding or fever. Other possible symptoms seen in acute lymphoblastic leukaemia are bone pain, particularly in children, and central nervous system involvement.

Pathology and genetics

Nearly all chronic myeloid leukaemia arises from an acquired genetic abnormality, translocation t(9;22), in a bone marrow stem cell, known as the Philadelphia chromosome. This translocation results when the *ABL* gene from chromosome 9 merges with the *BCR* gene on chromosome 22, resulting in a *BCR-ABL* fusion gene on 22q11 that encodes for uncontrolled tyrosine kinase activity. The Philadelphia chromosome is additionally seen in one fourth of adult acute lymphoblastic leukaemia.

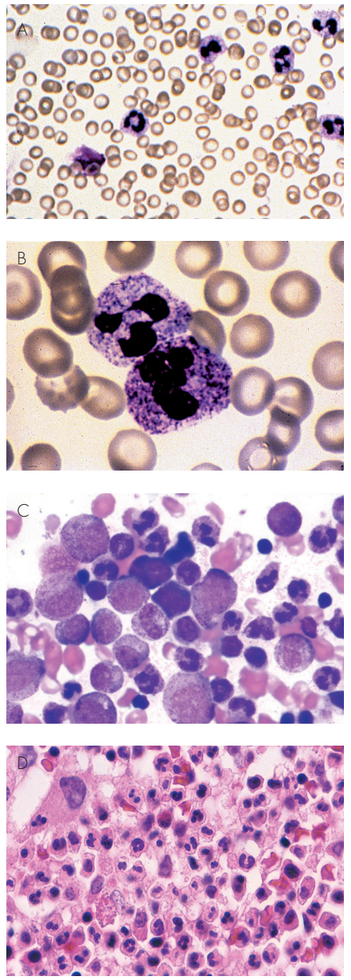
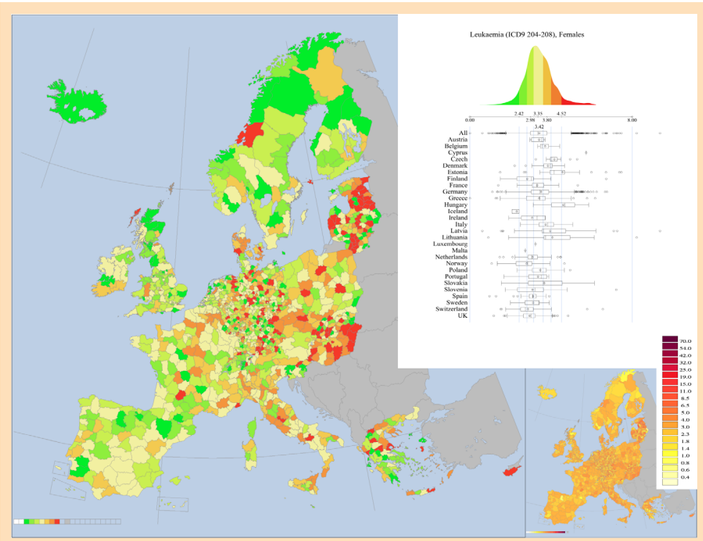


Fig. 5.25.4 *Chronic neutrophilic leukaemia. A The neutrophilia characteristic of the peripheral blood in CNL. B The toxic granulation commonly observed. C The bone marrow aspirate smear demonstrates neutrophil proliferation from myelocytes to segmented forms with toxic granulation, but no other significant abnormalities. D The bone marrow biopsy specimen is hypercellular, showing a markedly elevated myeloid: erythroid ratio with increased numbers of neutrophils, particularly mature segmented forms*



European Map 5.25.2 *The patterns in the variability in the rates of leukaemia mortality in women were closely similar to those in men: generally low rates in the Nordic countries (except Denmark) and the United Kingdom, and areas of high rates in the Baltic countries, the Czech Republic and Hungary [1].*

Acute myeloid leukaemia is a heterogeneous disease with regards to chromosome aberrations and clinical features. Broadly, this malignancy can be differentiated into three groups based on cytogenetics: the first group, comprising <15% of cases, includes generally younger patients who have more favourable chromosome abnormalities including inv(16), t(8;21), t(15;17) and t(16;16). These individuals respond well to specific chemotherapy regimens. The next group, comprising a nearly a third of patients, many of whom are older, have unfavourable cytogenetic profiles including deletions of the long arms of chromosomes 5 and 7 or complex karyotypes. The remaining intermediate prognosis group is comprised of persons with all other aberrations [5].

Chronic lymphocytic leukaemia is characterised by a proliferation of CD5 surface antigen-expressing B cells, and has been associated with a precursor condition, monoclonal B-cell lymphocytosis. Although specific susceptibility genes have yet to be identified for chronic lymphocytic leukaemia, familial aggregation is found among approximately 5% of cases [6]. Chromosomal abnormalities are common in CLL, with the most frequently documented being an interstitial deletion in 13q14 (>50% of cases), which is associated with a more favourable prognosis [7]. Aberrations associated with intermediate survival are trisomy 12 (15-20% of cases), while poorer survival is seen with del(11q), involving *ATM* (15-30%), and del(17p), involving P53 (10–20%) [7,8].

The importance of mutations in *IgVH* as a prognostic indicator has been recently recognised, with the presence of unmutated genes signifying a poorer cytogenetic profile and more advanced disease [8].

Acute lymphoblastic leukaemia is characterised by clonal expansion of lymphoblasts, either B-cell (80%) or T-cell phenotype. B-cell immunophenotypic subtypes exhibit a variety of genetic abnormalities. Multiple molecular pathways are involved in pathogenesis. Common genetic alterations include hyperdiploidy and translocations *(BCR-ABL, E2A-PBX1, TCR)* [9]. Among T-cell acute lymphoblastic leukaemia patients, half have a normal karyotype, while recurrent translocations are seen in one third of patients.

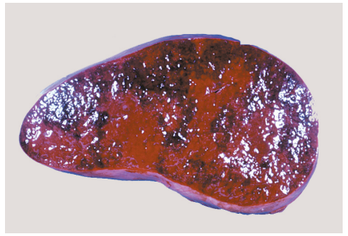


Fig. 5.25.5 *Splenomegaly in CML. The gross appearance of the spleen is solid and uniformly deep red, although areas of infarct may appear as lighter coloured regions*

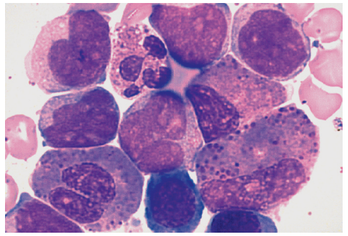


Fig. 5.25.6 *Acute myeloid leukaemia with associated inv(16)(p13.1q22). Abnormal eosinophils, one with large basophilic coloured granules, are present*

Management

In the last 50 years, marked improvements in the management of leukaemia have resulted in increasing survival among patients with leukaemia. Advances in treatment have contributed to 5-year survival reaching 80% among children [10]. The treatment process involves a cytogenetic workup, as this are used to select the treatment course. Supportive care is often required to manage the sequelae of myelosuppression and of severe, life-threatening infections.

For acute leukaemias, treatment strategy should include control both of systemic disease (bone marrow, liver) and central nervous system-directed therapy. Treatment choice and intensity is guided by risk stratification, which is determined by age and specific clinical and biologic markers. Current therapeutic regimens involve induction of remission using specific chemotherapy regimens, followed by consolidation or intensification of treatment, and with acute lymphoblastic leukaemia, are then followed by maintenance therapy. For ALL, induction therapy includes a glucocorticoid, vincristine, an anthracycline and possibly PEG-asparaginase [11]. Postremission therapies consist of chemotherapy and, if indicated, hematopoietic stem cell transplantation [12]. Minimal residual disease burden should be determined after initial treatment to assess treatment response.

Treatment of chronic leukaemias ranges from palliative care to a variety of therapies. Chronic lymphocytic leukaemia usually occurs in elderly patients and is not curable, and consequently is frequently treated conservatively. With the exception of patients with p53 mutations, treatment is not indicated for early-stage asymptomatic chronic lymphocytic leukaemia, as there is no evidence that treatment improves survival [13]. With advanced chronic lymphocytic leukaemia, the recommended first-line treatment is fludarabine in combination with cyclophosphamide [14]. At the present time, alemtuzumab, rituximab and autologous stem cell transplant are among the second-line treatments which appear promising [15]. The tyrosine kinase inhibitor Gleevec (imatinib mesylate) is the first-line therapy for chronic myeloid leukaemia. If resistance is seen, clinical strategies may involve imatinib dose escalation, interferon-α or several emerging therapies [16].

Given differing access to treatment due to cost, survival rates vary considerably between developed and developing countries. Survival rates for all leukaemias in the USA and Western Europe (43% among men and 45% among women) are the highest, while rates lag considerably in Eastern Europe (29% among both men and women), Japan (25% men, 29% women), India (19% among both), South America (24% among both), Thailand (15% among both) and sub-Saharan Africa (14% men, 17% women) [17]. Rates differ by condition. In the USA, 5-year survival rates in adults are 60% for acute lymphoblastic leukaemia and 75% for chronic lymphocytic leukaemia; lower survival rates are seen with acute myeloid leukaemia (17%) and chronic myeloid leukaemia (40%) [18].

WHO Classification of tumours of haematopoietic and lymphoid tissues

MYELOPROLIFERATIVE NEOPLASMS

- Chronic myelogenous leukaemia, *BCR-ABL1* positive
- Chronic neutrophilic leukaemia
- Polycythaemia vera
- Primary myelofibrosis
- Essential thrombocythaemia
- Chronic eosinophilic leukaemia, NOS
- Mastocytosis :
  - Cutaneous mastocytosis
  - Systemic mastocytosis
  - Mast cell leukaemia
  - Mast cell sarcoma
  - Extracutaneous mastocytoma
- Myeloproliferative neoplasm, unclassifiable

MYELOID AND LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND ABNORMALITIES OF *PDGFRA, PDGFRB* OR *FGFR1*

- Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
- Myeloid neoplasms with *PDGFRB* rearrangement
- Myeloid and lymphoid neoplasms with *FGFR1* abnormalities

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

- Chronic myelomonocytic leukaemia
- Atypical chronic myeloid leukaemia, *BCR-ABL1* negative
- Juvenile myelomonocytic leukaemia
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable
- *Refractory anaemia with ring sideroblasts associated with marked thrombocytosis*

MYELODYSPLASTIC SYNDROMES

- Refractory cytopenia with unilineage dyplasia
  - Refractory anaemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anaemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anaemia with excess blasts
- Myelodysplastic syndrome associated with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome
- *Refractory cytopenia of childhood*

ACUTE MYELOID LEUKAEMIA (AML) AND RELATED PRECURSOR NEOPLASMS

- **AML with recurrent genetic abnormalities**
- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- Acute promyelocytic leukaemia with t(15;17)(q22;q12); *PML-RARA*
- AML with t(9;11)(p22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- AML *with mutated NPM1*
- AML *with mutated CEBPA*
- **AML with myelodysplasia-related changes**
- **Therapy-related myeloid neoplasms**
- **Acute myeloid leukaemia, NOS**
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukaemia
- Acute monoblastic and monocytic leukaemia
- Acute erythroid leukaemia
- Acute megakaryoblastic leukaemia
- Acute basophilic leukaemia
- Acute panmyelosis with myelofibrosis
- **Myeloid sarcoma**
- **Myeloid proliferations related to Down syndrome**
- Transient abnormal myelopoiesis
- Myeloid leukaemia associated with Down syndrome
- **Blastic plasmacytoid dendritic cell neoplasm**

ACUTE LEUKAEMIAS OF AMBIGUOUS LINEAGE

- Acute undifferentiated leukaemia
- Mixed phenotype acute leukaemia with t(9;22)(q34;q11.2); *BCR-ABL1*
- Mixed phenotype acute leukaemia with t(v;11q23); *MLL* rearranged
- Mixed phenotype acute leukaemia, B/myeloid, NOS
- Mixed phenotype acute leukaemia, T/myeloid, NOS
- *Natural killer (NK) cell lymphoblastic leukaemia/lymphoma*

PRECURSOR LYMPHOID NEOPLASMS

- **B lymphoblastic leukaemia/lymphoma**
- B lymphoblastic leukaemia/lymphoma, NOS
- B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
- B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*
- B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL rearranged*
- B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)*
- B lymphoblastic leukaemia/lymphoma with hyperdiploidy
- B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)
- B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*
- B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)*
- **T lymphoblastic leukaemia/lymphoma**

MATURE B-CELL NEOPLASMS

- Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- *Splenic B-cell lymphoma/leukaemia, unclassifiable*
- *Splenic diffuse red pulp small B-cell lymphoma*
- *Hairy cell leukaemia-variant*
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Heavy chain diseases
- Alpha heavy chain disease
- Gamma heavy chain disease
- Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- *Paediatric nodal marginal zone lymphoma*
- Follicular lymphoma
- *Paediatric follicular lymphoma*
- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- *EBV positive DLBCL of the elderly*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

MATURE T-CELL AND NK-CELL NEOPLASMS

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- *Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK cell leukaemia
- Systemic EBV positive T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- *Anaplastic large cell lymphoma, ALK negative*

HODGKIN LYMPHOMA

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

Table 5.25.1 *WHO Classification of tumours of haematopoietic and lymphoid tissues*

WHO Classification of tumours of haematopoietic and lymphoid tissues

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	
• Histiocytic sarcoma • Langerhans cell histiocytosis • Langerhans cell sarcoma • Interdigitating dendritic cell sarcoma	• Follicular dendritic cell sarcoma • Fibroblastic reticular cell tumour • Indeterminate dendritic cell tumour • Disseminated juvenile xanthogranuloma

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)	
• Early lesions – Plasmacytic hyperplasia – Infectious mononucleosis-like PTLD • Polymorphic PTLD	• Monomorphic PTLD (B- and T/NK-cell types) • Classical Hodgkin lymphoma type PTLD

Table 5.25.1 *(cont.)*

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5.26 Cancer in Children

Summary

- Cancer in children is rare and specific in its occurrence, pathology, detection, treatment and outcome
- Most common cancers in childhood comprise leukaemia, lymphoma and brain tumours, with varying ranks across different populations
- Little is known about the etiology of childhood cancers, and the few established causal associations only explain a small proportion of cases
- Good long-term survival is achieved in the most developed countries, while in many developing countries it is considerably poorer
- Current priorities for childhood cancer management aim at improvement of quality of life of the growing number of childhood cancer survivors

The term childhood cancer usually comprises all cancers arising in individuals before the age of 15 years. These tumours are rare, but present specific ethical, psychological and societal concerns. Histologically, childhood tumours are very variable and are classified into twelve major groups (Figure 5.26.1), further divided into 47 diagnostic subgroups according to the International Classification of Childhood Cancer [2].

Occurrence

In childhood populations of Europe, North America and other developed regions of the world, cancer incidence rates are around 140 per million [3]. Cancer incidence in the developing countries is less well known, because there have been too few efficient population-based cancer registries. Overall incidence rates for the most recent period evaluated systematically among the world populations are shown in Figure 5.26.2. In some developing countries, where the children comprise 40–50% of the population, the proportion of childhood cancers represents 3–10% of the total, whereas in the developed countries, it is less than 1%. Mortality patterns also differ. Cancer accounts for some 4–5% of childhood deaths in developed countries, (where it is the second-leading cause of death among children aged 1–14), and less than 1% in developing countries, where deaths from infectious diseases are much more prominent. Globally, some 160 000 new cases and 90 000 deaths of cancer in children under 15 years of age are estimated to occur each year [4].

The proportion and rank of various cancers varies between childhood populations around the world, as shown in Figure 5.26.2. The sample of the world populations was selected to illustrate the geographical variability and the pattern is not necessarily the same in the neighbouring countries. Overall, the most common cancer groups are leukaemia, lymphomas and central nervous system (CNS) tumours. Acute leukaemia is the most common form of cancer in most countries, especially in early childhood. Only in tropical Africa, lymphomas seem to be more common. In the developed countries, brain tumours generally account for one fifth to one quarter of childhood cancers. Their rarer registration in developing countries is at least partly due to under-diagnosis. Wilms tumour is very rare in Asian children, as is Ewing sarcoma of bone. Retinoblastoma appears to be rather more common in African children than elsewhere, while neuroblastoma appears to be very rare in central Africa. Black children are more prone than others to development of Wilms tumour and osteosarcoma. Generally very rare Burkitt lymphoma is one of the most commonly registered tumours in some countries of sub-tropical Africa [3].

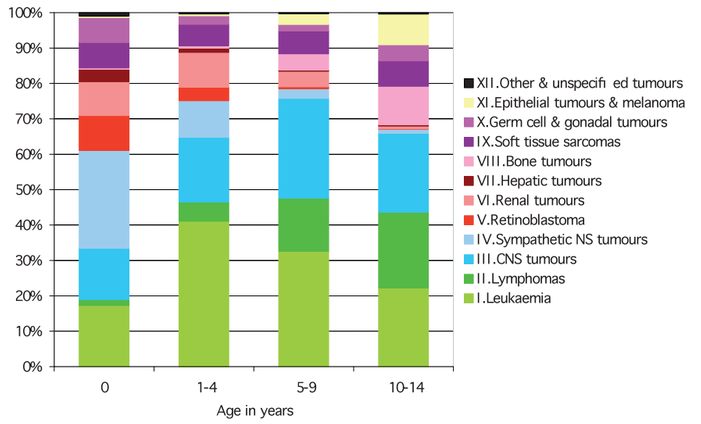

Fig. 5.26.1 *Composition of tumour types across childhood age groups. Based on the 51 395 cases of cancer registered in the European cancer registries in the 1970s–1990s and assembled in the ACCIS study [1] . NS, nervous system; CNS, central nervous system*

Pathology and genetics

Childhood cancers share a number of common characteristics which distinguish them from the tumours arising later in life. Typical tumours of childhood resemble embryonal tissues arrested at different stages of maturation (retinoblastoma, hepatoblastoma, Wilms tumour). The unique morphologic features of some childhood malignancies (clear cell sarcoma of kidney, malignant rhabdoid tumour, melanotic neuroectodermal tumour) are not generally encountered in those occurring in adults. Cancer in childhood is also typical by the frequent occurrence of the undifferentiated tumours, commonly referred to as "small round cell tumours" such as the Ewing family tumours, Burkitt lymphoma and several acute leukaemia types. Finally, childhood neoplasms are rarely preceded by precursor lesions [5].

Table 5.26.1 summarises selected identified genetic syndromes associated with childhood cancer, according to the review by Stiller in 2004 [6]. However, these genetic syndromes account for a very small proportion of the childhood cancer cases. Numerical chromosome abnormalities are also associated with childhood cancer. For example, Down syndrome (trisomy 21) appreciably increases the risk of acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) [6]. Recently, epigenetic alterations were implicated in the development of childhood neoplasms. An example is the loss of imprinting of IGF2, shown to be involved in the carcinogenesis of Wilms tumour [7].

Etiology

In general, little is known about etiological factors of childhood cancer, as most studies are limited in statistical power due to its rarity. Because of its onset early in life, exposure to environmental factors either *in utero* or after birth may be less determining than for cancers developing in adults. Only a few exposures, mostly exceptional, have been shown to cause cancer in children. For example, thyroid cancer has increased dramatically in the population of children living in the three countries surrounding Chernobyl, due to the radioactive fallout from the accident there [8]. A causal association has been shown between increased risk of cancer of the vagina in the female offspring of women who used a medication called diethylstilbestrol during their pregnancies to alleviate morning sickness in the 1970s [9]. In-utero diagnostic radiotherapy was associated with risk of childhood leukemia [10], but due to the substantially reduced doses used nowadays, the impact on incidence is undetectable.

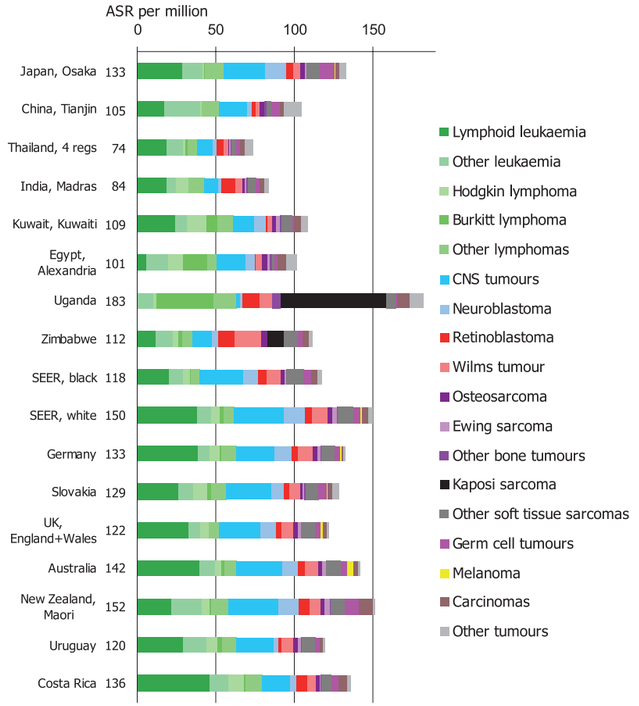

Fig. 5.26.2 *Cancer incidence rates in children aged 0–14 years in the countries shown in the 1980s and assembled in an international comparative study [3]. ASR, age-standardised incidence rate (world standard). CNS, central nervous system*

Syndrome	Locus	Gene	Childhood cancer
Some familial neoplastic syndromes			
Familial retinoblastoma	13q14	RB1	Retinoblastoma, osteosarcoma
Familial Wilms tumour	17q12-21	FWT1	Wilms tumour
Familial Wilms tumour 2	19q13	FWT2	Wilms tumour
Li-Fraumeni syndrome	17q13	TP53	Adrenocortical carcinoma,
	22q12	CHK2	Soft tissue sarcoma,
	22q11	SNF5	Osteosarcoma, central nervous system (CNS) tumours
Hereditary non-polyposis colon cancer	2p22-21	MSH2	Glioma
	3p21	MLH1	
	7p22	PMS2	
Familial adenomatous polyposis	5q21	APC	Medulloblastoma, hepatoblastoma
Gorlin syndrome	9q31	PTCH	Medulloblastoma, basal cell carcinoma
Neurofibromatosis type 1	17q11	NF1	Astrocytoma, juvenile myelomonocytic leukaemia (JMML), acute lymphoblastic leukaemia (ALL), rhabdomyosarcoma, malignant peripheral nerve sheath tumors (MPNST)
Neurofibromatosis type 2	22q12	NF2	Meningioma
Some inherited immunodeficiency and bone marrow failure syndromes			
Ataxia telangiectasia	11q22	ATM	Lymphoma, leukemia
Wiskott-Aldrich syndrome	Xp11	WAS	Non-Hodgkin lymphoma
Bloom syndome	15q26	BLM	Non-Hodgkin lymphoma, Wilms tumour, osteosarcoma
Nijmegen breakage syndrome	8q21	NBS1	Non-Hodgkin lymphoma
Fanconi anaemia	16q24	FANCA	Acute myeloid leukaemia (AML), hepatoma
Some other genetic syndromes			
Rothmund-Thomson syndrome	8p24	RECQL4	Osteosarcoma
WAGR syndrome	11p13	WT1	Wilms tumour
Denys-Drash syndrome	11p13	WT1	Wilms tumour
Beckwith-Wiedemann syndrome	11p15	Multiple genes	Wilms tumour, hepatoblastoma, neuroblastoma, pancreatoblastoma
Tuberous sclerosis	9q34	TSC1	Subependymal giant cell astrocytoma
	16p13	TSC2	

Table 5.26.1 *Genetic syndromes associated with childhood cancer [6]*

Pathogenesis of some childhood cancers involves both genetic changes and exogeneous risk factors. For example, the African type Burkitt lymphoma is associated with both the Epstein-Barr virus (EBV) and a chromosomal translocation deregulating expression of the c-myc oncogene [11]. Other co-factors, which must operate to activate the carcinogenic action of such a common infection as is the EBV might be the immuno-suppression caused by malaria, human immunodeficiency virus (HIV) infection or other conditions. In immuno-compromised children EBV is probably implicated also in Hodgkin disease, non-Hodgkin lymphomas, nasopharyngeal carcinoma and others.

Other risk factors have been studied, less conclusively. Childhood leukemia seems to be associated with high socioeconomic status, which might be a marker of yet-unidentified (cluster of) risk factors. Infection is suspected to play a role in the etiology of common childhood leukaemia, which may occur as an unusual response to a common infectious agent, as yet unidentified [12,13]. Additional hypotheses, concerning the timing of infections, or the presence of important co-factors, would be required to clarify the causal relationship.

A number of other risk factors have been studied to reveal their part in the causation of various childhood neoplasms, but the evidence is not decisive. The suspected exposures include non-ionising radiation, maternal smoking, alcohol consumption and diet, paternal occupation, exposure to various chemicals such as benzene, nitrosamines, pesticides, hair dyes and some medications, etc, and have been reviewed in several publications [6,14,15].

Detection

Many paediatric malignancies are seen predominantly in pre-school children, while others, such as non-Hodgkin lymphomas, most cases of Hodgkin disease, bone tumours and different epithelial tumours occur in older children and adolescents [Figure 5.26.1]. Cancer usually develops over a short time with no pre-cancerous stage, and it is often disseminated at diagnosis. Therefore, there is little room for implementation of screening practices. Screening for neuroblastoma, conducted nationally in Japan, and on population samples in Germany, France and the UK, did not reduce the mortality rate from this neoplasm. The increase in incidence in the screened population was thus due to over-diagnosis of non-symptomatic cases not necessarily requiring a treatment [16].

Being rare, detection of cancer in children often depends on the preparedness of primary health providers. In the poorest countries many cancers may remain undetected in children, due to the lack of training or experience of health professionals and paediatricians who are used to dealing primarily with infectious diseases. Other factors contributing to under-detection may be a preferential choice of a traditional healer and other traditional beliefs. In cancer registration data such prejudgments are reflected in a relative lack of infants among registered cases or excess registrations among boys as compared to girls [3].

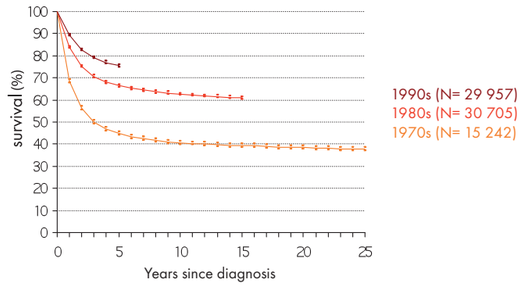

Fig. 5.26.3 *Survival of childhood cancer patients registered (age 0–14 years) during the periods shown in Western Europe and analysed in the ACCIS study [1]. 95% confidence intervals are represented by the dots around the yearly survival estimates. N, numbers of cases diagnosed in the period shown and followed up for 25, 15 and 5 years, respectively*

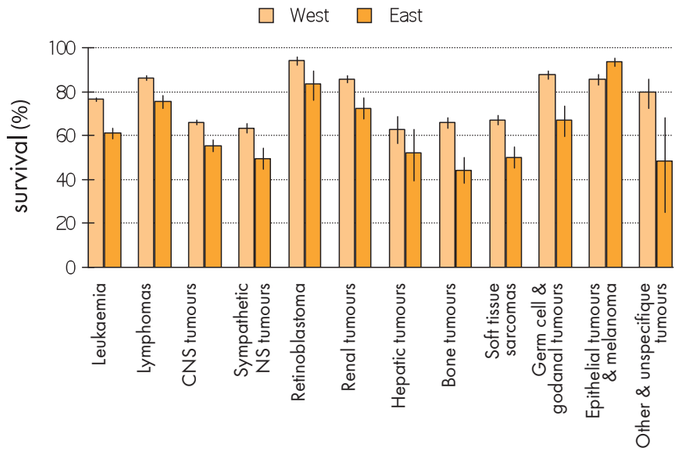

Fig. 5.26.4 *Five-year in survival from cancer in children aged 0–14 years registered during the 1990s in Europe and followed up for five years, according to the place of residence at diagnosis and the tumour type, as analysed in the ACCIS study [1]. CNS, central nervous system; NS, nervous system*

Continued development of non-invasive diagnostic methods, such as computerised tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine scans increase the accessibility, the timeliness and the precision of diagnosis [17]. These advances probably explain at least in part the rapid increase in the incidence of CNS tumours observed in the USA and Europe in recent decades [18,19], as well as their low incidence rates in developing countries [3].

Management

Survival of childhood cancer patients is good, at least in developed countries. Since the 1960s, when most children who were diagnosed with cancer died, the treatment has improved remarkably (Figure 5.26.3), such that nowadays 75% of children survive 5 years from diagnosis or more [1, 20, 21, 22]. The prognosis differs by tumour type, with highest survival for retinoblastoma, thyroid carcinoma, Hodgkin lymphoma, etc. Lowest survival is observed for some CNS tumours, certain leukaemias and some sarcomas of bone and soft tissues (Figure 5.26.4). To a variable degree the outcome also depends on the age at diagnosis. Within Europe, differences in survival were observed between countries grouped by the socio-economic level of development (Figure 5.26.4). The less favourable outcome in the countries with lower socio-economic status can be attributed to the longer delays in diagnosis and treatment, insufficient treatment potential, problems with tackling associated morbidity and lesser inclusion of patients in clinical trials [20].

Taking into account the differences observed in Europe and in the absence of data on childhood cancer survival in most of the developing world, it is generally assumed that the survival of these children is dismal. The main reasons are late diagnosis, unavailability of treatment, therapy abandonment, prior undernourishment, inadequate supportive therapy and unsuccessful follow-up. All these factors relate to lack of financial resources to support efficient health care system for childhood cancer patients [23].

The improvement of survival reported from high-resource countries [1,20,21,22] results from increasing use of intensive chemotherapy combined with other modalities of treatment, improved generalised supportive management, application of results of clinical trials and centralisation of care permitting each patient to benefit from the best of the multidisciplinary expertise and technology available for these rare conditions. The current challenge is to optimise treatment to achieve a maximal treatment effect with minimal toxicity. This may be achieved through elucidation of mechanisms of resistance and exploration of the potential of novel therapeutic approaches [17]. The aim is to eliminate or reduce the numerous late effects of treatment and thus improve the quality of life of the growing population of survivors of childhood cancer.

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5.27 Cancer in Adolescents

Summary

- Cancer occurs rarely in adolescence, though the incidence is roughly twice as high as in children
- Typical cancers of adolescents include lymphomas, bone and soft tissue sarcomas, germ cell tumours, melanoma and carcinomas of thyroid and nasopharynx. Leukaemias and brain tumours are also common. Adolescent cancers are often detected late
- Many tumours occurring in adolescents have characteristic pathological and genetic features, requiring a morphology-based classification
- The risk factors include various infectious agents, exposure to hormones, radiation (ionising and non-ionising) and some life-style factors
- Despite of a large proportion of cancers with a relatively good prognosis, the overall population-based 5-year survival of adolescents with cancer attains about 75% in developed countries. A more focused approach to the management of this group of patients would probably contribute to an improvement

Cancer in adolescents comprises all cases occurring in individuals aged 15 to 19 years. This definition reflects relatively well various biological, societal, statistical and clinical specificities of this life period, although other age-spans may be considered in some sources. The age group 15–19 years is convenient in population-based studies, because of the availability of population and other data for this age group. It coincides relatively well with the period of physical and sexual development, even though the onset of this process tends to occur a bit earlier in girls and has shifted towards younger ages in both sexes over the last few decades.

The range of tumours occurring in adolescents makes the usual classification by tumour site (used to classify cancers in predominantly adult population) unsatisfactory. International Classification for Childhood Cancer (ICCC) [1], reflecting primarily morphological entities, is therefore often used in descriptive studies. This is similar to the classification adapted specifically for adolescents [2].

Occurrence

Adolescence is a period characteristic of physical, sexual, mental and societal maturation. The two first aspects influence the spectrum of cancer types occurring in this age group, which is different from that in childhood and in adulthood. In the populations of Caucasian descent, the most common cancers are lymphomas and carcinomas (Figure 5.27.1). Other frequent cancer groups are CNS tumours, germ cell tumours and sarcomas of bone and soft tissues, with slightly different ranks in males and females (Figure 5.27.1). Worldwide, the rates vary about three-fold in males (90–300 per million) and in females (88–270 per million). In some populations, incidence rates in females are higher than in males, though. Overall incidence rate for large series was 202.2 per million person-years during 1986–1995 in the USA [4], with an estimated increase to 216 in year 2000 [5]. In Europe, the incidence rate was 186.0 per million person-years in the period 1988–1997 (Table 5.27.1) [3]. These variations are illustrated in Figure 5.27.2, which is based on the most recent international data series classified according to tumour site [6].

Adolescence is the age of predominant occurrence of a few specific tumour types. Bone tumours (both osteosarcoma and Ewing tumour) usually present the first age-specific peak in adolescents overall and in males (in females the first peak of the two types of bone tumours occurs in the age group 10–14) [7]. This peak is present in all ethnic groups in the US population, although it is worth noting that Ewing sarcomas are very rare in African Americans (Figure 5.27.3). Ovarian germ cell tumours, including dysgerminomas, malignant teratomas and mixed germ cell tumours, are most common in adolescent girls [8]. In the world regions with intermediate overall incidence rates of the nasopharyngeal carcinoma, the first age peak of this tumour is seen in adolescents [8].

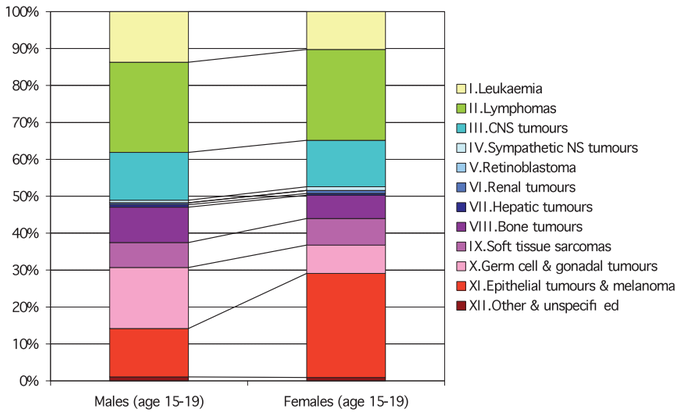

Fig. 5.27.1 *Relative frequency of various cancers in adolescents aged 15–19 years, based on 8272 cases registered in European cancer registries during 1988–1997 and included in the ACCIS study [7]. CNS, central nervous system. NS, nervous system*

The incidence rates were reported to increase in Europe by 2% per year over the period 1978-1997, mainly due to the increase of incidence of lymphoid leukaemia, Hodgkin lymphoma, astrocytoma, gonadal germ cell tumours, thyroid carcinoma and melanoma [8]. In the USA an overall annual increase of 0.7% was reported for the period 1975–2000 [5]. The highest increase was previously reported for the gonadal germ cell tumours in both sexes, acute lymphocytic leukaemia, non-Hodgkin lymphomas and osteosarcoma [4]. Although some of this increase may be related to improvement in diagnosis and reporting, the true rise in incidence of some of these tumour groups cannot be disregarded.

Pathology and genetics

Together with the particular spectrum, cancers in adolescents present special biological characteristics. Thus, acute lymphocytic leukaemia usually bears poorer prognosis in adolescence than in childhood. Astrocytic and glial tumours of the brain are usually diagnosed with higher grades. Common adulthood carcinomas occurring in this early period in life may be more often associated with genetic factors that cause these tumours to arise earlier in life. For example, 20% of breast cancers in women aged less than 30 years may be caused by pathogenic alterations in breast susceptibility genes [9]. Some tumours occur as part of familial syndromes, sometimes as second primary malignancies after a childhood cancer. As reviewed by Birch et al. [10], TP53 mutations were shown specifically in adolescents and young adults with anaplastic astrocytoma, glioblastoma and osteosarcoma, while medulloblastoma diagnosed in older children, adolescents and young adults may be more frequently associated with the APC gene. Ewing sarcoma is also conditioned genetically, as suggested by the variation of its incidence across ethnic groups (Figure 5.27.3) and various chromosomal aberrations, of which t(11;22)(q24;q12) is detectable in a large majority of cases [11]. Chromosomal changes have also been reported for germ cell tumours of testes and ovaries in adolescents with a typical amplification of the 12p chromosome [12]. Melanoma is common in fair-skinned populations, and may occur in a familial form, which indicates genetically underlined etiology [13]. However, inheritance probably explains only a small fraction of cancers in adolescents [5].

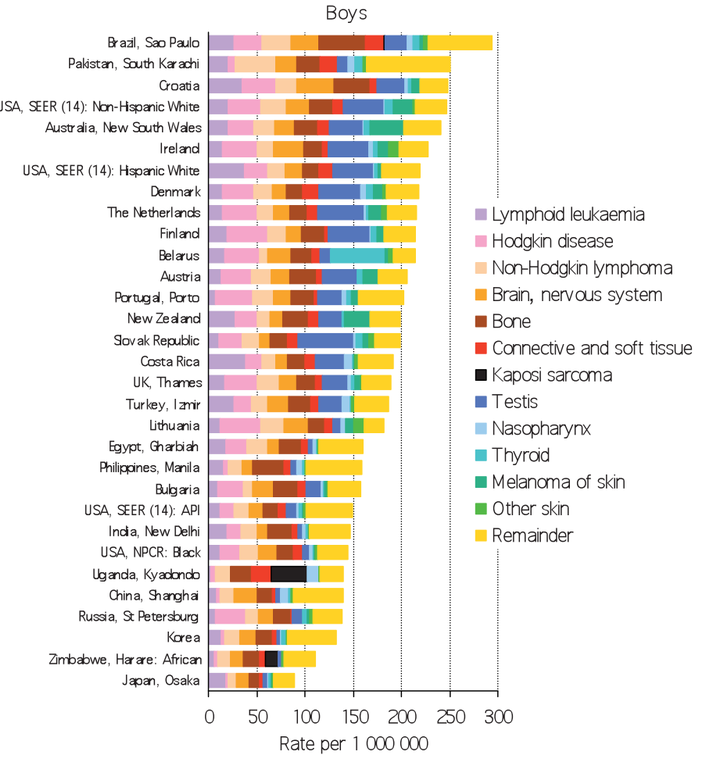

Fig. 5.27.2 *Incidence rates of cancer in adolescents (age 5–19 years) in various population-based cancer registries. Based on a total number of 10 528 cases in boys and 8 777 in girls [6]*

Etiology

Apart from genetic susceptibility, a large proportion of cancers in adolescents may probably be attributed to infection. Infectious etiology is a likely explanation for acute lymphocytic leukaemia (ALL) and lymphomas. While the infectious agent for ALL has not been identified as yet, Epstein-Barr virus (EBV) is implicated in several cancers. In Hodgkin lymphoma, its effect is modified by age, sex, geographical residence, ethnicity and the level of economic development [14]. Non-Hodgkin lymphomas are also linked to EBV, but also to human immunodeficiency virus (HIV) and human T-cell lymphotropic virus type 1 (HTLV-1). EBV is also implicated in nasopharyngeal carcinoma, especially in the areas of the highest incidence (East Asia). *Helicobacter pylori* may play a role in gastric lymphoma, possibly together with other infections [15,16]. Most cases of hepatic carcinoma, occurring with highest frequencies in Hong Kong and sub-Saharan African registries, are due to Hepatitis B and C viruses [17]. HIV infection is behind the spectacular rise in the incidence of the previously endemic form of Kaposi's sarcoma in some African countries (Figure 5.27.2) [17]. Simian-virus (SV40), the contaminant of the polio vaccine in the 1950s, was suspected to cause some brain and bone tumours [18], although the allegation has not been confirmed [19].

Some testicular germ cell tumours are thought to arise in response to hormonal stimulation by oestrogens in utero or oestrogen-like substances in the environment. However, sedentary lifestyle may also contribute to the explanation of the continuous increase of testicular germ cell tumours in western populations (Figure 5.27.2) [20].

The age-sex specific incidence rates for bone tumours further suggest that their occurrence may be associated with the growth spurt, which occurs earlier in girls than in boys (see Rare Tumours Figure 5.28.2 (c,d). A portion of osteosarcomas may also arise as secondary malignancy, often following radiotherapy for other tumours in childhood [21].

Ionising radiation released accidentally in 1986 in Chernobyl explains the record rates of thyroid carcinomas in adolescent girls (and to a lesser extent in boys) in Belarus (Figure 5.27.2) and some other most exposed countries [22]. The extreme incidence rates of melanoma in some white populations (Figure 5.27.2) are due to excessive exposure to UV radiation, entangled with socio-economic factors [23].

Detection

The single most important issue specific to the detection of a range of cancers occurring in adolescents is probably the delay in diagnosis. Diagnosis may be delayed in this age group more than in others due to a combination of specific circumstances, including the invincible attitude, unawareness, insufficient health insurance coverage, change of primary health care provider or inadequate training of attending practitioner [24].

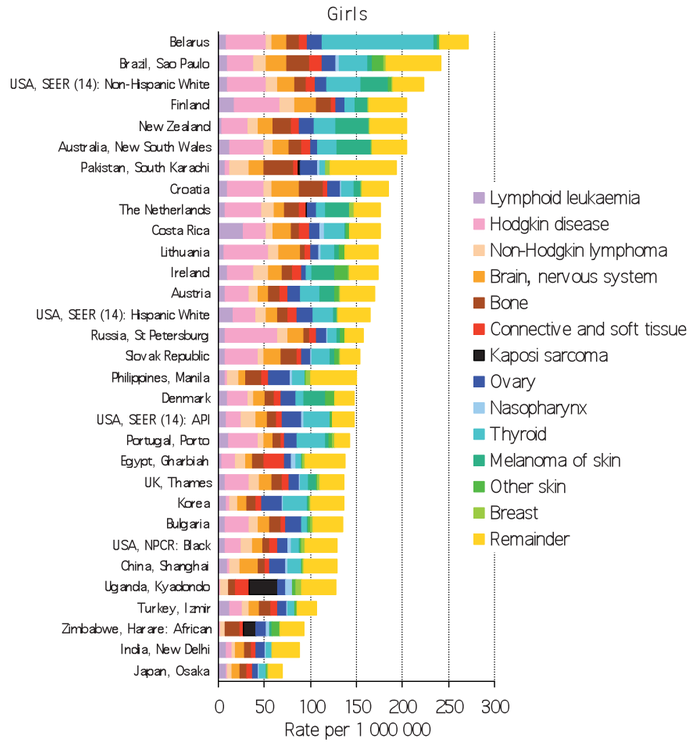

Fig. 5.27.2 *(cont.)*

Management

Compared to other age groups in the USA, adolescents and young adults (ages 15–45) have shown the smallest improvement in survival over the period 1975–1997 [5]. The reasons for this lag may be multiple: delay in diagnosis, lower participation in clinical trials, poor compliance with treatment and psychosocial issues [24]. The referral pattern for the adolescents with cancer is not clearly defined in most countries, although this group has specific needs that differ from those of children and adults. Adapted specialised cancer units for adolescents were established in the UK, although their number is largely insufficient to cover the totality of demand [25]. These units respect all aspects of the management specific for adolescents, including therapy, psychosocial support, palliative treatment and follow-up. The recent debate about the appropriate care for adolescents with cancer [26-28] will hopefully bring about a greater increase in survival for this group of cancer patients.

Overall survival at five years since diagnosis for adolescents diagnosed in the 1990s in Europe was almost 75% (Table 5.27.2), having improved over the last two decades of the 20th century (Figure 5.27.4). Should this trend continue, and specialised approach to the management of adolescents with cancer be adopted widely, the patients diagnosed nowadays may expect outcomes that are better still. Five-year survival of the adolescents diagnosed with cancer in the USA by the end of 1990s reaches 80%, based on SEER data [29]. Leukaemia (especially ANLL), bone tumours and soft-tissue sarcomas are the most challenging diagnoses.

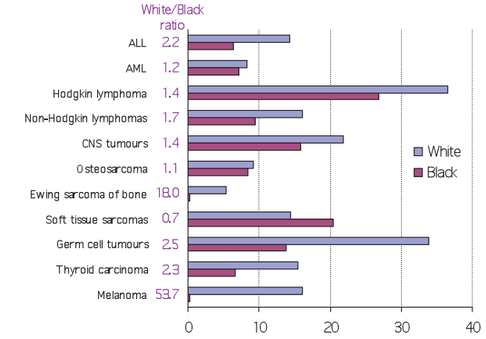

Fig. 5.27.3 *Incidence rates of cancer in adolescents aged 15–19 years (both sexes), based on 9814 cases registered in SEER registries in the USA during 1975–1995 [4]. ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia*

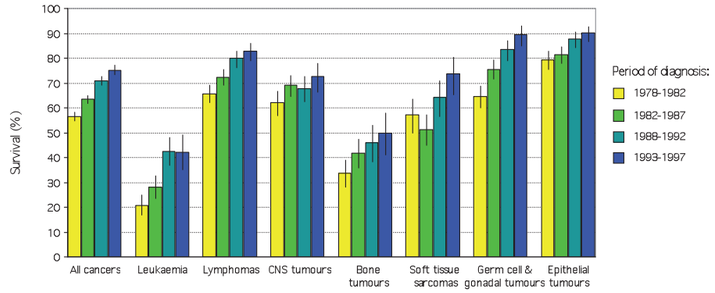

Fig. 5.27.4 *Five-year survival of adolescents aged 15–19 years (both sexes) diagnosed in the calendar periods shown in the European registration areas contributing to the ACCIS study [3]. Line sections represent the 95% confidence intervals of the survival estimate. N, total number of cases included in survival analysis for each tumour group. CNS, central nervous system*

Tumour type		N	B/G	Rate
All cancers		**8272**	**1.2**	**186.0**
Leukaemia		**1006**	**1.7**	**22.6**
	lymphoid	562	2.0	12.6
	acute non-lymphocytic	312	1.3	7.0
Lymphoma		**2027**	**1.2**	**45.6**
	Hodgkin	1319	1.0	29.7
CNS		**1057**	**1.3**	**23.8**
	astrocytoma	459	1.2	10.3
Bone tumours		**672**	**1.9**	**15.1**
	osteosarcoma	372	1.9	8.4
	Ewing sarcoma	185	2.0	4.2
Soft tissue sarcomas		**576**	**1.2**	**13.0**
	rhabdomyosarcoma	131	1.8	2.9
	fibrosarcoma	212	1.0	4.8
Germ cell & gonadal		**1040**	**2.7**	**23.4**
	gonadal germ-cell	773	5.1	17.4
	gonadal carcinoma	117	0.0	2.6
Epithelial		**1640**	**0.6**	**36.9**
	thyroid carcinoma	368	0.3	8.3
	melanoma	571	0.6	12.8
	skin carcinoma	165	0.8	3.7

Table 5.27.1 *Incidence rates of cancer in adolescents aged 15–19 years in 1988–1997 in Europe and included in the ACCIS study [3]. N, number of cases; B/G, boys to girls ratio; Rate, age specific incidence rate per million person-years*

Tumour type		N	OS (95%CI)
All cancers		**6494**	**73 (71,74)**
Leukaemia		**811**	**44 (40,48)**
	lymphoid	450	50 (44,54)
	acute non-lymphocytic	245	35 (29,42)
Lymphomas		**1597**	**81 (79,83)**
	Hodgkin	1045	89 (87,91)
	non-Hodgkin	360	64 (59,69)
	unspecified	137	74 (65,81)
CNS tumours		**866**	**70 (66,73)**
	astrocytoma	348	65 (59,70)
	other glioma	162	75 (67,81)
	unspecified	141	65 (56,73)
Bone tumours		**486**	**48 (43,53)**
	osteosarcoma	271	52 (45,58)
	Ewing sarcoma	144	31 (23,39)
Soft tissue sarcomas		**430**	**67 (62,71)**
	fibrosarcoma	164	81 (74,86)
	other specified	123	74 (64,81)
Germ cell tumours		**839**	**87 (84,89)**
	testicular	520	90 (87,92)
Carcinomas and epithelial neoplasms		**1245**	**88 (86,90)**
	thyroid	285	99 (97,100)
	melanoma	427	88 (84,91)
	skin	150	98 (92,100)
	other	331	79 (74,83)

Table 5.27.2 *Survival of adolescents aged 15–19 years (both sexes) diagnosed with cancer in Europe in 1988–1997 and included in the survival analysis in the ACCIS study [7]. N, numbers of cases included in the analyses; OS, observed 5-year survival; CI, confidence interval of the observed survival; CNS, central nervous system*

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5.28 Rare Cancers

Summary

> "Rare cancer" is an arbitrary term, because it is difficult to establish a standard definition

> Rare cancers are common when considered as a group

> Although their rarity is an obstacle to etiology studies, any cluster in unusual setting may quickly lead to identification of an external cause

> Some rare cancers are undoubtedly genetic in origin

> The wide variation in outcome reflects the variety of rare cancers, the diagnostic delay and the level of expertise in the management of a given malignancy

There is no precise definition of a rare cancer, and many cancers may or may not be considered rare, depending on the precision of the criteria employed. For example, a threshold incidence rate of less than 1/50 000 would place breast cancer in men in the rare category, but that is not so in women[1]. Neuroblastoma is rare, but in infants (below 1 year of age) it is the most common malignancy [2]. Even certain lung cancers may be rare, for example carcinoid tumors [3]. Kaposi sarcoma is unusual almost everywhere in the world except equatorial Africa [4]. Rarity may also depend on the time period, as is the case for melanoma, a rare cancer worldwide before its incidence started to rise in 1960s [5]. Finally, with advances in diagnostic techniques, new entities are being recognised, most of them rare.

Occurrence

Table 5.28.1 shows a list of cancers, as defined by the International Classification of Diseases, that may be considered rare because of their low incidence rates. Table 5.28.1 does not include those rare cancers that are described in other chapters of this World Cancer Report, such as gall bladder carcinoma, testicular cancer, thyroid cancer and others.

Figure 5.28.1 shows the combined incidence of 12 rare cancers in men and 13 rare cancers in women and the variability of their occurrence worldwide. Even though the rate for each group of tumours is very low (and much lower still for

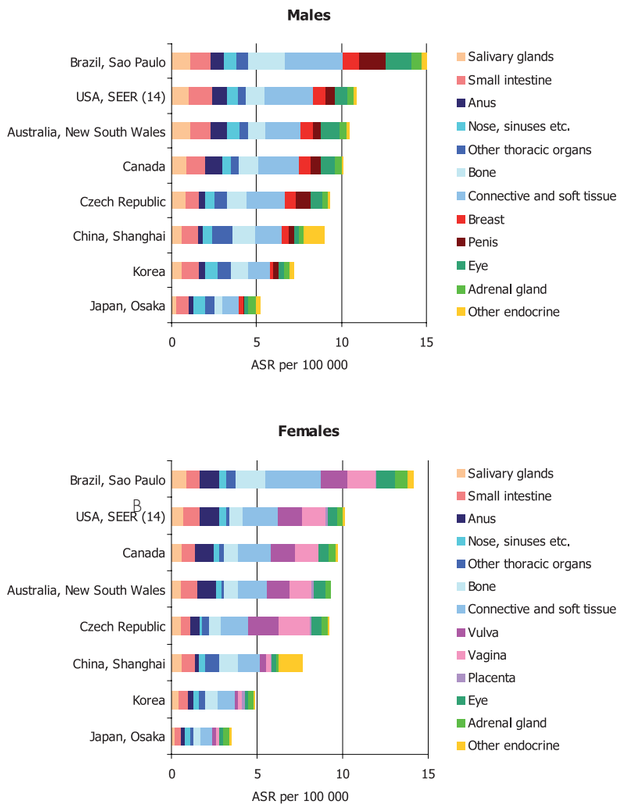

Fig. 5.28.1 *Age-standardised incidence rates (ASR, World standard) of some rare cancers in selected large registries included in Volume IX of Cancer Incidence in Five Continents [7], with cancers defined as in Table 5.28.1 SEER (14) is based on data from 14 registries contributing to the Surveillance, Epidemiology and End Results program . N, total number of cases comprised in the rates calculation.*
Males, comprising 49 381 cases / Females, comprising 53 466 cases

further specific entities), the combined incidence rate for this non-exhaustive list of cancers is comparable to those of common cancers, emphasising the importance of studies of rare cancers.

Schematically, the rare cancers have four main patterns of age distribution (Figure 5.28.2). A continuous increase with age (Figure 5.28.2a) is observed for malignancies of the salivary glands, small intestine, anus and vulva. The J-shaped curve (Figure 5.28.2b), which shows a higher incidence in very young children than in adolescents and young adults and which then rises again with age thereafter is characteristic for cancers of the nose, sinuses, thoracic organs, connective and soft tissue, male breast, vagina and adrenal cortex. Bone tumours and other endocrine neoplasms display a curve with bimodal distribution, with the first peak in adolescence (Figure 5.28.2c and d). A small transitory increase in incidence around adolescence is also seen for soft tissue sarcomas in some populations. Finally, placental cancer reaches its peak in the most common age of procreation, with low rates on both ends of the age-specific curve (inverse U-shape).

Pathology and genetics

Rare cancers comprise a large number of pathologic entities. For example, cancers of the small intestine include carcinoids, adenocarcinomas, lymphomas, sarcomas and others. Their behaviour is modified by their localisation within the small bowel, with carcinoids, lymphomas, and sarcomas occurring in order of decreasing frequency in the ileum, jejunum, and duodenum; the reverse is true for adenocarcinomas [9]. Cancers of the salivary glands vary widely in their histological appearance and molecular characteristics, ranging from low-grade, minimally invasive tumours to highly lethal malignancies [10].

Some rare tumours are found in association with certain familial syndromes. Werner syndrome, an autosomal recessive disorder characterised by premature aging and an increased risk of rare cancers, has been mapped to chromosome 8p. It seems to be more common in Japan than elsewhere. Associated cancers are soft tissue sarcoma, osteosarcoma, myeloid disorders, benign meningioma, adrenocortical carcinoma and others [11,12]. The Lynch Cancer Family Syndrome, characterised by the frequent occurrence of multiple types of common cancers, may also be associated with rare cancers [13]. Familial clustering of rare tumours has also been shown in Li-Fraumeni syndrome [14]. The syndromes associated with some rare cancers may result from both genetic and environmental causes [15] and may be influenced by individual cancer susceptibility [16].

Etiology

The etiology of many rare cancers is unknown, because recruitment of a sufficient number of cases requires very large studies. In addition, there is little comparability between the studies dealing with rare neoplasms due to the lack of standard definition. On the other hand, clusters of rare cancers detected in specific circumstances may lead to identification of some "signal cancers" [17], such as bone sarcoma after the occupational exposure to radium in dial painters [18]. Other occupational exposures have been also implicated in vinyl chloride workers developing liver angiosarcoma [19] or in furniture-makers diagnosed with nasal adenocarci-

Cancer site (ICD-10 codes)	Males		Females	
	N	ASR per 100 000	N	ASR per 100 000
Salivary glands (C07-08)	7507	1.0	5454	0.6
Small intestine (C17)	9691	1.3	8829	1.1
Anus (C21)	5995	0.8	9272	1.1
Nose, sinuses etc. (C30-C31)	4421	0.6	3161	0.4
Other thoracic organs (C37-38)	2800	0.4	1812	0.2
Bone (C40-41)	6323	1.1	5246	0.8
Connective and soft tissue (C47+C49)	18132	2.7	15124	2.0
Breast (C50)	6798	0.9	-	-
Vulva (C51)	-	-	14291	1.5
Vagina (C52)	-	-	4543	0.5
Placenta (C58)	-	-	506	0.1
Penis (C60)	4146	0.6	-	-
Eye (C69)	4871	0.8	4121	0.6
Adrenal gland (C74)	1680	0.3	1758	0.3
Other endocrine (C75)	895	0.2	613	0.1

Table 5.28.1 *Numbers (N) and age-standardised incidence rates (ASR, World standard) of some rare cancers in the National Program of Cancer Registries of the USA [6]. The cancers shown are those occurring with a frequency of around 1 in 50 000 or less in the majority of the world populations, as recorded in Cancer Incidence in Five Continents, Volume IX [7] except those included in other chapters of World Cancer Report 2008. ICD-10, International Classification of Diseases 10th revision [8]*

noma in the early 1960s [20]. The exogenous hormone diethylstilboestrol, used for therapeutic purposes, has caused vaginal carcinoma in the daughters of women using this drug during their pregnancy [21]. Dioxin (2,3,7,8 –TCDD), a toxic pollutant of pesticides, has been declared a human carcinogen [22], based on studies of both common and rare cancers (including soft tissue sarcoma) after exposure to dioxin. Viruses (HPV, HIV) may play a role in the origin of anal cancer [23]. A dose–response relationship was detected between alcohol intake and the risk of male breast cancer [24].

Detection

Rare cancers are often of low clinical and research interest, which may considerably delay their diagnosis and consequently, worsen the prognosis. Their rarity and diversity frequently challenge the diagnostic acumen of the clinician. Novel molecular biology techniques serve to enhance the diagnosis and classification of these tumours and are indispensable for application of tailored therapies [25].

Management

Surgical resection is probably the most commonly used therapy in rare cancers, with chemotherapy and radiation therapy as adjuvants. For rare tumours of the head and neck, new techniques of irradiation (e.g. intensity-modulated radiotherapy or three-dimensional conformal radiotherapy) appear to improve the control of these tumours [26. Radiotherapy has replaced resection as first-line treatment in anal cancer [27]. Progress in molecular biology techniques allows identification of new prognostic factors,

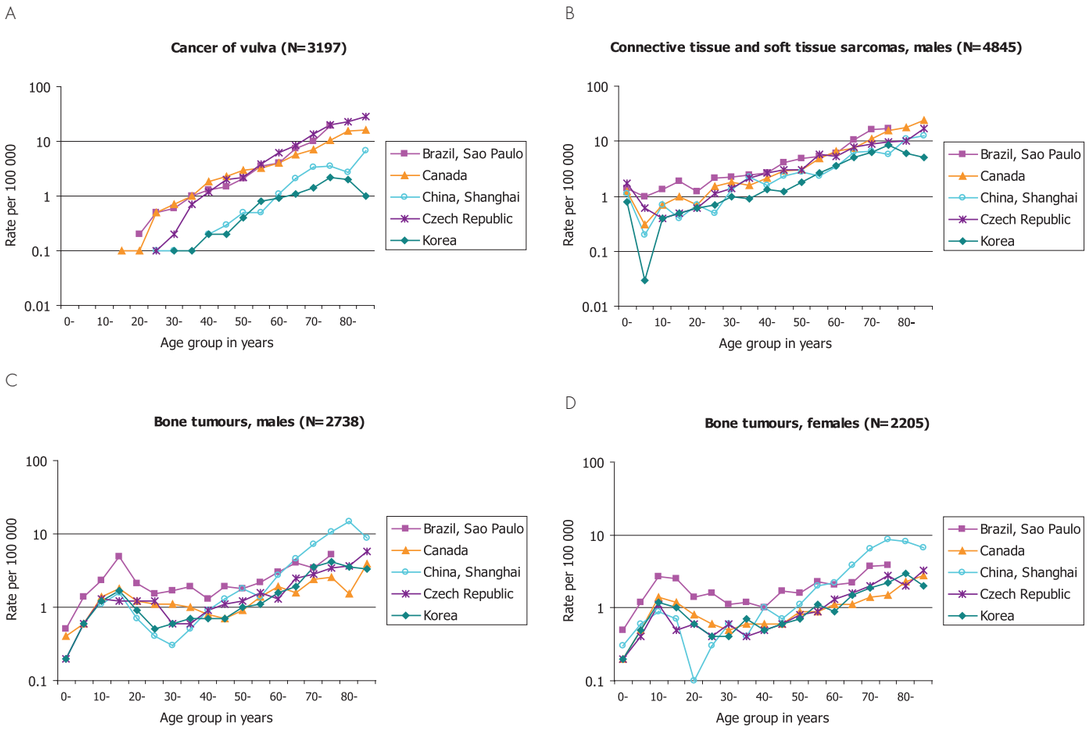

Fig. 5.28.2 *Age-specific incidence rates for some rare cancers in selected populations included in Volume IX of Cancer Incidence in Five Continents [7]. N, total numbers of cases contributing to the statistics in each graph*

and development of molecular-targeted therapies. For cancers with very bad prognosis (e.g. salivary glands, sweat glands), systemic palliative therapy should also be determined in clinical trials [10].

In a large European study, the population-based 5-year relative survival ranged from good to poor for 14 specific tumour types (Figure 5.28.3) [3]. In another population-based study, the 5-year relative survival for small intestine cancer was 54%, but varied with the histological type: 83% for carcinoids, 62% for lymphomas, 45% for sarcomas and 25% for adenocarcinomas [9]. Large clinical series show 5-year relative survival of 86% for patients with parathyroid carcinoma [28]. The relative 5-year survival rates of patients with anal cancer in the population covered by SEER registries is over 70% for women and 60% for men, with much lower rates (less than 30%) among black men. Earlier detection improves the survival of patients with anal cancer [29]. Five-year relative survival rates of vaginal carcinoma patients diagnosed from 1985 through 1989 ranged from 96% for stage 0 (in situ) to 36% for stages III–IV. An even lower five-year relative survival rate of 14% was observed for women with vaginal melanoma [30]. Five-year relative survival rates for vulvar melanoma (N=223) diagnosed between 1985 and 1989 differed by stage, with 77% survivors with stage 0 dropping to 24% for those with stage IV, while recurrent disease was associated with 100% fatality [28].

For some rare cancers, treatment outcome has been particularly successful. Examples include hairy cell leukaemia, chronic myelogeneous leukaemia, seminoma, gastrointestinal stromal tumour, (del)5q myelodysplastic syndrome, acute promyelocytic leukaemia. The reason for this success may be the same as the reason for their rarity, whereby a single molecular genetic aberration needs to be targeted, in contrast to multiple aberrations in the most common cancers [31]. The limited numbers of patients within each tumour type require large international trials to allow identification of prognostic factors or to compare the outcome. Translational research studies and a multidisciplinary approach in specialised centres are vitally important for rare cancers. The Rare Cancer Network, initiated in 1993 to carry out large retrospective studies on rare cancers with the participation of more than 70 institutions from 21 countries, may help in the definition of international standards for management of these tumours [32].

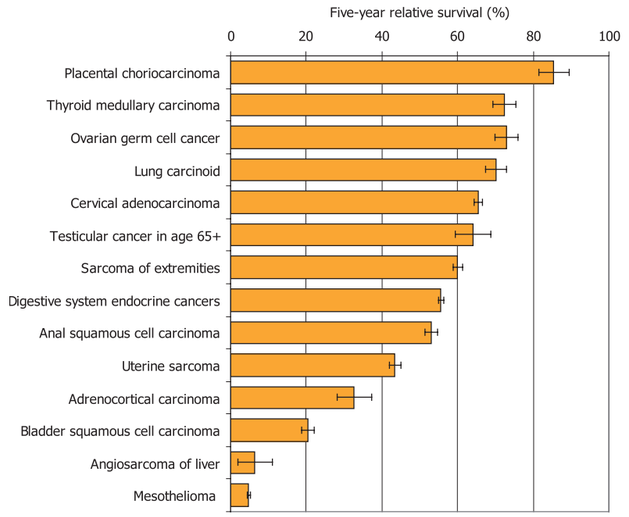

Fig. 5.28.3 *Five-year relative survival from some rare cancers in patients diagnosed during 1983–1994 in Europe, EUROCARE [3]. 95% confidence intervals are shown as line sections*