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WORLD HEALTH ORGANIZATION

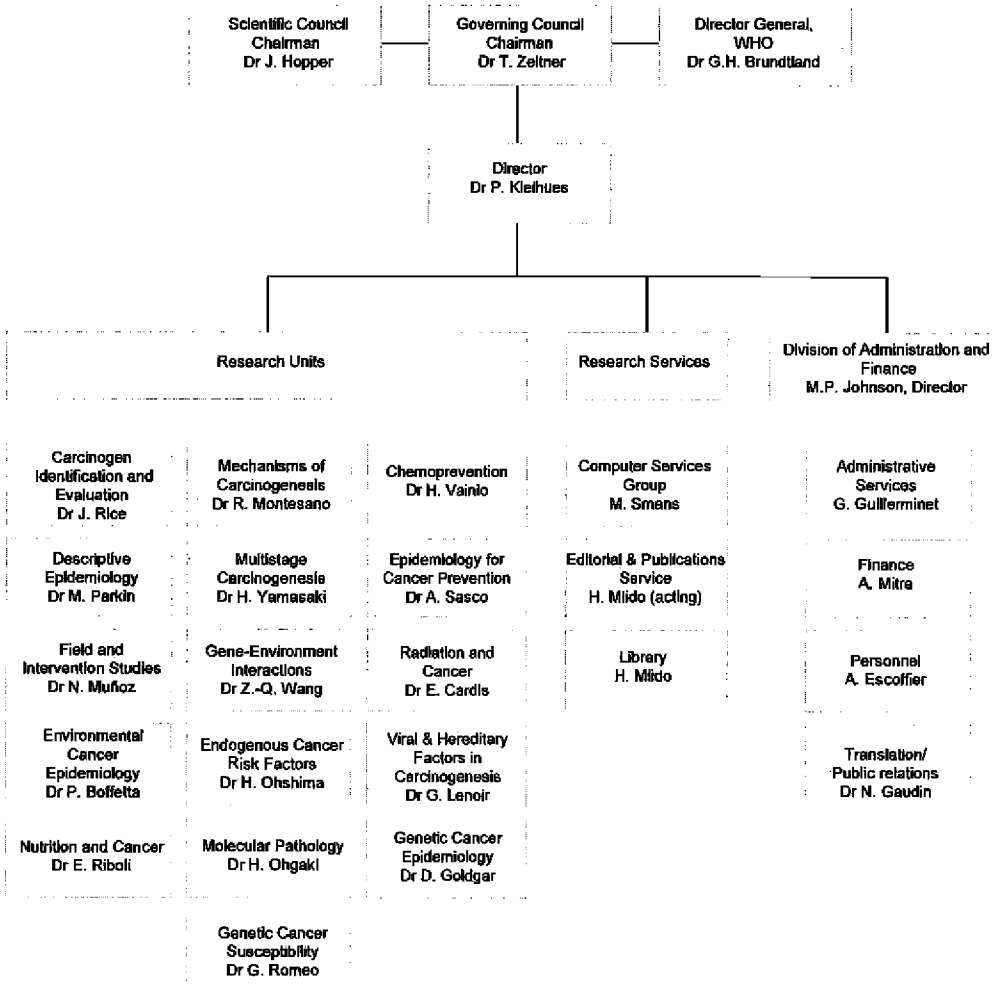
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

BIENNIAL REPORT

1998–1999

International Agency for Research on Cancer
Lyon, France
2000

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)



ISBN 92 832 1097 2

ISSN 0250-8613

Printed in France

150 cours Albert Thomas, 69372 Lyon, Cédex 08, France

Distributed on behalf of IARC by the Secretariat
of the World Health Organization, Geneva, Switzerland

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INTRODUCTION

This biennial report covers the calendar years 1998 and 1999 and is thus the last account of the activities of the International Agency for Research on Cancer in the second half of the past century. It is, therefore, appropriate to review recent achievements in the light of the knowledge base on cancer that has accumulated worldwide since the foundation of the Agency in 1965. During this period, our understanding of the process of carcinogenesis has increased dramatically, mainly due to advances in molecular biology, in particular cancer genetics. Although our hopes that this would rapidly lead to new, successful treatment strategies, such as gene therapy, have not yet been fulfilled, this approach remains a promising alternative to classical chemotherapy.

At the same time, epidemiologists have contributed a wealth of data on the causes of human cancer and how these account for geographical differences in the global cancer burden. Causative factors have been identified for the majority of human cancers, but much work remains to be done to estimate more reliably the attributable risk and to translate this knowledge into effective programmes of cancer prevention. One of the most exciting developments during the past decade is the steadily increasing collaboration between epidemiologists and laboratory researchers, which is particularly reflected in the design of large international collaborative studies that are expected to greatly improve our understanding of the pathogenesis of important human tumour types. An example is the EPIC study, which combines an unusually large epidemiological database on nutritional habits and anthropometric data with a laboratory research programme that includes analysis of hormones and growth factors as well as studies on genetic susceptibility.

Although the cancer research community is enthusiastic about the many new scientific developments, governments and the public justifiably ask to what extent the resources allocated to cancer research have led to a reduction in the cancer burden. Some good news is indeed emerging. In North America and several European countries, the overall mortality from cancer has been declining since the mid-nineties, due to advances in early diagnosis and treatment of cancer, but also as a result of successful control of tobacco consumption. The survival of cancer patients is also gradually improving, as reflected in the recent EUROCARE-2 study covering the years 1978–89, published by IARC*Press*. This epidemiological survey shows that in the European Union, 36% of men and close to 50% of women survive more than five years from malignant tumours at all organ sites combined. The fraction of surviving patients has further increased during the 1990s, but reliable, population-based data are not yet available.

Monitoring global cancer occurrence

Cancer registration. This continues to be the foundation for epidemiological research and is very actively promoted by our Unit of Descriptive Epidemiology. Staff members visit many registries to advise on procedures, while training, computer software and in some cases financial support are also provided. The Unit further plays a leading role in the International Association of Cancer Registries and the European Network of Cancer Registries. Descriptive studies of cancer incidence, mortality and survival in numerous countries have been conducted using data from these sources.

Attributable risks. An analysis of the fractions of cancer attributable to different causes in Europe is in progress, to provide

numbers to be applied in public health planning. Broad categories of causal factors considered include tobacco smoking, infection with certain viruses, bacteria or parasites, diet, reproductive factors in women, occupational causes, ionizing radiation and genetic factors.

Survival of cancer patients. Monitoring the survival of cancer patients has become an increasingly important task of cancer epidemiology. This allows estimation of the prevalence of various cancer types, which is of fundamental importance for developing health care strategies. In addition, it permits the effectiveness of early diagnosis, treatment and follow-up to be compared between different regions and countries. The EUROCARE-2 study has provided such data, showing that within the European Union, significant differences in survival rates still exist, in particular for cancers for which early detection is crucial. The first systematic comparison of cancer survival in developing countries has shown a direct effect of the inadequacy of health care resources.

Cancer etiology

IARC Monographs. This book series on the evaluation of carcinogenic risks to humans continues to be one of the pillars of the Agency's international reputation. Re-evaluations of many chemicals have been undertaken recently to incorporate new information that may change the classification of an agent. Among 121 mostly industrial chemicals re-evaluated in Volume 71, acrylonitrile was downgraded as a carcinogenic risk from Group 2A (probably carcinogenic to humans) to Group 2B (possibly carcinogenic) on the basis of epidemiological data. Evaluation of butadiene proved to be most difficult, in part because of uncertain diagnoses of lymphoid neoplasia in exposed workers. Hormonal contraceptives and postmenopausal hormone therapies were re-examined in Volume 72, while Volume 73 (1998) focused on re-evaluation of some chemicals that cause tumours in experimental animals, but possibly by mechanisms that would not operate in humans. Melamine, *d*-limonene and saccharin and its salts were classified in Group 3 (not classifiable), rather than the previous Group 2B. Surgical implants and other foreign bodies were evaluated in February 1999 (Volume 74). Although many implanted materials have induced tumours in animals, epidemiological data on surgical implants do not indicate an increased risk in humans and female breast implants appear associated with reduced risk of breast carcinoma. Renewed emphasis on physical agents began in 1999, with a review of external sources of ionizing radiation (Volume 75). X-rays, gamma rays and neutrons were all classified in Group 1 (carcinogenic to humans). During 1998–99, altogether five Group 1 carcinogens were identified or reconfirmed: combined oral contraceptives, postmenopausal oestrogen therapy, X-rays and gamma rays, neutrons, and the DNA topoisomerase II inhibitor etoposide given in combination regimens for antitumour chemotherapy.

Occupational cancer. The identification of carcinogenic exposures at the workplace has for many years been a major objective of the Unit of Environmental Carcinogenesis at IARC. Elimination of potential carcinogenic hazards at the workplace has lowered the incidence of occupational cancer, at least in countries with effective laws defining maximum allowed concentrations for exposed workers. However, several occupational risks remain to be assessed. During the period covered by this report, IARC epidemiologists have convincingly shown that several occupational exposures are associated with increased cancer risk, including workers exposed to phenoxyacid herbicides with dioxin contaminants, as well as workers employed in the production of man-made vitreous fibres, in the pulp and paper industry, in the wood and leather industries and in the asphalt industry.

An international study of cancer risk in biological research laboratory workers found

an overall decrease in mortality and cancer burden, possibly due to a healthy-worker effect and selection for social class. For some specific cancers, the risk may be elevated, but conclusive data are not yet available. An international study coordinated by IARC scientists revealed that in the European Union, the prevalence of occupational exposure to potentially carcinogenic agents in 1990 was still 23% and in men, some cancer types still have a significant association with occupational exposure, including sinonasal cancer (41% of cases), bladder cancer (4 to 10%), lung cancer (13%) and laryngeal cancer (8%). Female occupational cancers are much less frequent, the highest level of attributable risk being 3% for lung cancer. Recently launched studies are looking at exposures in the meat industry and in the titanium dioxide industry.

Tobacco and cancer. Tobacco consumption remains the most important preventable cause of human cancer and the Agency has continued its efforts to provide solid data on the adverse health effects of smoking. A major achievement was the publication of the results from the multi-centre study on lung tumours induced by passive smoking. This large study with 12 collaborating European centres showed that exposure to environmental tobacco smoke (ETS) from a spouse or at the workplace is associated with an increased relative risk of 1.14. Another study provided evidence that the lung cancer risk is similar for the smoking of cigarettes, pipe and cigars if the risk is adjusted for the average consumption and time since quitting smoking. The results of this study clearly indicate that cigars should be placed under the same regulations as cigarettes with respect to warning labels. In a related study, genetic susceptibility to lung cancer is being examined by analysis of genetic polymorphisms, DNA adduct formation and gene mutations. Molecular epidemiological studies of bladder cancer support a carcinogenic role of aromatic and heterocyclic amines and a protective role of catechol phenolic substances.

Radiation and cancer. Several important long-term studies of radiation-induced cancer are in progress, designed to improve our understanding of the effects of protracted exposure to low doses of ionizing radiation. Monitoring of the incidence of childhood leukaemia in Europe following the Chernobyl accident is continuing. A set of case–control studies has been set up to look for any effect of radiofrequency electromagnetic fields emitted by mobile telephones.

Nutrition and cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) has now enrolled over 480 000 subjects in nine countries, and questionnaire data, anthropometric measurements and blood samples have been collected from almost all. Methodological work has been conducted to improve food analysis, dietary assessment and statistical processing of the data. In 1999, collection of data on the occurrence of neoplastic disease in the probands was initiated, in parallel with the analysis of hormonal imbalances and serum growth factor levels, leading to the development of new hypotheses regarding common pathways operating in the pathogenesis of cancer, diabetes and cardiovascular diseases.

Infection and cancer. Viruses are increasingly implicated in human cancers. It is now clear that chronic infection with human papillomavirus (HPV) is the decisive risk factor for cervical cancer, and projects are being set up to evaluate newly developed vaccines. Cancers associated with human immunodeficiency virus (HIV) infection are being closely monitored in Uganda and Zimbabwe; the notable increase in Kaposi's sarcoma seems now to have reached a plateau in Uganda. Genetic factors involved in the etiology of Epstein–Barr virus (EBV)-associated nasopharyngeal carcinoma and Hodgkin's disease are being studied. Finally, liver cancer induced by hepatitis B virus is the focus of the Gambia Hepatitis Intervention Study, which is now in its long-term prospective follow-up phase.

The Unit of Molecular Pathology has identified SV40 viral sequences in brain tumours from countries that in the past used SV40-contaminated polio vaccines, but the etiological significance of this observation remains to be elucidated.

Mechanisms of carcinogenesis

Work on the regulation of cellular response to DNA damage has demonstrated a direct molecular link between proteins involved in double-strand break repair and the activation of cellular DNA damage responses. Alterations in such proteins appear to be associated with enhanced radiosensitivity and risk of breast cancer.

During the last 10 years, IARC has contributed to the identification of the genes predisposing to familial medullary thyroid cancer (in the framework of multiple endocrine neoplasia type 2), to neurofibromatosis type 2 and to familial breast cancer. Recent work on the *BRCA1* and *BRCA2* genes has focused on refining mutation detection strategies, in order to better estimate the contributions of these two genes to breast cancer susceptibility, studying the contribution of *BRCA1* and *BRCA2* germline mutations in early-onset breast cancer, and studying the implication of *BRCA2* in predisposition to ocular melanoma. In parallel, a descriptive study of *BRCA1* and *BRCA2* mutations in developing countries is in progress. IARC scientists have identified a new rearrangement in the *BRCA1* gene, undetectable by conventional strategies, that is likely to be a founder mutation, having been detected in four families with independent geographical origins. Therefore, the search for rearrangements appears mandatory in *BRCA1* mutation screening studies. Our data indicate that a substantial proportion of breast cancers occurring at young age (< 40 years) in the general population is attributable to mutations in the *BRCA1* and *BRCA2* genes.

IARC participated in a consortium of laboratories that succeeded in identifying the gene (*SH2D1A*) that is mutated in patients with the inherited X-linked lymphoproliferative (XLP) syndrome and encodes a protein that is expressed in cells of the immune system. This discovery constitutes a breakthrough after many years of intense 'gene hunting' and opens the door to a better understanding of the interaction of EBV with host cells. Knock-out mice lacking SH2D1A expression have already been generated at the Agency.

The interactions between inflammation, nitric oxide and the enzyme nitric oxide synthase, oxidative DNA damage, enzymes that prevent oxidative injury, dietary antioxidants, such as vitamins C and E, and the bacterium *Helicobacter pylori* form a complex pathway that is being revealed to have an important role in gastrointestinal tract tumorigenesis. Scientists at the Agency are conducting studies both with samples from human patients with stomach disease and in experimental animals to elucidate these interactions and identify the biochemical and cellular mechanisms that lead to cancer.

Communication between the cells of a tissue is a basic requirement for control of cell behaviour, including the uncontrolled growth that leads to cancer. Our research has revealed many details of how gap junctions and their component connexin proteins participate in these processes and how disorders of connexin structure arise and affect the ability of the proteins to form functional gap junctions. Enhancement of gap junctional intercellular communication may improve the effectiveness of gene therapy for cancers by a 'bystander' effect. It now appears that gap junctions not only mediate cell growth control but also participate in triggering apoptosis (programmed cell death). Connexins may also have roles other than gap junction formation, such as signal transduction; proteins with which they may interact in exercising such functions are currently being sought.

The function of poly(ADP-ribose)polymerase (PARP) in maintaining genomic integrity

is being studied using mice lacking the relevant gene or carrying mutations in it. This work has shown that nitric oxide, DNA damage and PARP activation play a critical role in DNA damage response, that PARP deficiency causes accelerated tumour progression and that PARP and p53 interact in suppressing tumorigenesis.

The conformation and activity of the p53 tumour-suppressor protein are being studied in experimental systems. The interaction of this protein with DNA is stabilized by binding of zinc, and changes in metal levels may act as physiological signals that mediate the fine tuning of p53 protein function. Modulation of p53 protein function may be one molecular mechanism of cadmium carcinogenicity.

Genetic alterations in certain tumour types are being analysed; for example, significant differences in p53 mutation profiles in squamous cell carcinomas of the oesophagus have been found between samples from Asia and from Europe, that may be related to different etiological factors.

Prevention and early detection of cancer

Cancer prevention is the ultimate aim of much of the research at IARC, and the Agency's active role in this area lies in evaluating the prospects for new preventive measures and the effectiveness of programmes scheduled to be introduced into national cancer control programmes.

As a member of the Alliance for Cervical Cancer Prevention (ACCP), the Agency has received a grant of 10 million US dollars from the Bill and Melinda Gates Foundation to investigate the effectiveness of early detection approaches in preventing cervical cancer and the feasibility of implementation in low-resource countries. The screening methods under consideration are (i) visual examination of the cervix after applying 4–5% vinegar solution; well demarcated, dense white patches on the cervix following the application of vinegar indicate the presence of precancerous changes that may become invasive cervical cancer later, (ii) the Pap test to identify women with precancerous conditions in the cervix; this is the test that has been proven effective in developed countries, and (iii) testing for the presence of certain types of HPV. There is increasing evidence that cervical cancer cannot develop in the absence of persistent HPV infection. IARC studies, headed by Dr Sankaranarayanan, of the Unit of Descriptive Epidemiology, will involve a total of 120 000 women in Barshi and Ambillikai, two economically backward rural areas in central and southern India. A parallel study will be conducted in Africa, in collaboration with the School of Medicine of the University of Ibadan (Nigeria). When completed in five years, this study should provide a clear indication of the most promising and cost-effective means of preventing at least 100 000 deaths from invasive cervical cancer worldwide annually.

The Gambia Hepatitis Intervention Study is well advanced and its database is now being used for ancillary studies. The most exciting of these is the recent detection in serum of short stretches of DNA containing a G→T mutation in codon 249 of the *p53* gene, which reflects exposure to the hepatocarcinogen aflatoxin B_1. This mutation was found in 40% of patients with hepatocellular carcinoma, but also in patients with liver cirrhosis and even some individuals without clinical symptoms. This mutation is not found in subjects from Europe, where aflatoxin exposure is not significant, and may in the future serve as an early diagnostic test.

Other projects are assessing chemoprevention of gastric precancerous lesions with antioxidant vitamins in Venezuela and of oral cancer by vitamin A supplements in India, as well as immunization against HPV as a preventive measure against cervical cancer. Secondary prevention programmes include the evaluation of screening for breast cancer by physical examination in the Philippines, but this has been hampered by poor compliance. Screening for oral cancer by visual

examination of the mouth is being evaluated in a large study in India.

The programme for evaluation of cancer-preventive agents has continued with the publication of new *IARC Handbooks of Cancer Prevention,* focusing on vitamin A and on retinoids. In addition, a new entirely electronic publication has been launched, the *Directory of On-going Research in Cancer Prevention*, which is available on the Internet.

Publications

During 1998–99, IARC staff published a total of 579 research articles. Of these, 397 (68%) were published in peer-reviewed journals, including many with a very high international reputation and impact. Our staff further contributed to 80 book chapters and edited 30 books.

In addition to the new volumes in the *IARC Monographs* and *IARC Handbooks* series mentioned above, nine volumes in the IARC Scientific Publications series were published during the biennium, including notably two dealing with childhood cancer and two with cancer survival, in Europe and in developing countries. The textbook on *Cancer Epidemiology: Principles and Methods* by Dr Isabel dos Santos Silva (London) was primarily intended for IARC courses but is in strong demand from epidemiology centres worldwide and had to be reprinted within a few months. The volume on *Pathology and Genetics of Tumours of the Nervous System* also experienced great success and a second edition, along with a volume on tumours of the digestive tract, will appear in early 2000 as the first members of a third edition of the WHO 'blue book' series, to be published jointly by WHO headquarters and IARC*Press*.

Alongside conventional paper publications, increasing use is being made of electronic dissemination of information, notably for epidemiological data. Several large data-sets have been made available on CD-ROM and distributed successfully by IARC*Press,* either as separate publications in the new CancerBase series, or in conjunction with printed volumes.

Fellowships and training courses

The traditional IARC fellowships programme was split into a branch for postdoctoral scientists wishing to spend a year at IARC (approximately 5 awards per year), and one for young scientists who prefer to work in other institutions (10 awards). Selection committees evaluate candidates on a competitive basis.

Twelve training courses were held. Now well established and popular features were summer schools on cancer registration and epidemiology in Lyon and courses on cancer genetics held in conjunction with the Gaslini Institute (Genoa) in Sestri Levante, Italy. Other courses were held in Costa Rica, Finland, New Caledonia, South Africa and Thailand. A total of some 420 participants attended these courses.

Staff and visitors

In December 1999, a total of 258 people from 40 countries worked at IARC, of whom 144 were staff members. Visiting scientists, who come to IARC as postdoctoral fellows, short-term staff members or consultants or on sabbatical leave, contribute greatly to our work, bringing new experience and fresh ideas. During the past biennium, IARC Visiting Scientist Awards enabled Dr P. Toniolo (United States), Dr C.B. Ijsselmuiden (South Africa) and Dr A. Metspalu (Estonia) to work at the Agency. Three staff scientists spent sabbatical periods in the United States: Dr P. Boffetta (National Cancer Institute), Dr M. Friesen (Johns Hopkins University) and Dr B. Sylla (Harvard University).

During the biennium, several staff members left the Agency. Mr Michael Johnson held the position of Director, Administration and Finance since 1993 and headed the administrative services of the Agency with much skill, being instrumental in the implementation of the organizational changes introduced at the

Agency during recent years. Following a plea by the Director General for greater mobility of staff within WHO, he accepted the position of Director, Administration and Finance, at the WHO Regional Office for the Western Pacific (WPRO) in Manila, as of 1 November 1999.

After 29 years of dedicated service, Dr Ruggero Montesano, chief of the Unit of Mechanisms of Carcinogenesis, retired in October 1999. His excellent leadership and his many important scientific contributions were well recognized in the international cancer research community. Dr Hisayoshi Nakazawa, of the Unit of Multistage Carcinogenesis, left the Agency in October 1998 to take up a position in Japan. Dr Maria Blettner of the Unit of Carcinogen Identification and Evaluation left Lyon in March 1999 to take a chair in epidemiology at the University of Bielefeld (Germany). Dr Sinead Jones, Scientific Officer in the Director's Office, departed in August 1999 to join a Public Health Programme in the United Kingdom. Dr Rolando Herrero, of the Unit of Field and Intervention Studies, left in December 1999 to return to his home country, Costa Rica, where he will supervise an HPV vaccination trial. After 29 years as a staff scientist with many accomplishments in the field of chemical carcinogenesis, Dr Jean-Jacques Castegnaro, of the Unit of Gene–Environment Interactions, retired at the end of 1999.

On behalf of the Agency, I would like to express my gratitude and appreciation for the excellent work carried out by all of these scientists, together with best wishes for their future activities.

Research groups

In accordance with recommendations by the Scientific Council, it was decided not to seek a successor for Dr Montesano as chief of the Unit of Mechanisms of Carcinogenesis. Instead, three research groups have been created for young scientists who, as group leaders, are scientifically independent, but share equipment, laboratory space and secretarial services. A Research Group on Genome Analysis is headed by Dr Federico Canzian and focuses on the development and application of new technologies for high-throughput genetic analyses, particularly in connection with the EPIC study on nutrition and cancer. Dr Janet Hall was appointed head of the Research Group on DNA Repair and will, in this capacity, continue her work on DNA repair deficiency syndromes, in particular ataxia telangiectasia (ATM) and its role in the development of breast cancer. Dr Pierre Hainaut is leader of the Research Group on Molecular Carcinogenesis. His work focuses on the mechanism of tumour-suppressor genes and transformation-associated genetic alterations at specific cancer sites, in particular oesophagus and liver.

New building

At its 39th and 40th sessions, the Governing Council provided funds for a new building along the rue Feuillat, consisting of a basement, ground and four floors, totalling 2125 m^2 of space. The construction of this building is already well advanced and it should be ready for occupation in the autumn of 2000. This building will be used by epidemiology units which are currently under severe space constraint, particularly for visiting scientists. Christian Drevet (Lyon) was chosen as the architect. We are very much looking forward to occupying this new building and are confident that it will provide better working conditions, allow expansion of our scientific activities and, at the same time, positively contribute to the architectural development in the quartier Lumière.

IARC Day

The tradition of the IARC Day, when Governing Council members have an opportunity to meet with the medical, scientific and political communities of Lyon, has been successfully continued. In 1998, the Sohier lecture was given by Dr Charles

Weissmann of the University of Zurich, Switzerland, who gave an intriguing talk on 'Mad cows, prions and transgenic mice'. His presentation was highly appreciated, not least because of the concern about transmission of prion disease through contaminated food from infected animals. On 14 May 1999, the Sohier lecture on IARC Day was presented by Dr Jan Pontèn, Uppsala University (Sweden) on 'Sunlight and skin cancer'. This presentation was innovative, stimulating and very well received by the audience. We heard with great sadness that Dr Pontèn, soon after his visit to Lyon, developed a disease of which he died in November 1999. We will remember his many achievements and his charming personality.

Scientific Council

The Scientific Council currently consists of 18 scientists with an international reputation in areas of cancer research pertinent to the work of the Agency. The Council members meet once per year, usually in January/February, to evaluate past and future projects. This critical evaluation is of great importance for the work of the Agency and I wish to thank those members who left the Council during the past biennium: Dr J.C. Barrett (Research Triangle Park), Dr H.E. Blum (Freiburg), Dr E. Dybing (Oslo), Dr I. Ernberg (Stockholm), Dr T. Hakulinen (Helsinki), Dr D. Kromhout (Bilthoven), Dr Elsebeth Lynge (Copenhagen), Dr U.A. Meyer (Basel) and Dr P. Vineis (Turin). My special thanks go to the chairmen of the Scientific Council, Dr J.C. Barrett (1997–98) and Dr H.E. Blum (1998–99). Under their guidance, the Scientific Council has maintained its exceptional scientific rigour and independence. Both chairmen have given valuable advice to the Director during their terms of office.

Governing Council

The IARC Governing Council, consisting of the delegates of Participating States and the Director-General, WHO, has over the past two years continued to generously support the Agency and its scientific programmes. At the 39th session in May 1998, Argentina and Brazil were admitted as new Participating States and this was very much welcomed by all delegates. These two countries are the first Participating States in South America; their membership will lead to an expansion of our programme in this region and an intensification of our collaborations with cancer researchers particularly in Argentina and Brazil.

In recognition of the country's profound political and economical restructuring, associated with severe financial restraints, the membership of the Russian Federation was suspended as of May 1999. The Governing Council agreed to this with much regret and it is hoped that Russia, which in the past has contributed greatly to the scientific achievements of the Agency, will be able to fully participate again in the near future.

At its 40th session in May 1999, the Governing Council determined the biennial budget for 2000/2001, with a real programme increase of 4.15%. On behalf of the entire staff, I should like to thank the Governing Council for its generous support, which will enable us to expand into new research directions.

The Chairman of the Governing Council, Dr Thomas Zeltner (Switzerland), has given much important advice between the meetings of the Council. The Vice-Chairmen were Dr Diana Dunstan (United Kingdom) for 1998–99 and Mr Neil Boyer (United States) for 1999–2000.

Interaction with WHO headquarters

In December 1998, the newly elected Director-General of the World Health Organization, Dr Gro Harlem Brundtland, visited the Agency in order to become acquainted with our work and to discuss the future role of the IARC within our parent organization. In accordance with the organizational restructuring at WHO Headquarters, she decided to

relocate the WHO Programme on Cancer Control to Geneva. This programme is now incorporated into the Cluster of Non-communicable Diseases, headed by the Executive Director, Dr Jie Chen. The interaction between this cluster and IARC scientists has steadily intensified over the past two years and we look forward to much fruitful interaction in the future.

In October 1999, on the occasion of a retreat in Lyon, members of the WHO Executive Board, the Director-General and WHO Regional Directors paid a visit to the Agency. This was the first occasion for IARC to present its activities to a WHO governing body and the lectures, demonstrations and laboratory visits were very well received by our guests. This visit has, in our view, greatly strengthened the interaction of the Agency with our parent organization, both at headquarters and in the regions.

Dr Paul Kleihues
Director

PART 1. CANCER OCCURRENCE AND OUTCOME

1.1 Support to cancer registries

Cancer registries are the source of information on incidence of cancer in defined populations, as well as on outcome, in terms of survival. They also provide a framework for conducting epidemiological studies into the cause of different cancers. In many parts of the world, cancer registries provide the only available information on the nature and evolution of the local cancer problem. The comparative value of the statistics which cancer registries produce depends upon the use of common methods, and definitions, so that international collaboration in this area has a very important role.

1.1.1 International Association of Cancer Registries (IACR)

D.M. Parkin, S.L. Whelan and B. Geoffre; in collaboration with J. Young, Atlanta, USA; and H.H. Storm, Copenhagen, Denmark

The International Association of Cancer Registries (IACR), a non-governmental organization (NGO) in official relations with WHO, is supported by a secretariat within IARC, and provides a link between registries across the world. In 1999 the Association had 430 members in 114 countries, 80% of them cancer registries.

Members work actively with IARC on projects using cancer registry data, and the preparation of publications presenting data on cancer occurrence and registration methodology. In 1998 members were asked about the terminology used for describing diagnoses of cancer, and during 1999 many participated in field-testing of the third edition of the International Classification of Diseases for Oncology (see Section 1.1.3.1). The *Cancer Incidence in Five Continents* series (Section 1.2.1) and *International Incidence of Childhood* Cancer, Vol. II (Section 1.4.1) are further examples of collaboration.

The secretariat maintains a specialized library containing over 2000 publications produced by member registries and presenting data on cancer incidence, mortality and prevalence.

A scientific meeting is organized each year. Over 200 participants from 40 countries came to the 1998 meeting in Atlanta, Georgia, USA. The 1999 meeting in Lisbon, Portugal, was attended by 350 participants.

The first Calum Muir Memorial Fellowship was awarded in 1998, to Dr Nguyen Manh Quoc, from Ho Chi Minh City, Viet Nam. Dr Quoc divided the time of his fellowship between the cancer registry in Madras and IARC. The second fellowship was awarded in 1999 to Mrs Leslie Banda from Malawi, who used it to work at IARC and to attend the IACR meeting in Lisbon.

A website has been set up for the IACR (www-dep.iarc.fr/iacr.htm). The IACR Newsletter gives news of activities and articles from cancer registries and national or regional associations of registries.

1.1.2 European Network of Cancer Registries

D.M. Parkin, R. Sankila, F. Bray, E. Démaret, J. Ferlay, and E. Kramárová; in collaboration with F. Berrino, Milan, Italy; D. Brewster, Edinburgh, UK; T. Davies, Cambridge, UK; J. Faivre, Dijon, France; F. Langmark, Oslo, Norway; J.W.W. Coebergh, Eindhoven, The Netherlands; C. Martínez García, Granada, Spain; F. Ménégoz, Meylan, France; R. Otter, Groningen, The Netherlands; L. Simonato, Padua, Italy; H.H. Storm, Copenhagen, Denmark; H. Tulinius, Reykjavik, Iceland; and H. Ziegler, Saarbrücken, Germany

The European Network of Cancer Registries (ENCR) was established in 1989

with support from the Europe Against Cancer Programme of the European Commission. Its aims are to improve the quality, comparability and availability of data from cancer registries, and to promote the use of these data in research and cancer control activities. IARC provides the secretariat.The ENCR has 152 member registries. Of these, 87 are population-based cancer registries in the member states of the European Union (EU) with full ENCR membership. Registries in non-EU countries in Europe are accorded associate member status, as are specialized registries which collect information on a limited range of cancers, for example, childhood cancer.

The main activities of the Network are:

(a) Surveillance of registration methods. Three surveys have been conducted and the results have revealed some differences in the definitions and data collection practices used in the European cancer registries.

(b) Establishing standards and definitions. Working groups have been established to review aspects of registration practice and to make recommendations for standards for the European registries. These groups have established recommendations for the coding of the date of diagnosis; multiple neoplasms; bladder cancer; brain and central nervous system tumours; and the extent of disease. Other working groups are focusing on the coding of basis of diagnosis; the registration of skin cancers; confidentiality issues in cancer registration; and auditing and certification of cancer registries.

(c) Training in cancer registration and data analysis methods. In 1998, two one-week ENCR courses in population-based cancer registration were held in Saarbrücken, Germany and in Macerata, Italy. The courses are mainly aimed at senior cancer registry personnel. Courses on statistical analysis are held annually. One of three themes is addressed each year: survival analysis (1997), geographical studies (1998) and time trends (1999).

(d) Fellowships. Registry personnel can obtain support to attend ENCR courses or to exchange skills through working visits to other cancer registries. Ten fellowships are available each year.

(e) Consultancy. Cancer registries can request a consultant visit by an experienced person to advise on cancer registration methodology or specific local problems. In 1999, ENCR consultants visited cancer registries in Belgium and Bulgaria.

(f) Workshops. A technical report based on a workshop on computerized data collection in cancer registries was published in 1998 [23]. The results of a workshop on monitoring and evaluating screening programmes, held in Luxembourg in February 1999, will be published as a monograph.

(g) Provision of cancer data. Information on the frequency of cancer in European populations is provided through traditional and, increasingly, electronic publications.

(i) A new user-friendly *EUROCIM* integrated database with powerful analytical software was introduced at the end of 1999 (see Section 1.2.2). EUROCIM is distributed free of charge to registries contributing data.

(ii) The new *EUCAN* dynamic database and software package provides incidence, mortality, prevalence and survival estimates for 1995 for the EU and its 15 member states for 24 major cancer sites. This was published in 1999 as IARC CancerBase No. 4 (see Section 1.2.2).

(iii) *Cancer in European countries and regions.* A programme of collaborative studies of trends in incidence and mortality in specific countries has been established. A report on trends in France was published in English [294], and French (Ménégoz & Chérié-Challine, *Le Cancer en France: Incidence et Mortalité. Situation en 1995, évolution entre 1975 et 1995*, Paris, Documentation Française, 1998). Estimates for Spain based on the EUROCIM data have

been prepared for publication as a bilingual report (Miñarro *et al.* (1999), *Cancer Incidence and Mortality in Spain: Patterns and Trends* (IARC Technical Report No. 36). Analysis of Portuguese data was performed at IARC in autumn 1999 by Dr P. Pinheiro.

(iv) *Cancer mortality projections for the European Union 1995–2010* were finalized in 1999, for publication in the IARC CancerBase series.

(h) The ENCR Internet home page at http://www-dep.iarc.fr/encr.htm provides comprehensive information on the activities of the ENCR and links to available data resources. The basic EUCAN incidence and mortality tables are available at the website.

(i) European Cancer Registries Newsflash is issued to members in English, Spanish, French and Italian. The latest Newsflash was published in April 1999.

1.1.3
Reliability and validity of registry data

1.1.3.1
International Classification of Diseases

D.M. Parkin and S.L. Whelan; in collaboration with C. Percy and A. Fritz, Bethesda, MD, USA; A. Jack, Leeds, UK; K. Shanmugaratnam, Singapore; and L. Sobin, Washington, DC, USA

An international working group met twice during 1998 and held a final meeting towards the end of 1999 to prepare the third edition of the *International Classification of Diseases for Oncology* (ICD-O). This revision was impelled by the rapid changes in understanding and terminology of the leukaemias and lymphomas, and the opportunity was taken to add new terms and to indicate terms which should be considered obsolete throughout the morphology section of the classification.

A field trial edition (IARC Internal Report No. 99/003) was sent to over 60 registries worldwide (excluding the USA) in 1999 for field testing. The US National Cancer Institute undertook the field trial in the USA. Each participant in the IARC trial coded a minimum of 400 cancer diagnoses using the new ICD-O, and sent the results as a case-listing with a commentary on problems encountered. The results were analysed in September and taken into account when preparing the final version of the ICD-O third edition, that was completed at the end of 1999.

1.1.3.2
Histological Groups for Comparative Studies

D.M. Parkin, J. Ferlay and S.L. Whelan (in collaboration with K. Shanmugaratnam, Singapore; and L. Sobin, Washington, DC, USA

Histological Groups for Comparative Studies [352] provides a description of the recognized histological subtypes of the principal cancers, together with the appropriate ICD-O morphology codes. The distribution of these codes is exhaustive for each site (which is not the case for the International Histological Classification of Tumours, with which it is compatible). Similarities and differences with other proposed groupings are discussed. The classification is that used in *Cancer Incidence in Five Continents*, Vol. VII and IARC CancerBase No. 2.

Accompanying software allows recoding of data to the proposed histological groups, to permit comparative studies. Although the groupings may be used in any comparative study involving case series coded by histological type, they will be most useful for investigations of incidence and survival.

1.1.4
Computer software for cancer registries

J. Ferlay and A. Cooke

1.1.4.1
Canreg

Canreg is a configurable computer program for use in cancer registration in population-based registries. The most recent

version—CanReg3—was released in late 1996 and has now been installed in some 80 sites around the world and training has been given in its use (Figure 1).

The program allows searching for duplicate records and multiple primaries using probability matching, consistency checking for impossible or rare cases, conversion from one classification system to another, and immediate language swapping. Frequency distributions, reports and incidence tables can be generated and an interface into EpiInfo6 is included. Recent updates to the program include Import/Export options allowing, for example, national registries to consolidate data from regional registries.

Special versions of Canreg are being developed in collaboration with the Middle East Cancer Consortium (funded by the US National Cancer Institute), to be installed in Egypt, Jordan, Cyprus, Israel and Palestine.

Development of a new 32-bit Windows NT version—CanReg4—has been initiated; this will allow integration of Chinese, Thai and Arabic character sets, and working in networked environments.

1.1.4.2 IARCtools

The new IARCtools package has been designed to replace the CONVERT and CHECK DOS-based programs. It runs under Windows and has a much improved user interface and on-line help facilities. It includes an updated version of the IARCCHECK program which performs validity checks both on individual data items and for consistency between items. It also provides various batch programs to convert data from the International Classification of Diseases (ICD version 9 or 10) or the International Classification of Diseases for Oncology (ICD-O) first edition, to the International Classification of Diseases for Oncology (ICD-O) 2nd edition. Also included are conversion programs from the ICD-O 2nd edition to ICD versions 9 and 10, and a new program to detect multiple primary tumours in an individual. The IARCtools package is distributed free to members of IACR or can be downloaded from the CANCERMondial web page.

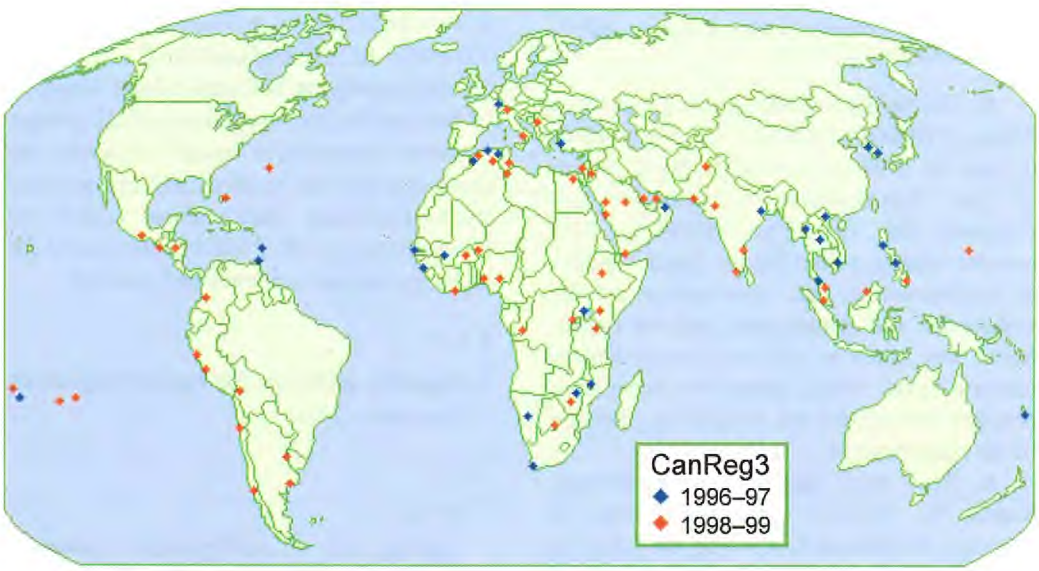

Figure 1. Locations of Canreg installations.

1.1.5
Support to specific cancer registries

D.M. Parkin, P. Pisani, R. Sankaranarayanan, S.L. Whelan and A. Cooke

Advice is given both to organizations wishing to set up cancer registries and to established registries on the methodology of registration and the analysis of data. Staff of the Unit of Descriptive Epidemiology have made visits to numerous cancer registries during the biennium, and many individuals working in cancer registries have visited the unit for training or discussion. The visits to IARC have largely been in connection with a structured course on cancer registration and applications in epidemiology (see Sections 7.3.4 and 7.3.9). A training course for cancer registry clerks from Africa was held in South Africa in March 1998, in collaboration with the South African Institute of Medical Research, with financial support from WHO (AFRO) and the US National Cancer Institute. 26 participants from 18 cancer registries received training in registry methods. A course held in Noumea, New Caledonia in July 1998 attracted 12 participants from 12 Pacific Island countries (see Section 1.1.5.4). A course in French was held in Lyon in November 1998 for five francophone Africans. In November 1999, a course was held in Bahrain for 40 participants, in collaboration with WHO (EMRO).

Several commonly used computer programs are available to registries free of charge (see Section 1.1.4).

The Unit of Descriptive Epidemiology also provides direct support and encouragement for cancer registration activities in Africa, Asia, Central and South America and Oceania, often in the form of collaborative research agreements with the registry.

1.1.5.1
Africa

Algeria, Setif (M. Hamdi-Cherif): The registry is supported through a Collaborative Research Agreement.

Oran (L. Mokhtari and N. Midoun): Dr Midoun spent a period of training in Lyon; Dr Mokhtari visited IARC to discuss methods and results.

Batna (H. Ziad): Mr Ziad received a fellowship for a period of training at IARC.

Burkina Faso (B. Sakande): Registration for the city of Ouagadougou commenced in 1998; a Collaborative Research Agreement provides support.

Congo, Brazzaville (C. Gombe-Mbalawa and S. Moubie): Results from the first three years of operation were analysed.

Côte d'Ivoire (A. Echimane and A. Ahnoux): Support to the registry continued through a Collaborative Research Agreement. The results of the registry have been prepared for publication (incidence 1995–97 and survival of patients from the oncology service). The registry is participating in the study of cancer survival in developing countries (see Section 1.5.1).

Ethiopia, Addis Ababa (E. Wondwossen and J. Schneider): Plans have been made to initiate cancer registration in Addis Ababa beginning in 2000. A computer and software have been provided.

Gambia (E. Bah): The cancer registry is the main component of Phase III of the Gambia Hepatitis Intervention Study (see Section 5.1.1). Active follow-up was initiated in 1999 to study survival of cancer cases (see Section 1.5.1).

Guinea (M. Koulibaly and I. Kabba): A Collaborative Research Agreement provides support.

Kenya (N. Buziba): A cancer registry was established in Eldoret covering Uasin Gishu district in western Kenya. A Collaborative Research Agreement was established in 1999 following a pilot project.

Libya (S. El-Fathali and K. Enowellyi): Registration covering a population of 525 000 in Zawia region in western Libya commenced in 1998.

Malawi (N.G. Liomba and L.T. Banda): The registry supervisor received a fellowship

Figure 2. Cancer registration in (above) Khon Kaen, Thailand and (below) Ho Chi Minh City, Viet Nam

to visit IARC to analyse the results of the registry from 1994–98.

Mali (S. Bayo and S. Kané): Analysis of data from about 12 years of registration, including a review of temporal trends for certain cancers, has been initiated.

Niger (H. Nouhou): A Collaborative Research Agreement is in operation.

Nigeria (J.O. Thomas): The Ibadan cancer registry has been re-activated. Support is provided via a Collaborative Research Agreement, and staff training provided.

South Africa (F. Sitas): The national (pathology-based) registry hosted a training course for cancer registry clerks (see above).

Swaziland (S. Okonda): A Collaborative Research Agreement was established in 1999.

Tanzania (E. Moshi): A population-based registry covering four districts of the north of Tanzania, centred in the town of Moshi, was established in 1998.

Tunisia: (B. Abdallah, M. Hsairi, S. Korbi and S. Hamissa). Nationwide population-based cancer registration is being attempted in Tunisia through the organization of three regional registries (Northern, Central and Southern regions).

Uganda (H. Wabinga and S. Nambooze): The cancer registry provides the framework for the studies of cancers related to human immunodeficiency virus (HIV) (Section 2.6.4) and surveillance of temporal trends in HIV-related cancers (Section 1.2.3). The registry results for the period 1960–97 have been analysed. The registry is participating in the studies of survival in Africa (see Section 1.5.1).

Zimbabwe (L. Levy, E. Chokunonga, B. Mauchaza and M. Bassett): A report for the period 1993–95 was published. Active follow-up was initiated in 1999 to study survival of cancer cases (see Section 1.5.1).

1.1.5.2 Asia

Bahrain: A national registry was established in 1994 and population-based registration began in 1995. The registry hosted a regional course for registry personnel in 1999, with assistance from IARC staff.

China, Guangzhou (D.S. Wan and Wu Yilong): A visit was made in 1998 to review registry methods and to advise on future developments.

Beijing (T.-C. Wang and Li Ling): A visit was made in 1999 to review registry methods and advise on quality issues.

Kunming: A visit was made in 1999 to plan for population-based cancer registration.

Qidong (J.G. Chen and R. Zhu): The registry is collaborating in studies of survival and follow-up of a cohort of subjects tested for HBsAg (see Section 3.3.4).

Tianjin (Q.S. Wang): The registry hosted the Chinese Cancer Registry Meeting in 1999.

India, Ahmedabad (D. Patel and D. Bala): A Collaborative Research Agreement has been established to provide technical support in data management and survival analysis.

Ambilikkai (J. Cherian and R. Rajkumar): The results from this rural registry for 1996–98 were prepared for publication.

Barshi (B. Nene, K. Jayant and A. Budukh): Support for this new registry serving a rural population in Maharashtra state was continued and analysis of survival from cervical cancer completed (Section 1.5.1). Survival of all cases registered during 1988–96 has been analysed. The registry supports a study of early detection of cervical cancer in a nearby locality (Section 5.4.2).

Bombay (B.B. Yeole and L. Sunny): Technical support for the analysis of survival for head and neck, colorectal and prostate cancer was provided. The registry assists in the follow-up of the cohort study of tobacco-related cancer (Section 2.4.3). The database for the period 1964–90 is being computerized.

Calcutta (M. Siddiqi and U. Sen): Results are available for 1997–98.

Madras (V. Shanta and C.K. Gajalakshmi): Collaboration, particularly in the field of methods of follow-up and survival studies, has continued.

Trivandrum (K. Nair and C. Varghese): The registry continues to provide information needed for various research projects in the Kerala population, particularly the oral cancer screening trial (Section 5.3.4) and the tobacco-related cohort study (Section 2.4.3).

Iran (A. Mohagheghi and A. Mosavi): Collaboration was strengthened within the framework of an agreement between IARC and Tehran University of Medical Sciences.

Korea, Republic of (H. Ohrr, M.H. Shin, Y.O. Ahn and C.W. Lee): A visit was made in 1998 to investigate the functioning of registration in Seoul, Kangwha and Pusan, and to plan future collaboration.

Mongolia (A. Munkhtaivan and Ozzidelger): A visit was made during 1999 to plan modernization of registry procedures and data handling, to be implemented in 2000.

Oman (J. Al Lawati): Technical support to improve coverage and data management is provided.

Pakistan, Karachi (Y. Bhurgri): A population-based registry covering the population of the southern part of Karachi has been established, supported by a Collaborative Research Agreement. Analysis of the first three years of registration has been completed.

The Philippines (D. Esteban, A. Laudico and B. Talaver): The two registries in greater Manila play an active role in the follow-up of the breast cancer screening project, and in the Rizal population extra staff ensure careful staging and follow-up of all breast cancer cases (Section 5.4.1). The data of the Manila registry are being used for studies of survival (see Section 1.5.1).

Saudi Arabia (N. Al Hamdan and S. Awadalla): The registry covers the entire country.

Singapore (H.P. Lee, K.S. Chia and A. Cheow): A Collaborative Research Agreement has been established to assist in analysis of survival of cases registered during 1968–92.

Thailand (S. Deerasamee, S. Srisukho, S. Sontipong, S. Sriamporn, H. Sriplung V. Vatanasapt and P. Srivatanakul): The results from five population-based registries (Lampang, Chiang Mai, Khon Kaen, Bangkok and Songkla) were included in a combined analysis (see Section 1.2.3). Khon Kaen registry provides follow-up for the cholangiocarcinoma study (Section 3.3.2).

Turkey (G. Aydemir, C. Fidaner and S. Eser): Registration for Izmir province is now complete and the 1993–94 results have been prepared for publication.

United Arab Emirates (M. Fikri and Z. Khazaal): Z. Khazaal visited Lyon in 1999 to participate in the training course and to prepare plans to initiate registration.

Viet Nam: (Pham Hoang Anh, Nguyen Chan Hung and Nguyen Manh Quoc): The registries are supported by Collaborative

Research Agreements. The results from the Ho Chi Minh City cancer registry were published, as was a separate analysis of childhood cancer [390, 391].

Yemen (H. Al-Kaff and A. Bawazeer): A Collaborative Research Agreement has been established to assist a cancer registry in Aden.

1.1.5.3

Americas

Argentina, Bahia Blanca (E. Laura): Continuing support is provided.

Concordia (M.A. Prince and D. Loria): Canreg software was installed.

Bolivia (J. Rios Dalenz and R. Calderon): Consultant visits were made with a view to enhancing completeness of data collection. A previously established database could not be recovered and plans were made for re-entry of the data.

Chile: A staff member visited the registries of Valdivia (Dr E. Beltran) and Antofagasta (Dr. Goycolea). Advice to improve coverage and coding accuracy was provided. A common Canreg system for the two registries is being developed.

Colombia, Cali (E. Carrascal): Consultant visits were made to upgrade the database and improve data quality.

Cuba (L. Fernandez): The registry received technical support for cancer survival analysis and to increase computing facilities.

Guatemala (C. Waldheim and M. Villeda): After review of registration, recommendations to improve coverage and data quality were made.

Honduras (Dr S. Bejarano): The registry covers the province of San Pedro Sula.

Paraguay (P. Rolon): An analysis of the information system and registry practices was made during a site visit.

Panama (P. Valdes): The registry is a new one and recommendations on methods have been made following a review visit.

Peru (P.J. Albujar): Continuing support was provided for the registry in Trujillo.

Trinidad (V. Roach): The registry covers the city of Port of Spain, but it is planned to extend coverage to the whole island.

1.1.5.4

Oceania

A training course for cancer registry personnel in collaboration with WHO Western Pacific Regional Office and the South Pacific Commission was held in Noumea, New Caledonia in July 1998. A core version of Canreg was developed during the course and individual installation systems were distributed to all participants. The Secretariat of the Pacific Community, Noumea, and WHO Country Representative Office, Suva, were active partners.

Several countries had expressed a need to set up cancer surveillance systems and sent representatives: Cook Islands, Samoa, Tonga, Kiribati, Solomon Islands, Federated States of Micronesia and Palau. Guam, Kiribati, Micronesia and Palau subsequently initiated registration activities that were still operating a year later.

New Caledonia (M. Vivier-Darrigol): After a review of the sources of information of the registry, a recommendation to include death certificates was made.

Fiji (L. Eseroma and J. Lesuma): Incidence data collected since 1985 have been transferred to Canreg and coding rules reviewed.

French Polynesia (L. Yen Kai Sun): Incidence data were published in *Cancer Incidence in Five Continents* Vol. VII for the first time.

Vanuatu (Y. Taga): Registration is passive, based on hospital discharges and pathology reports. Recommendations to improve coverage were made. Tumour coding was upgraded.

Guam (R.L. Haddock): A mortality database as a proxy for incidence has been maintained since 1971. An information system to monitor incidence has been developed and data are being collected.

1.2 Geographic variation in cancer occurrence

Documenting the enormous range in incidence and mortality from disease in different populations has been a powerful stimulus to research into the causes responsible. These may represent to varying degrees the presence or absence of environmental exposures, or differing susceptibility of the populations concerned. Therefore the collation, processing, analysis and presentation of cancer data are important activities. At the same time, it is possible to estimate how much of the cancer burden in different parts of the world might reasonably be ascribed to environmental exposures susceptible to modification; this provides a quantitative indication of the priorities for public health intervention.

1.2.1

Cancer Incidence in Five Continents, Volume VIII

D.M. Parkin, S.L. Whelan and J. Ferlay

Cancer Incidence in Five Continents has been published every five years since 1966. Since Volume III (1976), it has been produced in collaboration with the International Association of Cancer Registries. The aim is to provide comparable data on the incidence of cancer in different geographical locations and in distinct subpopulations (especially ethnic). Volume VII, published in 1997, included data on 182 populations in 50 countries.

The cycle of preparation for Volume VIII, to be published in 2002, began in 1999. Population-based cancer registries which might contribute data were identified. A questionnaire designed to obtain background information on the registries (on geographical and cultural features) and, in particular, to identify areas where differences in registration practices might affect international comparability, was finalized during the first editorial meeting, held in November. This was then sent to the registries with invitations to provide data.

Preliminary discussions were held on the format of Volume VIII. The decision on whether or not to continue with the traditional printed format for all the data, in addition to providing them on electronic medium, will be taken in 2000.

1.2.2

European cancer incidence and mortality database

1.2.2.1

EUROCIM

J. Ferlay, R. Sankila, F. Bray, and D.M. Parkin; in collaboration with the member registries of the European Network of Cancer Registries

EUROCIM is a powerful statistical software package which allows comparative analysis of data on cancer incidence and mortality contributed by members of ENCR (see Section 1.1.2). Approximately 12 million tabulated case records are held in the database. This is managed and maintained at IARC, while an external contractor is responsible for the development of the program. The new windows-based version of EUROCIM (Version 3) is now complete. It retains the same analytical features as the previous DOS version, but has a considerably improved user interface (Figure 3), and allows the extraction and analysis of larger datasets. The program will be distributed on CD-ROM to contributing ENCR members, together with the latest incidence and mortality databases containing data from 90 European cancer registries for the period 1960 to 1996.

A new statistical module is being incorporated that will allow the user to examine secular and birth cohort trends in cancer risk. This version will be available in summer 2000.

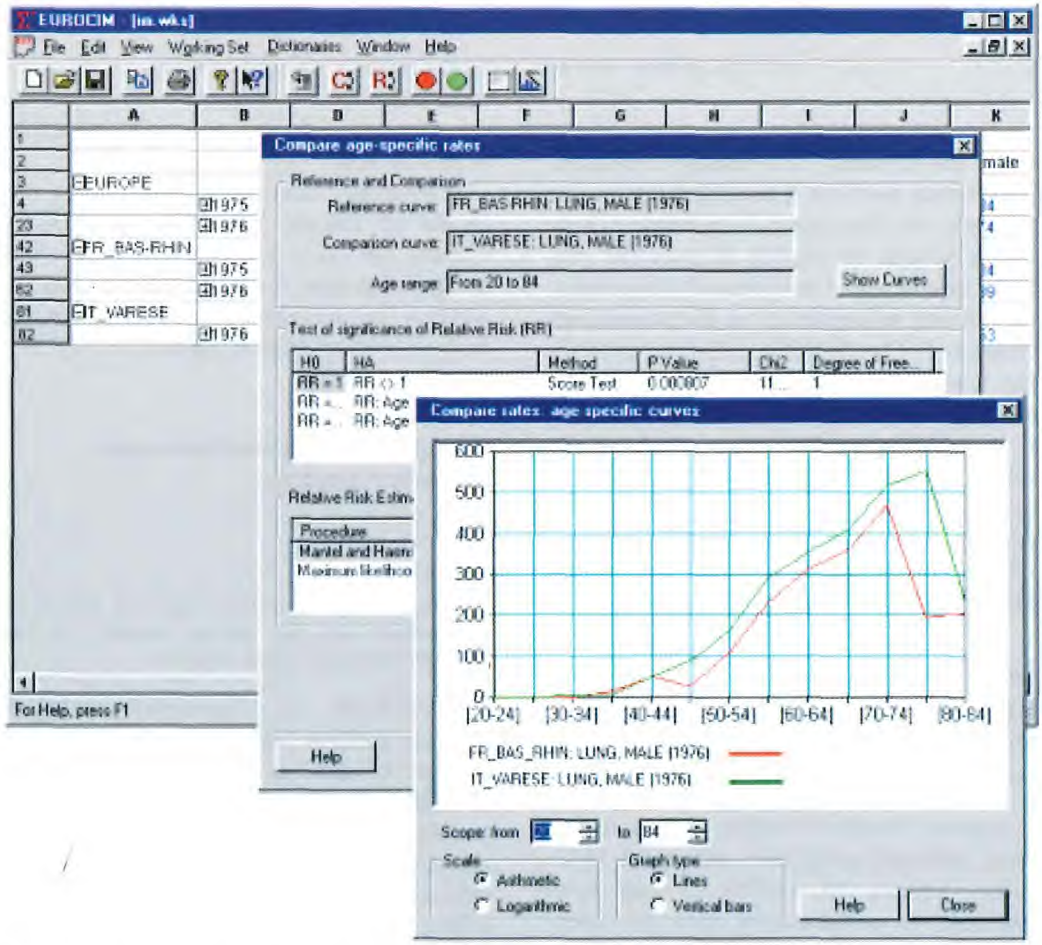

Figure 3. Example of a EUROCIM screen display; comparing age-specific incidence rates

1.2.2.2
EUCAN

J. Ferlay, F. Bray, R. Sankila and D.M. Parkin

This Windows-based software package [161] provides access to the most up-to-date information on cancer incidence, mortality, prevalence and survival in the 15 member states of the European Union for 24 major cancer sites. Various descriptive statistics such as the numbers of cases or deaths, the age-standardized rate and the cumulative risk can be displayed as tables or graphs (Figure 4) that can be easily printed or exported to other packages. In addition, countries and cancer sites can be grouped, allowing users flexibility in specifying their own requirements.

1.2.3
Analysis of data from collaborating cancer registries

Investigators working in cancer registries are assisted in analysing and presenting their data. Priority is given to data-sets of special interest, representing hitherto unpublished material, and to combined analysis from several registries in the same country.

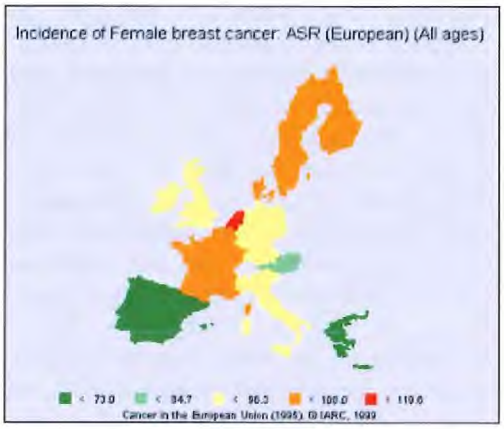

Figure 4. Example of a EUCAN screen display of female breast cancer incidence in the European Union

In Europe, incidence data from cancer registries have been analysed and published within the framework of ENCR (Sections 1.1.2 and 1.2.2).

The first results from the cancer registry of Ho Chi Minh City, Viet Nam [391] suggest high rates of liver, lung and stomach cancer in men, and (in contrast to the north of the country) cervix cancer in women. An analysis of childhood cancer incidence has been completed [390].

Following two editorial meetings, *Cancer in Thailand*, volume 2, was published in 1999 [139]. This brings together data from four population-based registries and presents national estimates of incidence and a review of epidemiological studies of various cancers in Thailand.

The results from the cancer registry of Harare, Zimbabwe, for its second three years of operation (1993–95) were published [112]. The manually filed data from the early years of the cancer registry in Kampala, Uganda (from 1960–80) were coded and entered into the registry database. After correction of erroneous records, an analysis of the registry results for a 38-year period (1960–97) was completed [545]. The first results from the cancer registry in Abidjan, Côte d'Ivoire (for 1995–97) were prepared for publication; they suggest that prostate cancer is now the most common cancer of men (a little more frequent than liver cancer) and that breast cancer is slightly more frequent than cervix cancer. The first results for the Malawi cancer registry (for Blantyre district) for 1994–98 have also been analysed. Almost all other registries in Africa submitted their most recent data in early 1999, with a view to their publication in *Cancer in Africa* (see Section 1.2.6).

In Asia, results from the cancer registry of Izmir, Turkey, were submitted for publication—the first incidence rates calculated for that country. The picture is dominated by tobacco-related cancer (in men) and breast cancer (in women). The data from the cancer registry of Karachi South (Pakistan) for 1995–97 were analysed [16]. The results suggest high rates of lung, oral cavity and larynx cancers in males and of breast and oral cavity cancers in females. Incidence data from the rural population-based cancer registry in Ambillikai, India, for 1996–98 reveal a very high risk of cervical cancer in females and a high incidence of oral cavity cancer in both sexes.

Survival data for different periods during 1980–91 from 10 cancer registries in five developing countries were analysed (see Section 1.5.1). Long-term (10 and 15 years from diagnosis) overall and stage-specific survival for cervical cancer in Bombay [568] and stage-specific survival for colorectal, prostate and head and neck cancers have been estimated. The results confirm the prognostic importance of clinical stage and socioeconomic status for cancer survival.

A database from collaborating cancer registries is maintained at IARC, for use in collaborative studies (with the permission of the registries). During the biennium, several studies have been completed or in progress. These include studies of time trends in the incidence of non-Hodgkin lymphoma in childhood [552] and of time trends in the

incidence of adenocarcinoma of the cervix [542]. A study of trends in squamous cell carcinomas of the cervix has been completed, as has an analysis of time trends in large bowel cancer. An analysis of time trends in the incidence of carcinoma of the oesophagus and gastric cardia, by histological type, is in progress.

1.2.4
Worldwide burden of cancer

D.M. Parkin, P. Pisani, J. Ferlay and F. Bray

Estimates of cancer incidence and mortality around 1990 for 25 cancers and all sites were published [349, 350]. A similar set of estimates of prevalence of cancer cases surviving 1, 3 and 5 years has been completed. The list of cancer sites considered has been expanded: separate estimates are available for cancers of the mouth, nasopharynx and pharynx, for non-Hodgkin lymphomas, Hodgkin's disease and multiple myeloma; additional sites included are brain and nervous system, thyroid and testicular cancer.

The most notable changes in the ranking of the cancer sites since 1985 are the rise in the more affluent countries of cancer of the prostate in men and of the lung in women. Similar trends are observed in mortality, with the number of deaths from cancer of the lung in women now close to that from colorectal cancer, and in men a marked increase in deaths from cancer of the prostate in developed countries. In developing countries, cancer of the liver shows an increase of 30% in men, possibly due to spread of infection with hepatitis C virus, while in women, breast cancer has overtaken cervix as the most common cancer.

The estimates of incidence and five-year prevalence, by sex and level of development, have been compared for selected cancer sites. Five-year prevalence measures the number of individuals alive at the same time who have had a cancer diagnosed within the preceding five years. It provides an indication of the number of patients in contact with health services at a particular time for treatment and clinical follow-up of their disease. The prevalence of cancer of the breast is over four times the number of new cases diagnosed every year in western countries. About three times as many annual new cases of prostate cancer in men and colorectal cancer in both sexes require medical monitoring. The numbers of individuals affected by cancers of the lung, liver or stomach, which are characterized by high fatality, are close to the numbers of newly diagnosed cases every year. The lower prevalence-to-incidence ratio in developing countries reflects less favourable survival due to the combination of late diagnosis and less effective treatment.

1.2.5
Cause-attributable cancer

P. Pisani, P. Boffetta, D.M. Parkin and E. Riboli; in collaboration with: H.-O. Adami, Stockholm, Sweden; D. Easton and N.E. Day, Cambridge, UK; M. Kogevinas, Barcelona, Spain; S. Rosso, Turin, Italy, H. Sancho-Garnier, Montpellier, France; and R. Saracci, Pisa, Italy

Rational planning of preventive interventions requires quantification of the number of cases which can theoretically be prevented by avoiding or reducing exposure to the causative agents.

The systematic evaluation of the amount of the cancer burden 'explained' and 'unexplained' by current knowledge has been extended and refined. The proportion of all cancers attributable to tobacco smoking has been estimated as 18% or 1.4 million new cases per year worldwide (29% in men and 6% in women) around 1990. In developing countries, at least 21% of all new cancer cases are due to infection with viruses (hepatitis B and C viruses, some human papillomaviruses, Epstein–Barr virus, HIV and HTLV-I), parasites (*Schistosoma* and liver flukes) or bacteria (*H. pylori*); the

corresponding figure in developed regions is estimated at 7% [350].

Systematic evaluation has also been undertaken of the following factors: diet, alcohol consumption, reproductive habits of women, obesity, drugs and exogenous sex hormones, occupational and environmental pollution, radiation and genetic factors. For each exposure/cancer association, a complete review of the literature has been performed to evaluate the evidence that the association is causal; data on the strength of the association (relative risk) are summarized by meta-analysis. The prevalence of the factor in the population is estimated from analytical studies and other sources. Percentage etiological fractions are then computed and applied to the estimated annual numbers of new cases and deaths. Detailed numerical results for countries of the EU have been completed for several factors (with support from the Europe Against Cancer programme). Figure 5 shows the proportion of cancers attributable to obesity by cancer site and sex. Overall excess weight explains only 3% and 6.4% of all cancers in men and women, respectively. We estimated high proportions of attributable cases only for cancers of the endometrium (39%), kidney (25% in men and 24% in women) and gall bladder (24% in both sexes). The proportions of cases in women resident in the EU attributable to low parity (less than 3 children) or delayed first pregnancy (age 30 years or later) were estimated at 11% of all female cancers; detailed etiological fractions are 28% of breast cancers, 29% and 37% of ovarian and endometrial cancers respectively.

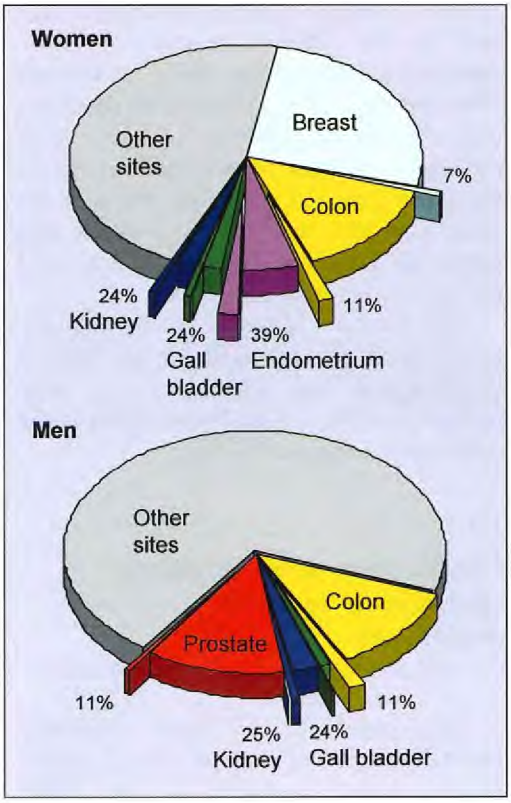

Figure 5. Proportions of cancers attributable to obesity by cancer site and sex

For each site, the thin slice represents the cases attributable to obesity.

1.2.6
Cancer in Africa

D.M. Parkin, S.L. Whelan, J. Ferlay and E. Bah: in collaboration with M. Hamdi-Chérif, Sétif, Algeria; F. Sitas, Johannesburg, South Africa; and H. Wabinga, Kampala, Uganda

Data on cancer patterns in Africa are sparse, but the considerable effort which has gone into fostering the development of population-based cancer registration in the continent is now bearing fruit. Despite the circumstances in which the registries work, with poor medical infrastructure and limited access to diagnostic services, medical and vital records and population denominators, the information they are producing gives a unique insight into cancer patterns in the continent.

A publication is being prepared that will include results from the cancer registries, published case-series and incidence data from the literature, and a comprehensive

review of cancer occurrence for selected sites and for the different regions in Africa. Editorial meetings were held in October 1998 and June 1999. During 1999 data from over 20 cancer registries in Africa were analysed and tables of incidence or relative frequency prepared. The final drafts of the country profiles, including all available data previously published for each country, and the site reviews were completed.

The estimates of incidence and mortality in Africa by country, available for 1990 in GLOBOCAN (see Section 7.1.7), were updated to 1995, and will be included in the publication, to appear in 2000.

1.2.7
Cancer genes: from families to epidemiology in world populations

D.E. Goldgar, G.M. Lenoir, C. Szabo and O. Sikilnikova

Our knowledge of genes conferring markedly increased susceptibility to cancer remains largely restricted to the highly industrialized countries of western Europe, North America and Australia. To examine the contribution of mutations in these genes to cancer in other populations, an IARC-coordinated effort has been initiated to investigate the mutational patterns and associated risks of known genes which predispose to cancers that are common in the industrialized world, but whose incidence is rising in developing nations. The focus is on recurrent mutations found in diverse populations, mutations unique to specific populations, and on the transfer of country-specific mutation detection methods to areas where they are not yet available. The next phase is to conduct population-based studies to examine the interaction between genes and environmental factors in determining cancer risk in these populations. Scientists from Iran, Algeria, Turkey, India, China and Mexico have received training in *BRCA1* and *BRCA2* mutation detection techniques. Collaboration with visiting scientists from Algeria, Brazil, China, Cuba, Iran, India, Mexico, Thailand and Turkey has already permitted identification of novel *BRCA1* mutations in Indian, Thai, Mexican, and Chinese breast cancer families.

1.3 Cancer incidence and mortality in migrant populations

Studies of migrant populations are of particular value in estimating the relative contributions of genetic and environmental factors in cancer etiology. In such studies, the risk of cancer in a migrant population is compared with that in persons of the same genetic background (living in the place of origin of the migrants), or with persons in the host country sharing a common external environment. The aim is to see how much the risk of cancer changes from that of the country of origin to that of the host country, and to determine how rapidly such changes occur.

1.3.1
Cancer in migrants to Australia

D.M. Parkin, P. Pisani and H. Garcia-Giannoli

The mortality data-set from Australia has been updated, so that it contains information on deaths from cancer for a 30-year period (1964–93). Each record contains information on cause of death, place of residence, place of birth, and date of migration to Australia. It is possible, therefore, to examine not only the variation in the risk of death from cancer according to birthplace, but also how this is modified by age at migration or the duration of residence in Australia. This information is

of relevance to etiological mechanisms (period of life at which environmental factors modify risk) and preventive strategies (how soon lifestyle modifications can change risk). This study is focusing upon cancers of the breast, stomach, colon-rectum and prostate.

1.4 Childhood cancer

Analysis of reliable and comparable data on childhood cancer incidence from around the world has revealed geographical and ethnic differences in risk that have provided clues as to the etiology of childhood cancers.

1.4.1 International Incidence of Childhood Cancer, volume 2

D.M. Parkin, E. Kramárová and E. Masuyer; in collaboration with G.J. Draper, Oxford, UK; J. Michaelis, Mainz, Germany; J. Neglia, Minneapolis, MN, USA; S. Qureshi, Islamabad, Pakistan; and C.A. Stiller, Oxford, UK

Following rigorous selection of high-quality data, 121 cancer registries in 56 countries around the world finally contributed. The data were analysed and classified according to International Classification of Childhood Cancer. The resulting publication [347] presents standard detailed tables containing data for the individual registries, or, for some countries, combined national data. To facilitate comparison of occurrence of different cancers, summary tables at the end of the publication list figures for selected tumour types in all contributing centres.

1.4.2 Descriptive studies of various aspects of cancer in childhood

D.M. Parkin, E. Kramárová and E. Masuyer; in collaboration with M. Linet, Bethesda, MD, USA; and C.A. Stiller, Oxford, UK

A series of studies dealing individually with the most common types of childhood cancer is planned; two are already under way. The large database from both volumes of *International Incidence of Childhood Cancer* (Section 1.4.1) is the foundation for these studies.

Work has started on estimation of the global incidence of childhood cancer. This involves estimating the numbers of cases and sex- and age-specific incidence rates in each country of the world, based on the available figures from about half of the world's

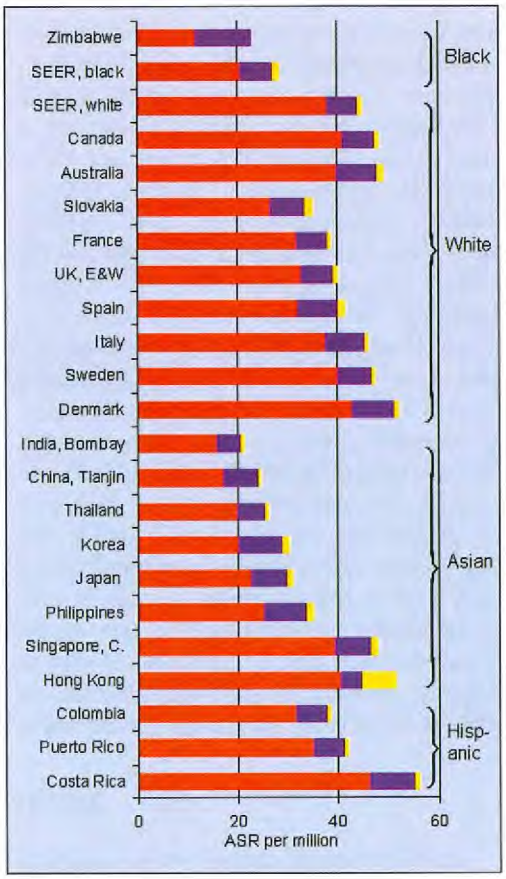

Figure 6. Age-standardized incidence of leukaemias in children: lymphoid; acute non-lymphocytic; chronic myeloid

countries. The method of estimation is analogous to that decribed in Section 1.2.4 [349]. An electronic publication presenting the results (GLOBOCANChild) is in preparation.

A study of the geographical distribution and time trends of childhood leukaemia incidence (Figure 6), based on 20 years of data, has been initiated.

1.4.3
Neonatal and childhood tumours

A.J. Sasco, M. Marsot, I. Gendre and A. van Rosmalen; in collaboration with D. Satgé, Tulle, France; F. Freycon, Saint-Etienne, France; and E. Robert, Lyon, France

The association between a genetic condition, Down's syndrome and childhood cancer is being examined. A study conducted in 11 European countries on neuroblastoma associated with Down's syndrome revealed a clear deficit. Among 6724 infants and children with neuroblastoma in Denmark, Finland, France, Germany, Iceland, Italy, Netherlands, Norway, Sweden, Switzerland and the United Kingdom, no cases of Down's syndrome were found although more than five were expected [452]. This contrasts with an excess of germ-cell tumours at several sites [455]. A deficit of some tumours such as stomach cancer is also seen in adult Down's syndrome patients and has led us to propose that a tumour-suppressor gene may be present on chromosome 21 [453]. To clarify such associations and examine others such as with brain tumours, a study is now being conducted in France in one of the largest institutes caring for Down's syndrome patients, looking at habitual life-style of these persons using simple questionnaires to be administered to the subjects and their families and care-takers.

Another axis of research is the effect of exposure to drugs *in utero* on neonatal occurrence of tumours. A comprehensive review has suggested some associations such as phenytoin with neuroblastoma, antibiotics with leukaemia, and hormonal treatment with vascular tumours [454]. A description of some pertinent cases has been published [445].

A review has been conducted on passive smoking and smoking in pregnancy and childhood cancer. Although current evidence of a link is weak, public health recommendations should aim at protecting foetuses and babies from tobacco smoke [450].

A case-control study of neonatal angiomas has been conducted in the three largest public obstetric units in Lyon to evaluate, in particular, the role of maternal diseases and exposures during pregnancy. Preliminary results based on 176 cases and 427 controls matched on date and hospital of birth indicate that slightly more girls than boys are affected and that the disease is more frequent among children born to mothers who had problematic pregnancies and had taken drug treatment. In addition, the risk of angiomas is higher among children born in families already affected by this disease.

A study has been initiated in the 1606 cases younger than 15 years at diagnosis and included in the childhood cancer registry based in Saint-Etienne, France, to look at survival and possibly also the occurrence of second events, recurrences, cancers and sequelae, following a first diagnosis of cancer in childhood.

1.5 Survival from cancer

Population-based cancer survival estimates of unselected groups of cancer patients permit valid and unbiased comparisons between populations. Though these cannot be used to assess the efficacy of specific treatments (which is the function of randomized clinical trials), they provide a measure of effectiveness of overall cancer diagnosis

and treatment services in a community. Comparison of survival between different populations and population-subgroups provides valuable leads for the planning and improvement of national and regional cancer control strategies. Only limited data are available on population-based survival from cancer in developing countries, despite the importance of such information for cancer control.

1.5.1 Survival from cancer in developing countries

R. Sankaranarayanan, D.M. Parkin and R. Sankila; in collaboration with E. Bah, Banjul, The Gambia; Y. Bhurgri, Karachi, Pakistan; R.J. Black, Edinburgh, UK; J. Chen, Qidong, China; J. Cherian and R. Rajkumar, Ambillikai, India; A. Echimane and A. Ahnoux, Abidjan, Côte d'Ivoire; D. Esteban, Manila, The Philippines; Fan Jin, Shanghai, China; M. Graupera and L. Fernandez Garrotte, Havana, Cuba; M. Hamdi-Cherif, Setif, Algeria; K. Jayant, B.M. Nene and A.M. Budukh, Barshi, India; H. Lee, K. Chia, and A. Cheow, Singapore; L. Levy, M. Bassett, B. Mauchaza and E. Chokunonga, Harare, Zimbabwe; V. Lornvidhaya and S. Srisukho, Chiang Mai, Thailand; D.D. Patel and D.V. Bala, Ahmedabad, India; A.C. Rodriguez, San Jose, Costa Rica; V. Shanta, C.K. Gajalakshmi and R. Swaminathan, Madras, India; S. Sriamporn and V. Vatanasapt, Khon Kaen, Thailand; H. Wabinga and S. Nambooze, Kampala, Uganda; and B.B. Yeole and L. Sunny, Bombay, India

Population-based cancer registries in Algeria, China, Costa Rica, Colombia, Côte d'Ivoire, Cuba, The Gambia, India, the Philippines, Singapore, Thailand, Uganda, Viet Nam and Zimbabwe are collaborating with IARC to study long-term and stage-specific survival from cancer. A mixture of both passive and active methods are used to collect information on vital status. The first comparable cancer survival data for 1982–91 from 10 participating registries have been published [418]. Age-standardized relative survival at five years from diagnosis for selected cancer sites in the 1980s is shown in Table 1.

For tumours associated with poor prognosis, such as oesophagus, stomach, liver, pancreas and lung, the differences observed in survival between populations were minimal. On the other hand, the differences between developed and developing country regions were marked for cancer sites such as leukaemia and lymphoma, for which intensive therapy has increased long-term survival in more affluent health services.

Studies are in progress to address stage-specific survival [419, 568], prognostic factors, methods to improve follow-up (particularly in Sub-Saharan Africa), issues in analysis, interpretation [22], comparability of data and factors responsible for observed variations in survival. A study of population-based survival in two countries in West Africa (Côte d'Ivoire and Gambia) and two in East Africa (Uganda and Zimbabwe) has been initiated. The prognostic importance of concomitant HIV infection will be addressed in Uganda and Zimbabwe.

Table 1. Age-standardized relative survival at five years from diagnosis for selected cancer sites in the 1980s

Registry	Stomach	Colorectum	Lung	Breast	Cervix	Leukaemia
Qidong	17.2	29.6	3.9	55.7	42.0	4.7
Shanghai	28.2	45.5	13.8	72.7	61.9	16.9
Cuba	–	37.2	10.2	57.9	54.3	21.3
Bangalore	–	–	–	44.1	39.9	22.6
Barshi	–	–	–	–	32.0	–
Bombay	–	37.1	–	55.1	49.5	–
Madras	7.5	–	7.9	48.4	56.7	20.6
Rizal	13.9	36.5	7.7	44.5	28.0	15.9
Chiang Mai	8.7	29.2	3.2	62.7	64.9	9.8
Khon Kaen	16.7	33.4	9.3	47.0	55.4	17.4
Europe	23.0	43.1	9.9	68.7	61.5	35.4
US SEER white	19.5	62.3	15.7	83.6	70.1	48.1

PART 2. ENVIRONMENTAL CAUSES OF CANCER

2.1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

J.M. Rice, R. Baan, M. Blettner, C. Genevois-Charmeau, Y. Grosse, D. McGregor, C. Partensky and J.D. Wilbourn. The following members of other units have contributed to the programme: E. Amoros, P. Boffetta, I. Bray, P. Brennan, E. Cardis, M. Friesen, J. Hall-Posner, Z. Herceg, A. Kesminiene, V. Krutovskikh, C. Malaveille, M. Mesnil, A.B. Miller, N. Muñoz, F. Nyberg, H. Ohshima, I. Persson, B. Rachet, E. Rapiti, A.J. Sasco, J. Smith, I. Thierry-Chef, P. Toniolo, E. Ward and R. Winkelmann

The *IARC Monographs* are founded on an international consensus approach to qualitative identification of environmental causes of human cancer. Each volume is produced by a working group of some 20 independent scientific experts from 8–10 countries. For an agent or exposure circumstance to be evaluated in the programme, there must be evidence or suspicion of cancer causation in humans or animals and documented human exposure. As new data become available, re-evaluations may be made. The seventy-six published volumes of *Monographs* contain evaluations of about 850 agents or exposure circumstances, based on critical reviews of the published scientific literature. Lists of evaluations and summaries of individual evaluations are available in searchable form on the Internet via the IARC home page (http://www.iarc.fr) or directly from the Monographs webserver (http://193.51.164.11) (see Section 7.1.8).

In addition to the *Monographs* themselves, the programme organizes scientific meetings on mechanisms of carcinogenesis and other topics relevant to evaluations of carcinogenic hazard, and ad-hoc meetings of scientific and public health experts to advise on priorities for evaluations and related matters. Six working group meetings and three advisory group meetings were convened during the period under review.

The programme also maintains, as an electronic publication accessible through the Internet, a *Directory of Agents being Tested for Carcinogenicity* (see Section 7.1.6).

2.1.1 Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide

(Volume 71, 17–24 February 1998)

A working group of 30 experts from 12 countries met to update and re-evaluate data on 121 organic compounds and groups of compounds, most of them industrial chemicals, that had previously been reviewed at least once within the *IARC Monographs* programme. Four of these compounds were evaluated as full monographs: acrylonitrile, 1,3-butadiene, chloroprene and dichloromethane. The remaining compounds were re-evaluated on the basis of data published since their most recent previous evaluations.

Acrylonitrile is a potent multi-site carcinogen in rats, and earlier epidemiological studies suggested an increased risk of lung cancer in exposed workers. More recent studies have not confirmed this risk, and acrylonitrile was re-evaluated as *possibly carcinogenic to humans (Group 2B)*, rather than Group 2A in which it had previously been placed. 1,3-Butadiene is also a potent multi-site carcinogen in rats and mice. Evaluation of the human carcinogenicity of butadiene hinges on evidence of leukaemia risks from one large and well-conducted study and two smaller studies, which neither support nor contradict the evidence from the larger study. This body of evidence does not allow assessment of the consistency of results

among two or more studies of adequate statistical power. Therefore the human evidence remained limited and butadiene remained classified as *probably carcinogenic to humans* (Group 2A). Chloroprene was re-evaluated as *possibly carcinogenic to humans* (Group 2B), on the basis of new bioassays that provide *sufficient evidence* of carcinogenicity in rats and mice. Dichloromethane remained classified as *possibly carcinogenic to humans* (Group 2B): bioassays for carcinogenicity by inhalation exposure in both mice and rats provided *sufficient evidence* for carcinogenicity to experimental animals.

For the remaining compounds, one or more lines of evidence for carcinogenicity were re-evaluated and the strength of the evidence was reclassified. In some cases, the result was a change in the overall evaluation.

2.1.2 Advisory group on physical agents

(27–29 April 1998)

An ad-hoc group of nine scientists from seven countries met in Lyon to consider the preparation of a series of IARC monographs on physical agents. Following discussion of human exposures to various forms of ionizing and non-ionizing radiation and the current state of research on each subject, the group recommended that the Monographs programme should include such physical agents in a series of four volumes. The first meeting was held in June 1999, on external sources of ionizing radiation: X-rays, gamma rays and neutrons (see Section 2.1.7). A second meeting (June 2000) will review internally deposited radionuclides, including α- and β-particle emitters.

Many epidemiological and laboratory studies are in progress on non-ionizing radiation. Evaluation in the Monographs programme will await publication of the results of these studies. Static and extremely low frequency (ELF) fields will be evaluated in the year 2001. Radiofrequency (RF) fields and radar are tentatively scheduled for 2003.

A meeting report was issued as IARC Internal Report No. 98/002.

2.1.3 Hormonal contraception and post-menopausal hormonal therapy

(Volume 72, 9–16 June 1998)

Re-evaluations of evidence relevant to carcinogenicity of some hormone preparations used for contraception or for therapy after menopause were made by a group of 25 experts from 10 countries. Oral contraceptives combined, a combination of a synthetic estrogen and a progestogen, were classified as *carcinogenic to humans (Group 1)*, chiefly on the basis of an increased risk for hepatocellular carcinoma in the absence of hepatitis virus infection observed in studies of predominantly high-dose preparations. The working group also noted that there is conclusive evidence that these agents have a protective effect against cancers of the ovary and endometrium. Progestogen-only contraceptives were classified as *possibly carcinogenic to humans (Group 2B)* on the basis of sufficient evidence in experimental animals.

For postmenopausal hormone therapy, natural estrogens are used, generally in combination with a progestogen. While for most anatomical sites the relationship between estrogen therapy and cancer risk is not clear, there is a clear increased risk of endometrial cancer after estrogen therapy. Whether this risk is removed by including a progestogen in the therapy remains unclear. In experimental animals, the evidence is sufficient for the carcinogenicity of estradiol-17β and estrone, limited for conjugated equine estrogens, equilin and estriol and inadequate for *d*-equilenin as well as for the estrogen combined with progestogen. Postmenopausal estrogen therapy was classified as *carcinogenic to humans (Group 1)* and post-

menopausal estrogen–progestogen therapy as *possibly carcinogenic to humans (Group 2B).*

2.1.4 Advisory working group on priorities for future IARC Monographs

(16–18 September 1998)

An ad-hoc advisory group of 12 experts from 10 countries met in Lyon to recommend priorities for agents and exposures nominated for future evaluations. Biological and physical agents were not addressed by this group.

For re-evaluations of agents or exposures previously considered, the advisory group determined that highest priority should be accorded to agents other than those already in Group 1, and that relevant data concerning agents in Groups 2A and 2B should be subjected to regular review to allow re-evaluations of these agents to be scheduled in a timely way. In re-evaluating previously covered industrial exposure circumstances, future working groups should address specific processes or chemicals, rather than whole industries or occupations.

A meeting report was issued as IARC Internal Report No. 98/004.

2.1.5 Some chemicals that cause tumours of the kidney or urinary bladder in rodents, and some other substances

(Volume 73, 13–20 October 1998)

A working group of 22 experts from nine countries met in Lyon to evaluate or re-evaluate 23 chemicals, some of which cause tumours of the urinary bladder in rats under conditions in which urinary calculi or phosphate-containing urinary precipitates are formed. Also evaluated were some substances that induce epithelial tumours of the renal cortex in male rats, under conditions in which alpha-2-urinary (α_{2u}) globulin nephropathy occurs. For both categories, questions have been raised about the predictive value of experimental carcinogenicity bioassays for identification of cancer hazard to humans. Also evaluated were two chemicals affecting the pituitary–gonadal axis in female rats. In making the overall evaluations, the working group specifically sought to apply the principles developed by a scientific advisory group that critically reviewed such issues at a meeting in November 1997 [81].

Substances re-evaluated with some change in the previous evaluation included atrazine, butyl benzyl phthalate, chlorothalonil, cyclamates, *ortho*- and *para*-dichlorobenzenes, hexachloroethane, *d*-limonene, melamine, paracetamol (acetaminophen), *ortho*-phenylphenol, saccharin and its salts, and simazine.

Saccharin and its salts were re-classified from Group 2B to Group 3, *not classifiable as to their carcinogenicity to humans*. The salts (but not the conjugate acid) are carcinogenic to the urinary bladder in male rats, but to no other organ or species. It was considered that the available data indicate that the irritant phosphate-containing urinary precipitate that may mediate carcinogenesis in rats cannot form in human urine and thus the rat tumours do not predict human carcinogenic hazard.

In addition, melamine causes bladder tumours in rats under conditions where urolithiasis occurs. Urinary tract calculi are a cancer hazard to humans, regardless of composition, and melamine was classified in Group 3, but with the condition that this evaluation applies only to circumstances in which no bladder stones develop.

d-Limonene was classified in Group 3, although it causes renal cortical tumours in male rats (and at no other site), because the α_{2u}-globulin nephropathy that leads to renal tumours in male rats does not occur in humans. However, *para*-dichlorobenzene, which also causes renal tumours in male rats by the α_{2u}-globulin nephropathy mechanism, remained classified in Group 2B, *possibly*

carcinogenic to humans, because it also causes liver tumours in mice, and the available data were inadequate to convince the working group that the liver tumours occurred by a mechanism that could be confidently considered not relevant to humans.

For eight other substances, no change was made in any element of the previous evaluation. Methyl *tert*-butyl ether and *meta*-dichlorobenzene were evaluated for the first time and considered *not classifiable as to their carcinogenicity to humans (Group 3)*.

2.1.6 Surgical implants and other foreign bodies

(Volume 74, 23 February–2 March 1999)

A working group of 22 experts from 10 countries met in Lyon to evaluate evidence on the carcinogenic risks of foreign bodies, surgical implants and prosthetic devices. This meeting was restricted to foreign bodies implanted in tissues; foreign objects within body cavities were not considered.

A wide range of metals and their alloys, polymers, ceramics and composites are used in surgically implanted medical devices and prostheses and dental materials. Most implanted devices are constructed of more than one kind of material. In addition, foreign bodies, such as bullets and pellets from firearms and metallic fragments from explosions may penetrate and remain in human tissues for long periods of time.

In the large number of patients with metallic implants that also include some nonmetallic components, a total of 34 cases have been reported of malignant neoplasms arising from bone or soft connective tissue in the region of the implant. Twelve cohort studies from six countries have investigated cancer incidence in patients following total knee or total hip replacement. One study showed a small increase, while the remaining ones showed a decrease in overall incidence. Four of the studies suggested an excess risk at specific sites. However, the other studies were not consistent with these observations. Neither of two case–control studies, one including cases with soft-tissue sarcoma, the other including lymphoma and leukaemia, showed an association with a history of an implant of complex composition.

Cohort studies of women treated with surgical prostheses made of silicone (or polyurethane-coated silicone) for cosmetic breast augmentation consistently found no evidence of increased risk of breast cancer. The combined results of the four largest cohort studies show a 25% reduction in risk.

One cohort study of dogs found no association between metallic implants used to stabilize fractures and the development of sarcomas. In contrast, there is an estimated annual incidence of 1–13 sarcomas per 10 000 vaccinated cats that are mostly associated with administration of recently introduced adjuvant-containing feline vaccines.

Numerous metals, alloys, ceramics and polymeric materials have been tested for carcinogenicity in mice and rats, often with positive results, and occasionally in other animal species, with generally negative findings.

Polymeric materials that persist for long periods and which also present a large surface area and a flat and smooth surface morphology generally induced a significantly increased incidence of sarcomas at the site of implantation in rats and mice. In most studies, perforated or foam materials or textiles induced lower incidences of sarcomas in comparison with flat films. Surface roughening decreases the incidence of local sarcomas. Segmenting or pulverizing polymeric materials significantly decreases local sarcoma incidences, often to nil.

Overall evaluations resulting in a classification of Group 2B (*possibly carcinogenic to humans*) were reached for (1) polymeric implants prepared as thin smooth films (with the exception of polyglycolic acid, which does not persist for long periods), (2)

metallic implants prepared as thin smooth films and (3) implanted foreign bodies consisting of metallic cobalt, metallic nickel and a particular alloy powder consisting of 66–67% nickel, 13–16% chromium and 7% iron. All other evaluations reached were for Group 3 (*not classifiable as to carcinogenicity to humans*). Specifically, Group 3 classifications were made for (1) organic polymeric materials as a group, (2) orthopaedic implants of complex composition and cardiac pacemakers, (3) silicone breast implants, (4) dental materials and (5) ceramic implants.

2.1.7

Ionizing radiation: Part I: X-rays, gamma rays, and neutrons

(Volume 75, 26 May–2 June 1999)

A working group of 18 experts from 11 countries met in Lyon for the first monograph meeting in a series on radiation (see Section 2.1.2). Evaluations were made of the evidence for the carcinogenicity of X-rays, γ-rays and neutrons from external sources.

The greatest exposure of the general population to X-rays and γ-rays comes from natural terrestrial radiation. The next most significant source is the use of X-rays and radiopharmaceuticals in diagnostic and therapeutic medical procedures.

The carcinogenic effects of ionizing radiation have been extensively investigated in human populations, mainly in epidemiological studies of survivors of the atomic bombings in Japan and patients exposed to radiation for medical reasons. In both groups, an excess number of cases of leukaemia and other cancers has been observed. Irradiation during childhood increases the risk of thyroid cancer, while an increase in breast cancer risk has been observed after irradiation of pre-menopausal women.

X-rays and γ-rays have been tested for carcinogenicity at various doses and under various conditions in several animal species. In adult animals, the incidences of leukaemia and of mammary, lung and thyroid tumours increased in a dose-dependent manner with both types of radiation. Prenatal exposure also gave rise to increased incidences of various types of tumour.

X-rays and γ-rays were classified as *carcinogenic to humans (Group 1)* on the basis of *sufficient evidence* for carcinogenicity in humans and in animals.

Exposure to neutrons normally occurs from a mixed irradiation field in which neutrons are a minor component. The exceptions are exposure of patients to neutron radiotherapy beams and exposure of aircraft passengers and crew. In high-altitude cities, neutrons can constitute as much as 25% of cosmic background radiation.

Neutrons with wide ranges of mean energy have been tested for carcinogenicity in several animal species, at various doses and dose rates. In adult animals, the incidences of leukaemia and ovarian, mammary, lung and liver cancer increased in a dose-related manner. Prenatal and parental exposure resulted in increased incidences of liver tumours in the offspring. In almost all studies, neutrons were more effective in inducing tumours than were X-rays and γ-rays in terms of absorbed dose.

There are no adequate epidemiological data on which to evaluate whether neutrons are carcinogenic to humans. On the basis of *inadequate evidence* for carcinogenicity in humans and *sufficient evidence* for carcinogenicity in animals, the working group classified neutrons as carcinogenic to humans *(Group 1)*, taking into consideration that:

(i) when interacting with biological material, neutrons generate α-particles and γ-radiation, which are human carcinogens;

(ii) gross chromosomal aberrations are induced in the lymphocytes of people exposed to neutrons;

(iii) the spectrum of DNA damage due to neutrons is similar to that of X-rays, but contains relatively more of the less readily reparable types;

(iv) every relevant biological effect of X- or γ-radiation that has been examined has been found to be induced by neutrons;

(v) neutrons are several times more effective than X- and γ-radiation in inducing genetic damage.

The classification of neutrons as a human carcinogen is the first example of a *Group 1* evaluation based solely on animal cancer data supported by other relevant information.

2.1.8

Some antiviral and antineoplastic drugs and other pharmaceutical agents

(Volume 76, 12–19 October 1999)

A working group of 17 experts from 8 countries met in Lyon to evaluate some antiviral (including antiretroviral) drugs, some members of the topoisomerase inhibitor class of antineoplastic agents and other pharmaceutical drugs. This was the first evaluation of nucleoside analogues that act as antiviral agents, and was stimulated in part by recent findings that zidovudine (AZT), an effective antiretroviral agent now given to pregnant women infected with human immunodeficiency virus (HIV) to prevent viral transmission to the fetus, is a transplacental carcinogen in mice. The antiretroviral nucleoside analogues AZT, zalcitabine (DDC) and didanosine (DDI), and the antiherpesvirus drug aciclovir were evaluated. The topoisomerase inhibitors/antitumour drugs etoposide (alone and in combination with bleomycin and cisplatin), teniposide, mitoxantrone and amsacrine were also evaluated, as were vitamin K substances (acetomenaphthone, menadione, menadiol sodium phosphate and phytomenadione), hydroxyurea and phenolphthalein. Vitamin K substances are used in bleeding disorders. Hydroxyurea is used in the treatment of myeloproliferative disorders and has also been given to HIV-infected persons in combination with didanosine. Phenolphthalein was used until recently in over-the-counter laxative preparations.

Etoposide given in combination regimens with cisplatin and bleomycin was evaluated as carcinogenic to humans (Group 1). Etoposide and teniposide were evaluated as probably carcinogenic to humans (Group 2A); in making these evaluations data on mechanistic considerations were taken into account. Mitoxantrone, amsacrine, zidovudine, zalcitabine and phenolphthalein were classified as possibly carcinogenic to humans (Group 2B). The remaining agents (aciclovir, didanosine, hydroxyurea and vitamin K substances) could not be classified as to their carcinogenicity to humans (Group 3).

2.1.9

Advisory group on the predictive value of gastric neuroendocrine and forestomach tumours in rodents

(29 November – 1 December 1999)

An advisory group met in Lyon to critically assess the predictive value of rodent forestomach tumours and of tumours of gastric neuroendocrine cell origin in evaluating carcinogenic risks to humans. The forestomach is an organ present in rodents but not in humans and is a frequent site of carcinogenesis in rodents. It is difficult to predict carcinogenic risk to humans from the few agents that induce tumours in rodents at this organ site alone and lack demonstrable genotoxicity, as the underlying mechanism(s) of carcinogenic action are not fully known. Such agents must be evaluated on a case-by-case basis. Neuroendocrine cell tumours of the stomach may be induced by some chemicals in rodents by apparently non-genotoxic endocrine mechanisms. It is not fully understood how corresponding human tumours arise. Induction of such tumours, irrespective of mechanism, may predict human cancer risk, but a consensus was not reached on this issue. The proceedings of the meeting include individually authored papers, a series of case studies on chemicals producing these tumours in rats, mice, or other species and a consensus report.

2.2 *Occupational causes of cancer*

Occupational cancers have long been a focus of attention in research on the etiology and mechanisms of cancer because individual exposures, and therefore risks, in the work environment tend to be higher than in the general environment. In addition, the exposed population can be relatively easily defined, and exposures can be estimated from measurements or known characteristics of the work environment.

Studies at IARC have adopted two main approaches: on the one hand, multicentric international studies have been conducted, mainly in industrialized countries, to investigate effects of either low-level exposure to known carcinogens or suspected carcinogens with relatively weak potency; on the other hand, collaborative studies have been conducted in specific circumstances in developing countries, where high levels of exposure are often encountered but the conduct of studies focused on occupational risks may be problematic (Figure 7). These studies in developing countries are based on the case–control approach, and are listed by cancer site.

In addition, IARC has been active in methodological developments in the field of occupational epidemiology, in particular with respect to mortality of short-term workers [48] and on the use of meta-analysis in occupational epidemiology [176]. Extensive reviews have also been prepared on occupational risk factors of cancer [3, 50, 52, 355–359, 361, 549]; on occupational cancer in Europe [42] and on cancer risk in the rubber industry [245].

Figure 7. Textile dyeing in Ahmedabad, India. Protection against occupational exposures is often neglected in developing countries.

2.2.1 Workers exposed to phenoxyacid herbicides and contaminants

P. Boffetta, P. Brennan and D. Colin; in collaboration with H. Becher, Heidelberg, Germany; T. Benn, Bootle, UK; P.A. Bertazzi, Milan, Italy; H.B. Bueno de Mesquita, Bilthoven, The Netherlands; D. Coggon, Southampton, UK; M. Fingerhut and K. Steenland, Cincinnati, OH, USA; D. Flesch-Janys, Hamburg, Germany; L.M. Green, Toronto, Canada; D. Heederik, Wageningen, The Netherlands; T. Kauppinen, Helsinki, Finland; M. Kogevinas, Barcelona, Spain; M. Littorin, Lund, Sweden; E. Lynge, Copenhagen, Denmark; J.D. Mathews, Casuarina, Australia; M. Neuberger, Vienna, Austria; N. Pearce, Wellington, New Zealand; R. Saracci, Pisa, Italy; and J. Vena, Buffalo, NY, USA

Excesses of soft-tissue sarcoma and non-Hodgkin lymphoma have been observed in populations exposed to phenoxyacid herbicides, chlorinated phenols and dioxins during manufacture, spraying or accidents. Dioxins present as contaminants in some types of phenoxyacid herbicide, in particular 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), have been suggested as a causal factor, although excess risks have also been associated with exposure to herbicides believed not to have been contaminated with dioxins. IARC coordinates a cohort study of workers exposed to phenoxy herbicides, chlorophenols and dioxins in pesticide manufacturing and spraying. Following the publication of the cancer mortality follow-up, analyses of deaths from other causes showed increased risks of ischaemic heart disease (RR = 1.67) and diabetes (RR = 2.25) among TCDD-

exposed workers, compared with workers with minimal or no TCDD exposure [530].

TCDD serum levels are available for sizable subgroups of workers in this cohort in three countries. An analysis in the Dutch cohort identified three main determinants of serum TCDD level: duration of employment in main production, exposure before 1970 and presence at the time of an industrial accident [201]. These factors explained 85% of the variance of TCDD serum levels and were applied to all cohort members to derive estimates of TCDD exposure. This estimated exposure was associated with a linear increase in the risk of lung cancer, non-Hodgkin lymphoma and ischaemic heart disease (Figure 8). A similar analysis of the combined data-set of the three countries (Germany, the Netherlands and the United States) with serum measurements is planned.

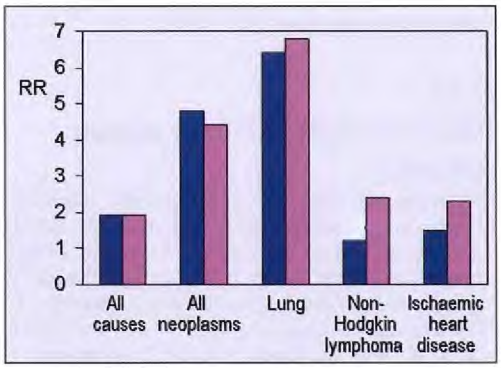

Figure 8. Mortality by estimated TCDD level among herbicide workers from the Netherlands

Reference category: <7.2 ppt. 7.2–124.1 ppt; >124.1 ppt

2.2.2

Workers employed in the man-made vitreous fibre production industry

P. Boffetta, D. Sali and G. Ferro; in collaboration with A. Andersen and K. Kjaerheim, Oslo, Norway; P.A. Bertazzi and D. Consonni, Milan, Italy; J. Chang-Claude, Heidelberg, Germany; J. Cherrie, Edinburgh, UK; R Frentzel-Beyme, Bremen, Germany; K. Guldner, Würzburg, Germany; J. Olsen and J. Hansen, Copenhagen, Denmark; N. Plato, Stockholm, Sweden; R. Saracci, Pisa, Italy; L. Teppo, Helsinki, Finland; P. Westerholm, Solna, Sweden; and P. Winter, Southampton, UK

Occupational exposure to man-made vitreous fibres may entail a risk of lung cancer [30]. In a cohort study of European workers of the man-made vitreous fibres study, an increased risk of lung cancer has been detected that, however, did not show a dose–response relationship between lung cancer mortality and estimated cumulative fibre exposure, when short-term workers were excluded and time since first exposure was accounted for [119]. A case–control study of lung cancer has been conducted in the rock/slag wool component, to disentangle the contributions to the lung cancer excess of fibres, other occupational agents such as asbestos, and extra-occupational factors such as tobacco smoking. This study concerns 200 cases of lung cancer and over 800 controls. Analysis of cancer incidence until 1995/1996 among workers from Denmark, Finland, Norway and Sweden confirmed the results of the mortality analysis in suggesting a possible association between rock/slag wool exposure and lung cancer risk [36]. No association was detected between rock/slag wool or glass wool exposure and the risk of other neoplasms. Analysis of non-neoplastic mortality showed no increase in risk of bronchitis, emphysema or asthma (SMR 1.03) [414]. While there was no overall excess mortality from non-malignant renal diseases (SMR 0.97), there was a small increase in risk with duration of employment. Similarly, mortality from ischaemic heart disease was not increased overall (SMR 1.03), but workers with long latency or highest estimated fibre exposure had a higher risk.

2.2.3

Workers employed in the pulp and paper industry

P. Boffetta, P. Brennan and D. Colin; in collaboration with A. Andersen, Oslo, Norway; A. Bergeret, Lyon, France; D. Coggon and B. Pannett; Southampton, UK; L.A. Facchini, Pelotas, Brazil; P.K. Henneberger,

Morgantown, WV, USA; P. Jäppinen, Imatra, Finland; T. Kauppinen and T. Liukkunen, Helsinki, Finland; D. Kielkowski, Johannesberg, South Africa; E. Lynge, Copenhagen, Denmark; H. Miyaki, Sapporo, Japan; N. Pearce, Wellington, New Zealand; B. Persson, Linköping, Sweden; L. Settimi, Rome, Italy; J. Sunyer and M. Kogevinas, Barcelona, Spain; I. Szadkowska-Stanczyk, Lodz, Poland; K. Teschke, A. Keefe and G. Astrakaniakis, Vancouver, Canada; and H. Westberg, Örebro, Sweden

A multicentric international cohort study is being conducted among personnel employed in plants producing pulp, paper and paper products and in mills involved in recycling are included. The study has been completed in Brazil, Denmark, Finland, France, Italy, Japan, New Zealand, Norway, Poland, South Africa, Spain, Sweden, the United Kingdom and the United States. The results for the combined study population of over 100 000 workers show a lower risk among these workers compared with the respective national populations. Excesses were seen for pleural neoplasms, soft-tissue sarcomas and male genital tract cancers (Figure 9). An industrial hygiene study is being conducted [500], that will be used to derive mill- and department-specific estimates of exposure to 41 chemicals and groups of chemicals.

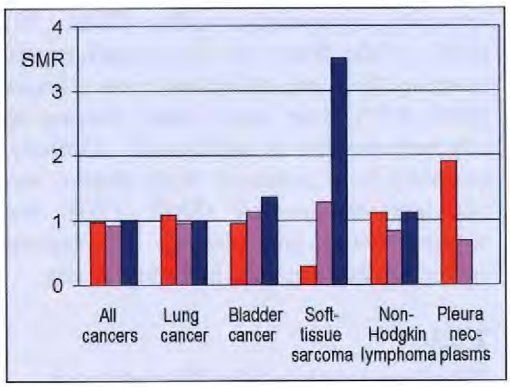

Figure 9. Mortality from selected neoplasms among workers in pulp, paper and paper product manufacture

2.2.4 Workers employed in the wood and leather industries

P. Boffetta, A. 't Mannetje and D. Colin; in collaboration with P. Demers, Vancouver, Canada; M. Kogevinas, Barcelona, Spain; A. Leclerc, Paris, France; and S. Stellman, New York, NY, USA

Employment in the wood and leather industries entails exposures that are carcinogenic to humans. The main target sites in both cases are the nose and the nasal sinuses. However, the role of specific exposures such as wood dust, leather dust, formaldehyde, solvents and wood preservatives is not clear. Following the completion of a pooled analysis of relevant cohort and case–control studies [142], an analysis has been conducted on the data of the American Cancer Society prospective study. The results showed increased risks of cancers of the lung, prostate and brain and of non-neoplastic respiratory diseases [143, 491]

2.2.5 Workers employed in the asphalt industry

P. Boffetta, I. Burstyn, M. Castegnaro and C. Genevois-Charmaud; in collaboration with S. Binet, P. Bonnet and M. Lafontaine, Vandoeuvre, France; H. Brandt, Amsterdam, The Netherlands; M. de Méo, Marseille, France; R. Frentzel-Beyme, Bremen, Germany; D. Heederik and H. Kromhout, Wageningen, The Netherlands; B. Jarvholm, Umeå, Sweden; T. Kauppinen, T. Partanen and P. Heikkilä, Helsinki, Finland; A.J. Kriech, Indianapolis, IN, USA; S. Langard, Oslo, Norway; A. Pfohl-Leszkowicz, Toulouse, France; J. Shaham, Raanana, Israel; I. Stücker, Paris, France; and O. Svane, Copenhagen, Denmark

The investigation of a possible cancer risk from exposure to asphalt fumes is particularly difficult because of the complex and variable nature of asphalt, the occurrence of co-exposures (motor engine exhaust, tobacco smoking) and the characteristics of the workforce (seasonal employment, instability, low skill). A historical cohort study was initiated in 1996 in Denmark, Finland, France, Germany, Israel, the Netherlands, Norway,

Sweden. The study has been completed in Finland, France, Israel and Sweden, and should be completed in the remaining countries in early 2000, after which combined statistical analyses will be carried out.

Extensive published and unpublished data on occupational exposure of asphalt workers have been compiled. Company questionnaires have been completed in each participating company, and an assessment of exposure to bitumen fumes and other agents present in the working environment is in progress, which will allow assignment of individual indices of exposure to cohort members.

Further analysis, in collaboration with Shell, the Institut National de Recherche et de la Sécurité (INRS) and the Heritage Research Group (United States), has been performed on bitumen and coal-tar fumes to explain the results on DNA adduct formation in rats [57, 64] With nose-only inhalation, a DNA adduct was induced in the lung that corresponded to the major one induced in the lung and on the skin of animals treated by skin application of bitumen fume condensates. A new study has been initiated at INRS in collaboration with IARC to develop an improved fume generation system and to expose BigBlue™ mice and rats to various concentrations of fumes for different length of time in order to measure DNA adducts and mutations at target organs.

The Ah receptor has been found to play an important role in the biotransformation of both bitumen and coal-tar fumes [172]. CYP1A isoforms (1A1 and 1A2) are not exclusively responsible for the genotoxicity of the condensates. These CYPs are both involved in the genotoxicity of compounds found in coal-tar vapours, and the reactive metabolites formed via CYP1A1 are substrates for microsomal epoxide hydrolase. In the case of bitumen fumes, genotoxicity is dependent on CYP1A1 alone, and the reactive metabolites are not substrates for microsomal epoxide hydrolase, whereas CYP1A2 may have detoxifying activity or no activity at all for these compounds.

2.2.6

Workers exposed to inorganic mercury

P. Boffetta, P. Brennan and D. Colin; in collaboration with T. Bellander, Stockholm, Sweden; M. Garcia-Gomez, Madrid, Spain; E. Merler, Florence, Italy; V. Pompe-Kirn, Ljubljana, Slovenia; G. Sallsten, Gothenburg, Sweden; and D.G. Zaridze, Moscow, Russian Federation

An increase in lung cancer risks has been suggested in a number of epidemiological studies of workers exposed to mercury in mining or milling of the metal, thermometer production and felt-hat manufacture. IARC has coordinated a historical cohort study of workers involved in these occupations in Italy, Slovenia, Spain and Ukraine. Special care was given to the reconstruction of industrial hygiene data. The analysis of cancer mortality suggested an increased risk of lung cancer mortality that was not associated with estimated mercury exposure. A possible increase in liver cancer mortality was not confirmed by the analysis of cancer incidence [40]. An analysis of non-neoplastic mortality showed increased mortality from hypertension (SMR 1.46), heart diseases other than ischaemic (SMR 1.36), pneumoconiosis (SMR 27.1) and chronic renal disease (SMR 1.55). Mortality from hypertension and other heart diseases increased with time since first employment and estimated cumulative mercury exposure; mortality from ischaemic heart disease and cerebrovascular diseases increased with time since first employment and with duration of employment, but not with estimated exposure.

2.2.7

Workers exposed to vinyl chloride

P. Boffetta, E. Ward, D. Colin and D. Sali; in collaboration with A. Andersen and S. Langard, Oslo, Norway; S. Belli and R. Pirastu, Rome, Italy; G. Engholm and I. Lundberg, Stockholm, Sweden; L. Hagmar, Lund, Sweden; and J. Hodgson, Bootle, UK

An international cohort study of cancer mortality and incidence among workers exposed to vinyl chloride has been updated,

to enhance the statistical power to evaluate the risk of neoplasms other than liver angiosarcoma possibly linked to vinyl chloride, such as hepatocellular carcinoma and brain tumour, with 12 additional years of follow-up. The increase in mortality from liver cancer was confirmed, but was due only to an excess of angiosarcoma. No increase in mortality from lung or brain cancer was found. Excess risks of melanoma and soft-tissue sarcoma were detected, based on small numbers of cases (Figure 10).

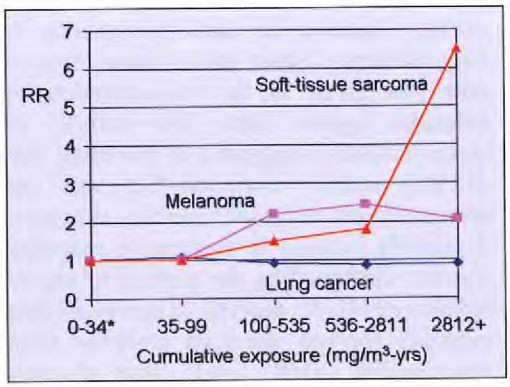

Figure 10. Mortality from non-hepatic neoplasms by cumulative exposure to vinyl chloride: European multicentric study

* Reference category.

2.2.8

Biology research laboratory workers

A.J. Sasco and B. Rachet; in collaboration with A. Ahlbom and H. Wennborg, Stockholm, Sweden; A. Andersen, Oslo, Norway; S. Belli, Rome, Italy; S. Benhamou and A. Laplanche, Villejuif, France; F. Berrino, Milan, Italy; C. Chilvers and T. Brown, Nottingham, UK; B. Herity and L. Daly, Dublin, Ireland; T. Kauppinen, Helsinki, Finland; J.J. Moulin, Vandoeuvre-les-Nancy, France; P. Pajot, Paris, France; M. Tirmarche, Paris, France; F. van Leeuwen and T. van Barneveld, Amsterdam, Netherlands; and D. Vecchio, Genoa, Italy; supported by the Europe Against Cancer and BioMed programmes of the European Union

Following the occurrence of several cancer clusters at various research institutions and confronted with the lack of any large-scale assessment of cancer risk linked to occupational exposure to biological agents, a retrospective cohort study of all staff (approximately 45 000) employed for at least one year and one day in public research institutions in eight European countries (Finland, France, Ireland, Italy, the Netherlands, Norway, Sweden and the United Kingdom) was performed. The mortality and incidence data from Sweden confirm results previously published from other centres such as Rome, Italy, Ireland, the Netherlands and the United Kingdom, with a low overall death rate. However, some excesses were found for brain tumours in male and breast cancer in female scientists in biomedical research laboratories [555]. Similarly, preliminary results from the final analysis of the whole cohort are quite reassuring [448]. Overall, a large mortality and global cancer deficit is seen, resulting in part from the healthy worker effect, as well as that of social class. However, there are some excesses for specific cancers in certain subgroups. Final results will be available in 2000. The issues of ensuring validity [432] as well as confidentiality [446] of the data in all centres in large international studies have been reviewed.

2.2.9

Asbestos exposure and mesothelioma risk in Europe

P. Boffetta; in collaboration with A. Biggeri and E. Merler, Florence, Italy; A. Burdorf, Rotterdam, The Netherlands; M. Goldberg, Paris, France; and J. Siemiatycki, Montreal, Canada

Asbestos is the main cause of pleural and peritoneal mesothelioma [480]. Following a meeting of European investigators [37], a project was initiated with the aims of describing the patterns of asbestos use and of mesothelioma incidence and mortality in European countries. Based on mortality data, models are being developed to predict future trends, and to study detailed aspects of the asbestos–mesothelioma relationship, including

the pattern of risk after cessation of exposure. Results are expected in 2000.

2.2.10

The burden of occupational cancer in Europe

P. Boffetta and P. Brennan; in collaboration with A. Andersen, Oslo, Norway; W. Ahrens and K.H. Jockel, Hessen, Germany; L. Barlow, Stockholm, Sweden; F. Berrino, Milan, Italy; R. Cartwright, Leeds, UK; J. Chang-Claude, Heidelberg, Germany; S. Cordier and D. Luce, Paris, France; C.A. González and J. Sunyer, Barcelona, Spain; T. Kauppinen, Helsinki, Finland; M. Kogevinas, Barcelona, Spain; E. Lynge and J. Olsen, Copenhagen, Denmark; F. Merletti and P. Vineis, Turin, Italy; T. Partanen and E. Pukkala, Helsinki, Finland; L. Simonato, Padua, Italy; and T. Tzonou, Athens, Greece

The prevalence and intensity of occupational carcinogenic exposures and the incidence of occupational cancer in countries of the European Union have been estimated, as a basis for a comprehensive programme of prevention and control of occupational cancer in Europe. The estimated prevalence of exposure in 1990 was 23% of the European workforce (inter-country range 17–27%) [243]. In addition, combined analyses of data from previous European case–control studies yielded the following estimates of proportions attributable to occupational exposures: sinonasal cancer, 41% in men and 7% in women; bladder cancer, 4–10% and 0–9%; laryngeal cancer, 8% and 0%; and lung cancer, 13% and 3%.

2.2.11

Occupational cancer in women

P. Boffetta, A. 't Mannetje and P. Brennan; in collaboration with E. Lynge, Copenhagen, Denmark; H. Gunnarsdottir, Reykjavik, Iceland; M. Kogevinas, Barcelona, Spain; A. Miranda, Lisbon, Portugal; T. Partanen, Helsinki, Finland; L. Settimi and R. Pirastu, Rome, Italy; E. Roman, Leeds, UK; and E. Weiderpass, Stockholm, Sweden

Relatively few epidemiological studies have specifically examined cancer risks among female workers and these studies have tended to be inconclusive, largely because insufficient numbers of events were studied [473, 554].

A project was carried out in the Nordic countries, England and Wales and in Italy. An evaluation of the feasibility of analysis of data on women's occupation and cancer in other countries highlighted the poor recording of women's occupation in cancer registration and other routine data-sets. A joint protocol was developed including the definition of standard occupational/industrial groups, a list of cancers to be evaluated and development of an *ad hoc* job–exposure matrix. The type of data available did not allow construction of a unique European database and analysis was done separately, using distinct statistical techniques. Women working in several high-risk occupations (identified from studies in men) were found also to have a higher risk for cancer. This was the case for bladder cancer in the rubber industry; lung cancer in occupations with high prevalence of active smoking and high exposure to environmental tobacco smoke, such as journalists and waitresses; pleural cancer in occupations such as craft and other production processes with high potential for asbestos exposure; and non-Hodgkin lymphoma in agricultural workers. Excess risks were also found for breast, skin and melanoma in clerical workers; cervical and ovarian cancer in shop workers; larynx, lung and cervix cancers in building caretakers and cleaners; lung cancer in gardeners; breast, melanoma and other skin cancers in teachers; colon and skin cancers in assistant nurses; lip and cervical cancer in home helpers; colorectal, bladder and cervical cancer in textile workers; and non-Hodgkin lymphoma and multiple myeloma among farmers. Various occupations showed excess risks for female reproductive system cancers such as health-related occupations, but findings were not consistent concerning specific occupational exposures and risks for those cancers. In particular, for ovarian cancer, associations were seen with exposure to aromatic hydro-

carbon solvents, leather dust, man-made vitreous fibres, asbestos and gasoline [529]. A similar analysis of breast cancer suggested that occupational exposure to ionizing radiation poses an increased risk [551]. Analyses of various data sets on female occupational cancer indicate that approximately 3% of lung cancer in women and between 0% to 9% of bladder cancer can be attributed to occupation.

2.2.12

Workers exposed to crystalline silica

K. Steenland, A. 't Mannetje, and P. Boffetta; in collaboration with H. Checkoway, Seattle, WA, USA; J.Q. Chen, Hubei, China; J. Costello, Morgantown, WV, USA; N. De Klerk, Perth, Australia; M. Dosemeci, MD, Bethesda, USA; E. Hnizdo, Johannesburg, South Africa; L. Stayner, Cincinnati, OH, USA; and G. Swaen, Maastricht, The Netherlands

A pooled historical cohort study of workers exposed to crystalline silica was initiated in 1998 (*a*) to develop exposure–response data for lung cancer across a number of studies and (*b*) to increase the power to detect rarer outcomes such as lymphoma and kidney disease. A total of 10 cohorts from different countries are included. A common measure of exposure has been developed. Lung cancer risk showed a linear increase with estimated cumulative exposure to crystalline silica in the combined data-set, but not in the separate groups of underground miners and other workers (Figure 11).

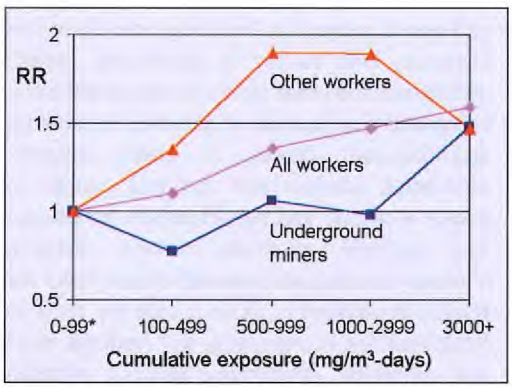

Figure 11. Relative risk of lung cancer according to estimated cumulative exposure to crystalline silica

* Reference category.

2.2.13

Workers employed in the meat industry

P. Brennan and P. Boffetta; in collaboration with W. Ahrens, Bremen, Germany; A. Andersen, Oslo, Norway; D. Coggon, Southampton, UK; F. Forastiere, Rome, Italy; L. Fritschi, Melbourne, Australia; H. Gunnarsdottir, Reykjavik, Iceland; D. Heederik, Wageningen, The Netherlands; J. Olsen and H. Hansen, Copenhagen, Denmark; T. Partanen, Helsinki, Finland; N. Pearce, Wellington, New Zealand; and I. Stücker and J. Clavel, Paris, France

Epidemiological evidence has suggested an increased risk of cancers of the lung and larynx and of lymphohaematopoietic neoplasms among butchers, slaughterhouse workers and other meat workers. Previous studies have addressed, often with limited power, exposure to polycyclic aromatic hydrocarbons and nitrosamines. However, additional agents are worth investigation, including animal viruses and organic dusts. The feasibility of conducting a large cohort study of meat workers in Europe and Oceania has been examined. On the basis of this, a larger retrospective cohort study is now being planned which should have sufficient power to analyse the risk of lung cancer and lymphatic neoplasms in subgroups of workers defined according to job tasks or exposure to specific agents. A cross-sectional component will also be conducted to measure the prevalence of infection with various animal viruses among meat workers.

2.2.14

Workers in the titanium dioxide industry

P. Boffetta and V. Gaborieau; in collaboration with A. Andersen and S. Langard, Oslo, Norway; M. Blettner, Bielefeld, Germany; D. Luce, Paris, France; F. Merletti and D. Magnani, Turin, Italy; B. Miller and J. Cherrie,

Edinburgh, UK; E. Pukkala and A. Anttila, Helsinki, Finland; and E. Weiderpass, Stockholm, Sweden

Titanium dioxide is a white pigment widely used in paints and plastic products. Experimental studies have shown an increased incidence of lung tumours in rats, but no adequate epidemiological studies have been conducted. A historical cohort study of workers exposed to titanium dioxide has been initiated in five European countries.

2.2.15 Other collaborative studies of occupational cancer

P. Boffetta; in collaboration with M. Bulbulyan, Moscow, Russian Federation; S. Lea, Berkeley, CA, USA; and L. Settimi, Rome, Italy

A number of additional projects have been conducted based on bilateral collaborations. A methodological exercise has been conducted on the data collected within two studies of styrene and man-made vitreous fibre workers (see Section 2.2.2), to assess the contributions of occupational and extra-occupational factors to the origin of higher mortality among workers with less than one year of employment compared with longer-term workers [48]. Analysis of the healthy-worker effect among women employed in the man-made vitreous fibre cohort revealed that this part of the workforce is particularly vulnerable to the healthy-worker survival effect [256]. A cohort study of shoe workers in the Russian Federation exposed to chloroprene revealed an increased risk of liver cancer [73], that was confirmed in a further study of chloroprene production workers [74]. A hospital-based case–control study among women in five rural areas of Italy suggested an increased risk of malignant melanoma, bladder cancer and a decreased risk of postmenopausal breast cancer [472]. A meta-analysis of studies of asbestos exposure and kidney cancer risk revealed a possible weak carcinogenic effect at high levels of exposure [413]

2.3 Diet, nutrition, hormones and cancer

Western diet and lifestyle are generally associated with high incidence of cancers of the colorectum, breast, prostate and endometrium, but low incidence of cancers of the stomach, oesophagus, liver and cervix uteri. In most developing countries of Asia and Latin America, however, the pattern of cancer incidence is almost the opposite. The balance between different types of food appears to be as important as the absolute intake of any single food. Dietary patterns characterized by high intake of vegetables and fruit are associated with a reduced risk of cancers of the digestive and respiratory tracts and possibly of other cancer sites (breast), while diets characterized by high intake of meat, particularly red meat and animal fat, are associated with an increased risk of cancer of the colon and rectum. Certain foods consumed in limited geographical areas have been found to increase the risk of specific cancers, e.g., salted and fermented fish and nasopharyngeal cancer in some areas of south-east Asia. Epidemiological and laboratory research is now attempting to identify the specific food constituents which are biologically responsible for these complex effects of either reduction (vegetables and fruit) or increase (meat and meat products) in cancer risk.

Some metabolic factors related to nutritional status, such as obesity and physical activity, also appear to contribute to the risk of certain cancers, as seems to be the case for cancer of the breast after menopause and cancer of the endometrium at any age. Prospective studies have lent strong support to the hypothesis formulated decades ago

regarding the prominent role of endogenous hormone levels in determining risk of breast cancer. Variations in patterns of estrogens, androgens, insulin-like growth factors (IGFs) and their binding proteins are probably determined by both nutritional and lifestyle factors, but also by inherited genetic characteristics, as suggested by studies on polymorphisms of genes encoding for enzymes that regulate steroid hormone metabolism and hormone receptors.

2.3.1

European Prospective Investigation into Cancer and Nutrition (EPIC)

E. Riboli, R. Kaaks, N. Slimani, R. Charrondière, P. Ferrari, A.L. van Kappel, E. Kramárová, C. Casagrande and B. Hémon; in collaboration with: *Denmark*: A. Tjønneland, Copenhagen; K. Overvad, Aarhus; *France*: F. Clavel, M. van Liere and C. Guibout, Villejuif; *Germany:* H. Boeing and A. Kroke, Potsdam; A.B. Miller, J. Wahrendorf and N. Becker, Heidelberg; *Greece:* A. Trichopoulou and K. Katsouyanni, Athens; *Italy:* F. Berrino and V. Krogh, Milan; P. Vineis and B. Terracini, Turin; D. Palli and E. Buiatti, Florence; R. Tumino and L. Gafà, Ragusa, S. Panico, Naples; *The Netherlands:* P. Peeters, Utrecht; H.B. Bueno de Mesquita, J. Seidell, Bilthoven; *Spain:* C.A. González and A. Agudo, Mataró; J.R. Quiros, Oviedo; C. Martinez, Granada; M. Dorronsoro, San Sebastian; C. Navarro, Murcia; A. Barricarte, Pamplona; *Sweden*: G. Berglund, Malmö; G. Hallmans, Umeå; *UK*: N.E. Day, S. Bingham, S. Oakes and A. Welch, Cambridge; T.J.A. Key and G. Davey, Oxford; and R. Saracci, Pisa, Italy (coordinator of the EPIC-HEART European Concerted Action)

The EPIC project is a multi-centre prospective cohort study of the relation between diet, nutritional status, various lifestyle and environmental factors and the incidence of different forms of cancer and other chronic diseases (e.g., cardiovascular diseases, stroke and diabetes). It includes over 480 000 subjects in nine European countries for whom detailed data on diet and lifestyle as well as biological samples (plasma, serum, lymphocytes and erythrocytes) have been collected. The study is designed to address the major issues regarding the role of diet in relation to the occurrence of specific cancers, namely:

(1) Search for specific food components which could explain why diets rich in fruit and vegetables can reduce the risk of cancer of the digestive, respiratory and upper aerodigestive tracts and of other anatomical sites.

(2) Identification of the factors responsible for the elevated risk of cancers of the colorectum associated with high consumption of meat and meat products.

(3) Search for factors which could explain the wide geographical variations in cancers of the reproductive system, particularly of the prostate, testis, breast, ovary and endometrium.

(4) Investigation of the interaction of genetic predisposition and metabolic host factors with the environment and lifestyle

Table 2. Subject recruitment in the EPIC Study (September 1999)

	Subjects included in the study with		Completion of subject recruitment
	Questionnaire	Blood collection	
Spain	41 446	40 040	1996
Italy [a]	53 097	53 077	1998
UK	88 171	43 430	1998
Netherlands	40 110	36 357	1997
France	69 321	24 371	1993
Germany	53 130	50 719	1998
Greece	27 883	28 632	1999
Sweden	53 830	53 830	1996
Denmark	57 054	56 800	1997
Total	484 042	387 256	

[a] Including the EPIC-associated project in Naples

in determining cancer risk.

Studies of effects of endogenous hormones on cancer risk within the EPIC framework are described in Section 2.3.2.

The study originally included 17 centres in seven countries (France, Germany, Greece, Spain, the Netherlands, the United Kingdom). Four similar prospective studies subsequently joined EPIC as associated projects: in Sweden the Malmö Diet and Cancer Study (Malmö) and the Västerbotten County project (based in Umeå), in Denmark (one study in two centres, Copenhagen and Aarhus), and in Italy (the ATENA study in Naples). The extension of the study to these two Nordic countries and one additional Mediterranean region further increased the diversity of the populations included and the total study size.

For most cohorts, study subjects were from the general population residing in a defined geographical area, a town or a province. However, the French cohort was based on female members of the health insurance for state school employees (with the aim of facilitating long-term follow-up), a component of the Italian and Spanish cohorts included members of local blood donor associations, and the Utrecht cohort was based on women attending breast cancer screening. Eligible subjects who accepted to participate signed an informed consent form.

Data were collected on a large number of lifestyle and health factors that may be related to nutritional status or may be known or suspected cancer risk factors. The questionnaires included a common core set of questions and possible answers covering (*a*) education, socioeconomic status, (*b*) current job, current and past occupation in industrial settings which might have led to exposure to carcinogens, (*c*) life status of parents and siblings and their cause of death, (*d*) history of previous illness and disorders or surgical operation (*e*) lifetime history of tobacco smoking (*f*) lifetime history of consumption of alcoholic beverages, (*g*) physical activity: occupation, walking, cycling, gardening, housework, physical exercise, climbing stairs, and (*h*) sexual maturation, contraception and reproduction.

Three dietary assessment methods were adopted: (*a*) an extensive self-administered dietary questionnaire, which can provide data on up to 300–350 food items per country, was used in seven countries; (*b*) an interview-based dietary questionnaire, very similar in content to the above, but administered by direct interview was used in Spain and in Ragusa (Italy) to increase compliance, and (*c*) a food frequency questionnaire combined with a seven-day record was adopted by the two centres in England, where compliance with the method was very high.

To calibrate dietary measurements across countries and correct for systematic over- or under-estimation of intakes, a second dietary measurement was taken from an 8–10% random sample of the cohort using a specially developed computerized 24-hour diet recall method [489, 544]. Statistical methods were developed to correct for biases so as to make the cohort-specific estimates more comparable between study centres.

Biological samples have been collected from an unprecedentedly large number of study subjects and stored at very low temperature (–196°C in liquid nitrogen), so as to allow biochemical, molecular biology and genetic studies to be conducted. Blood samples collected from subjects in France, Germany, Greece, Italy, Netherlands, Spain, and United Kingdom were aliquoted in plastic straws (12 plasma, 8 serum, 4 erythrocytes, 4 buffy coat for DNA) of which half are stored locally and the other half shipped to IARC. For the Swedish and Danish cohorts the blood samples are, however, stored locally in tubes, and are shipped to IARC when needed.

The recruitment of study subjects, the collection of questionnaire data and anthropometric measurements (height, weight, waist, hip and sitting height), and the

collection and storage of blood samples, took place from 1993 to 1998. By September 1998, 484 042 subjects had provided questionnaire data, and from 387 256 of them blood samples had been collected and stored (Table 1). In addition, 33 200 24-hour diet recalls were collected on an age- and sex-stratified sample of the cohort. The age distribution of the calibration sample was designed to be as close as possible to the age distribution of the expected cancer cases during the first 10 years of follow-up. Over 22 000 cases of cancer are expected to occur in the EPIC cohorts during the first 10 years of follow-up (by 2005).

Cohort members are contacted 3–4 years after recruitment, and information is collected on some aspects of lifestyle which are known or strongly suspected to be related to cancer risk: tobacco smoking, alcohol drinking, physical activity, weight, menstruation, pregnancies, menopause, etc., and on whether the subjects suffered from any major diseases.

The identification of cancer cases is based on population cancer registries in six of the participating countries (Denmark, Italy, the Netherlands, Spain, Sweden, United Kingdom) and on a combination of methods including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin in three countries (France, Germany and Greece). Mortality data are also collected from either the cancer registry or mortality registries at the regional or national level. By the end of 1999, fairly complete and reliable follow-up data up to 31 December 1997 were available. In defining and implementing the follow-up protocol, the EPIC study has greatly benefited from the support of the European Network of Cancer Registries (see Section 1.1.2).

Intake of specific nutrients is computed from the food consumption data, by applying food composition tables. In Europe, several national tables exist, but have major differences in the criteria and methods used [140]. A protocol for compiling such tables following a standardized procedure has been prepared, involving

- standardization of terminology for identification and description of foods across centres;
- identification of foods that can be considered common to all countries (e.g., most fruits and vegetables, some beverages, legumes, some dairy products, pasta, rice, fish, oil);
- identification of country-specific foods (processed meat, meat, poultry, bread, margarine, confectionery, cakes, soups, sauces);
- application of common nutritional values, mostly derived from the British food composition table, to common foods;
- application to country-specific foods of the best available data on each food, mainly derived from local food composition data.

Preliminary results of statistical analysis of the dietary data confirm that dietary habits still differ substantially between countries (Figure 12).

We have developed methods for high-performance liquid chromatographic measurement of seven carotenoids (lutein, zeaxanthin, canthaxanthin, β-cryptoxanthin, lycopenes, α-carotene and β-carotene), tocopherols (α and γ) and retinol (Steghens *et al.*, 1997, *J. Chromatogr. B*, **694**, 71–81) and for gas chromatographic measurement of 22 fatty acids (from short-chain saturated fatty acids, C:12:0 to long-chain n–3 and n–6 fatty acids) [102].

For a descriptive cross-sectional study of these nutritional markers, as well as other studies on biomarkers, we selected a subsample of subjects from 16 geographical regions and countries: Denmark, France, Germany (eastern and western), Greece, Italy (southern, central and northern), the

Netherlands, Spain (southern, central and northern), Sweden (northern and southern), and the UK (Cambridge, the vegetarian subcohort of Oxford). For each area, we selected a random sample of 100 men and 100 women, stratified by age. The analyses of carotenoids and tocopherols and fatty acids have been carried out at IARC, and blood lipid profile (total, HDL- and LDL-cholesterol, and plasma triglycerides), vitamin C and phytoestrogens, and folic acid, homocysteine, B_6 and B_{12} will be measured in collaboration with external laboratories.

Plans have been made to study genetic predisposition to cancer and possibly gene-environment interaction studies, by analysing DNA in stored Buffy coat from EPIC blood samples for mutations in genes carrying high cancer risk and genetic polymorphisms with metabolic implications. A working group on genetic studies associated with the EPIC project (GenEPIC) has been set up, including geneticists from IARC and external laboratories.

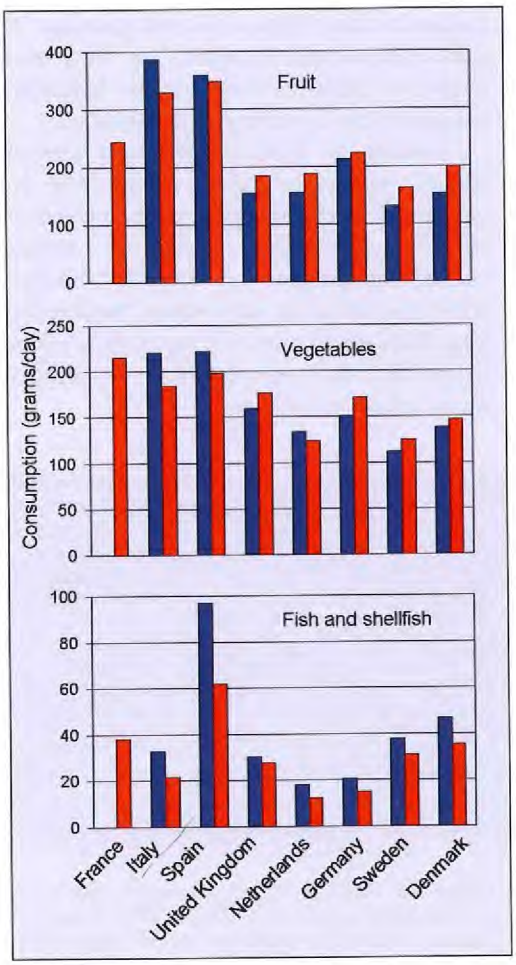

Figure 12. Consumption of certain foods in the different countries participating in the EPIC study. ■ men, ■, women (In France, only women are included in the EPIC study.)

2.3.2

Endogenous hormones and cancers of the colorectum, prostate, breast, endometrium and ovary

R. Kaaks, S. Rinaldi, A. Lukanova, C. Bressy, P. Ferrari and E. Riboli; in collaboration with G. Berglund, Malmö, Sweden; F. Berrino, Milan, Italy H. Dechaud, Lyon, France;; P. Gann, Chicago, IL, USA; G. Hallmans, Umeå, Sweden; P. Peeters, Utrecht, the Netherlands; P. Toniolo, New York, NY, USA; and the EPIC collaborators (see Section 2.3.1)

Current theories suggest that a western lifestyle may increase the risk of cancers of the breast, endometrium, ovary, colorectum and prostate through alterations in endogenous hormone metabolism. Two series of hormonal parameters of particular interest are, on the one hand, the gonadal sex steroids and sex hormone-binding globulin (SHBG) and, on the other hand, insulin, insulin-like growth factors (IGFs)-I and -II, and IGF-binding proteins (IGFBPs). Circulating levels of both series of hormones can be profoundly modulated by variations in nutritional status and energy metabolism.

One etiological factor potentially shared by cancers of the endometrium, ovary and breast is increased ovarian production of androgens, which is often associated with a decrease in hepatic production and plasma levels of SHBG, and hence increased bioavailability of both androgens and estrogens. In men, the development of prostate cancer is

believed to be related to increased intraprostatic levels of dihydrotestosterone, which could be due to an increase in circulating levels of bioavailable testosterone unbound to SHBG.

Overnutrition and obesity tend to increase plasma insulin and IGF-I bioactivity, whereas plasma insulin and bioactive IGF-I are decreased by energy restriction, which protects against many forms of cancer in animal models. In both men and women, insulin and IGF-I stimulate the gonadal and adrenal synthesis of sex steroids, which starts with the production of androgens, and both decrease the hepatic production and plasma levels of SHBG. An increase in IGF-I bioactivity might thus form a physiological link between nutritional aspects of a western lifestyle, and increased ovarian (possibly also adrenal) androgen production. Insulin and IGF-I can also directly stimulate anabolic processes, and, in excess, this may promote tumour development by inhibiting apoptosis and by stimulating cell proliferation.

In collaboration with the New York Women's Health Study (New York University, USA), the 'ORDET' study (National Cancer Institute, Milan, Italy), the Northern Sweden Health and Disease Study (Umeå University, Sweden), the Malmö Diet and Cancer Study (University of Malmö, Sweden) and two cohorts (Risk Factor Monitoring Project and the DOM cohort) at the University of Utrecht, the Netherlands, we have conducted studies on insulin, IGF-I and IGFBPs as possible predictors of the risk of colorectal cancer (New York) and prostate cancer (Umeå). A strong increase was seen in colorectal cancer risk in women with high serum levels of C-peptide, a marker of pancreatic insulin secretion, and with reduced levels of IGFBP-1 (see Figure 13). The prostate cancer study showed a moderate increase in risk with rising levels of total plasma IGF-I and IGFBP-3, but failed to confirm other results (Chan *et al.* 1998 *Science*, **279**, 563–566) showing a strongly increased risk in men with elevated IGF-I adjusted for IGFBP-3.

Further studies have been initiated on the relationships between circulating levels of insulin, IGF-I and IGFBPs, SHBG, androgens and estrogens and risk of cancers of the breast, endometrium and ovary. For breast cancer, a large study has started in Sweden, within the cohorts of Umeå and Malmö combined. Another study, pooling the resources from cohorts in New York, Umeå and Milan, has been started on breast cancer in young women (diagnosis before age 50 years) and cancers of the ovary and endometrium. A radio-immunoassay laboratory has been established at IARC to carry out the hormonal measurements for these and further studies.

Starting in 2000, nested case–control studies within the EPIC cohort will be conducted to relate plasma hormone levels to risk of developing cancers of breast, colorectum, prostate or lung (for insulin/IGF-I metabolism), for which sufficiently large numbers of cases are expected to occur in the next few years to allow statistically meaningful comparisons.

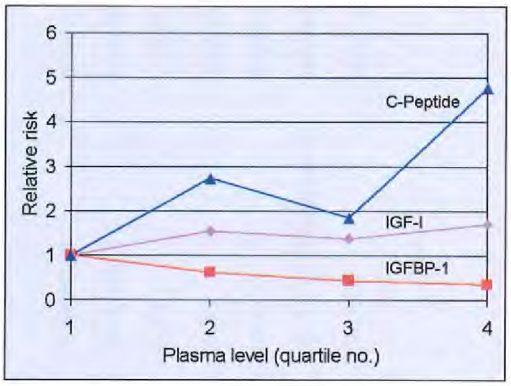

Figure 13. Relative risk of colorectal cancer for quartile plasma levels of IGF-I, IGFBP-1 and C-peptide (adjusted for smoking). No. of cases = 101; No. of controls: 200.

◆ IGF-I; *p* for trend 0.22; ■ IGFBP-1, *p* for trend 0.04; ▲ C-peptide, *p* for trend 0.0004

2.3.3
Studies on breast cancer and pre-diagnostic levels of carotenoids, tocopherols and retinol

E. Riboli, A.L. van Kappel, P. Ferrari, B. Vozar and D. Achaintre; in collaboration with F. Berrino, Milan, Italy; G. Hallmans, K. Hulten and A. Winkvist, Umeå, Sweden; J.P. Steghens and C. Collombel, Lyon, France; and P. Toniolo and R.E. Shore, New York, NY, USA

While consumption of fruits and vegetables has consistently been found to be related to reduced risk of cancer of the digestive and respiratory tracts, results have been inconsistent for breast cancer. Blood concentrations of various carotenoids (natural pigments generally found in plants) are related to consumption of fruits and vegetables in general and to specific types of vegetables, to the way that they are cooked, and to a number of nutritional and biological factors influencing carotenoid absorption and metabolism. We have found that repeated measurements of serum levels of different carotenoids are stable over one- or two-year periods, indicating that these levels are not only sensitive but reliable markers of the consumption of fruits and vegetables.

A nested case–control study within the cohort of the New York University Women's Health Study, including 270 breast cancer cases and 270 matched controls, revealed a two-fold higher incidence of breast cancer among women with low pre-diagnostic levels of α- and β-carotene and lutein, compared with women with higher levels (Figure 16) [511]. In a similar study on 201 cases and 390 matched controls from Umeå (Sweden), however, these effects were not confirmed.

2.3.4
Studies on breast cancer and fatty acid concentrations in plasma and cell membrane phospholipids

E. Riboli, M. Sadaatian-Elahi, B. Vozar and D. Achaintre; in collaboration with F. Berrino, P. Muti and A. Micheli, Milan, Italy; P. Bougnoux and V. Chajès, Tours, France; and G. Hallmans and K. Hulten, Umeå, Sweden

Ecological and migrant studies, as well as animal experiments, have suggested that high-fat diets can increase mammary tumorigenesis. According to these data, n–3 polyunsaturated fatty acids (PUFA) and particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish may have an anti-carcinogenic effect, while saturated and monounsaturated fatty acids (present mainly in vegetable oils and meat) may promote mammary tumour development and metastasis. While the majority of case–control studies of the relationship between dietary fat and risk of breast cancer have confirmed the protective effect of n–3 PUFA (especially EPA and DHA), prospective cohort studies have failed to find this effect.

In order to investigate whether the fatty acid composition of plasma phospholipids in samples collected before diagnosis is related to the risk of developing breast cancer, a case–control study, nested within a large prospective cohort, was initiated in the north of Sweden (the Västerbotten study) with 196 cancer cases and 388 matched controls. Capillary gas chromatography was used to determine the plasma phospholipid levels of 23 saturated, monounsaturated and polyunsaturated (n–3 and n–6) fatty acids. The fatty acid profile was not highly different between cases and controls. Contrary to the starting hypothesis, no protective effect against breast cancer was observed for DHA and EPA. Among the saturated fatty acids, palmitic acid (16:00) was associated with increased risk, whereas stearic acid (18:0) had an apparent protective effect. Moreover, the relative risk for women in the highest quartile of the ratio between stearic and oleic acid (18:0/18:1 n–9 cis) was 0.5 (95% CI, 0.32–1.10). An explanation for these results may be that the activity of delta 9 desaturase, the enzyme which desaturates stearic acid into oleic acid, is increased in women who develop breast cancer, perhaps due to up-regulation by higher insulin levels.

In another case–control study nested within the ORDET cohort study (Milan,

Italy) with 144 cases and 288 matched controls, we analysed the fatty acid composition of phospholipids in red blood cell membranes by capillary gas chromatography. Preliminary results confirm the protective effect of stearic acid found in the Västerbotten study, and indicate associations of linoleic acid (18:2 n–6) levels with reduced breast cancer risk and of oleic acid and arachidonic acid (20:4 n–9) with increased risk. It is planned to extend this work to examine colorectal cancer risk.

2.3.5

Estimation of the proportion of cancers preventable by dietary changes worldwide

E. Riboli, T. Norat-Soto, A. Lukanova and P. Ferrari; in collaboration with G. Cannon and T. McMichael, London, UK; and P. Toniolo, New York, NY, USA

Following the World Cancer Research Fund report (*Food, Nutrition and the Prevention of Cancer: A Global Perspective*, WCRF, London, 1997), we have initiated a study to estimate the proportion of cancers which could be prevented worldwide if dietary habits changed in a favourable direction. This requires estimation of (1) the average distribution of consumption of various foods in different populations and (2) the relative risk associated with quantitative differences in consumption of particular foods.

For the estimation of average food intake, the main problem is the absence of dietary surveys conducted with standardized methods in different regions of the world. Data published by the FAO, based on economic figures (production plus imports minus exports, animal feed and waste), tend to overestimate average *per capita* intake to varying degrees, especially in economically developed countries, where more food is wasted. To correct for this overestimation, correction factors were derived by dietary studies based on actual individual food consumption. Relative risks are being estimated by statistical meta-analyses. All published studies were reviewed, and those fulfilling pre-defined criteria of quality and presentation of results were selected. Dose–risk relationships were estimated by fitting logistic regression equations using both fixed-effect and random-effect models to take into account the heterogeneity of relative risk estimates across different studies. Statistical analyses are being carried out to estimate the proportion of cancers preventable by different hypothetical dietary changes.

2.3.6

Consumption of dairy products and cancer risk

E. Riboli, H. Vainio, T. Norat-Soto, N. Slimani, M. Saadatian-Elahi and P. Ferrari; in collaboration with: P. Bongnoux and V. Chajès, Tours, France; and E. Hietanen, Turku, Finland

It has been hypothesized, on the basis of experimental studies, that calcium in milk products may prevent colorectal cancer, mainly through intraluminal effects (Newmark *et al.*, 1994, *J. Natl Cancer Inst.*, **72**, 1323–1325). In contrast, high calcium intake may increase prostate cancer risk by down-regulation of vitamin D synthesis, mediated through a feedback involving parathyroid hormones (Giovannucci, 1998, *Cancer Causes Control*, **9**, 567–582).

Fats in milk and dairy products contain more short-chain saturated fats than other common foods such as meat, fish or vegetables, and it has been suggested that these may increase risks of not only cardiovascular disease but also cancer.

Milk and, particularly, aged cheese contain conjugated linoleic acid (CLA), a derivative of linoleic acid which is formed by the microflora of the rumen. CLA protects against mammary carcinogenesis in rodents treated with certain chemical carcinogens.

In order to study the relationship between dairy products and cancer, we have reviewed published epidemiological studies and carried out meta-analyses of the results for

cancers of the breast, colorectum and prostate in relation to consumption of different types of dairy products.

In a case–control study on breast cancer in Tours, France, the fatty acid composition of breast adipose tissue has been measured by gas chromatography in samples from 241 cases and 88 controls with benign lesions. Preliminary results suggest a protective effect of high levels of CLA and n–3 PUFA in breast adipose tissue.

We are evaluating measurements of CLA and of two fatty acids with uneven numbers of carbon atoms (C15:0 and C17:0) as biomarkers of dairy product consumption.

2.3.7

Nutrition, hormones, genetic predisposition and cancer of the prostate

E. Riboli, T. Norat-Soto, R. Kaaks, F. Canzian and G. Romeo; in collaboration with: G. González and A. Agudo, Mataró, Spain; and L. Fernandez, Y. Galan and R. Jimenez, Havana, Cuba

The incidence of prostate cancer varies as much 20-fold between different populations. It is highest in black Americans, intermediate in white Americans and western Europeans, and lowest in Asians. These differences are thought to be due to a combination of genetic susceptibility and lifestyle factors.

Two genetic polymorphisms have been identified which could play a role in prostate cancer incidence, one on the androgen receptor gene (chromosome X) and another on the testosterone 5α-reductase gene (SRD5A2 on chromosome 2). The genetic polymorphisms of these genes encoding for the most active forms of the receptor and the enzyme are more frequent among American and African blacks than in white Caucasians or Asians.

A case–control study was started in 1998 in Havana, Cuba, and by September 1999, 240 cases and 140 hospital controls had been enrolled. Questionnaire data are collected on current diet, lifestyle and reproductive and sexual history; anthropometric measurements are taken using standardized methods and past height and weight information is sought. In addition, blood samples and tumour and normal prostate tissue from both cases and controls are collected and stored for laboratory analysis of genetic polymorphisms of genes involved in steroidogenesis, steroid hormones and biomarkers of diet.

2.4 Tobacco and cancer

Tobacco is the most widely disseminated carcinogen in the world. Although some countries have made effective efforts to control tobacco use and promotion, others clearly lag behind and for the developing world, predictions are extremely pessimistic. Currently the annual world burden of tobacco-related deaths is about four million, but by the year 2020 it will be around 10 million. Scientific questions remain to be solved, in particular in terms of genetic susceptibility to tobacco, both for smokers and non-smokers, as well as interaction with putative dietary anticarcinogens. For public health purposes, urgent action is needed with careful evaluation of its outcome.

Several studies of lung, bladder and head and neck cancers addressing various aspects of the carcinogenic effect of tobacco smoke are reported in Sections 3.6, 3.7 and 3.8.

2.4.1

Population studies of tobacco use in Europe

A.J. Sasco; in collaboration with M. Jambon, Lyon, France; L. Joossens, Brussels, Belgium; S. Linn, Haifa, Israel; P. Mélihan-Cheinin, Paris, France; and T. Sahi, Helsinki, Finland

Detailed investigations are being carried out among children, adolescents and young adults to evaluate risk factors for smoking

and other substance abuse behaviour. Studies are in progress among schoolchildren and adolescents. Since 1985, more than 30 000 questionnaires have been collected on subjects aged 6 to 18 years old, mostly in the Rhône department of France. A study on about 15 000 military recruits is also being conducted in Finland, France and Israel using a common questionnaire. The data are being prepared for analysis. In the meantime, specific aspects of cancer prevention in relation to health promotion have been studied [430] and the importance of control of tobacco smoking in cancer prevention has been emphasized [429].

Reviews have been published on smoking among women in Europe [435], demonstrating how the use of light cigarettes may be a deterrent to stopping smoking [226, 227] as well as on passive smoking [436, 442].

2.4.2

Evaluation of the efficacy of tobacco control strategies

A.J. Sasco, D. d'Harcourt and R. Ah-Song; in collaboration with P. Mélihan-Cheinin and A. Hirsch, Paris, France; supported by the Europe against Cancer programme of the European Commission

Evaluation of tobacco control strategies is being carried out at the local, national and European levels. The most important activity is the EuroLego project, a programme funded by the Europe Against Cancer programme of the European Union, which is exhaustively compiling, reviewing and critically analysing current and past legislation for tobacco control in all 15 member states of the European Union. Altogether more than 450 legislative texts have been collected, translated and analysed. Over time, trends are seen towards more uniform legislation as well as more restrictive texts, in particular on advertising and smoking in public places and more recently at the workplace [428]. The full report, to be published in 2000, includes detailed discussion of definition of tobacco products, limits on specific constituents, labelling, advertising and sponsoring, smoking in public places and at the workplace, protection of the young and other issues.

2.4.3

Cohort study of tobacco use and mortality in India

R. Sankaranarayanan and D.M. Parkin; in collaboration with R. Collins and R. Peto, Oxford, UK; P.C. Gupta and H. Mehta, Bombay, India; P. Jha, Washington, DC, USA; A. Lopez, Geneva, Switzerland; and B. Mathew, B. Kuruvilla, G. Thomas and K.T. Shenoy, Trivandrum

Though it is well known that overall mortality rates are higher among cigarette smokers than in non-smokers, very little is known about the effect of other forms of tobacco use widely prevalent in developing countries, such as *bidi* smoking and various forms of smokeless tobacco use. Two cohort studies in India are addressing this issue. The cohort study in Bombay, initiated in 1991, has recruited over 160 000 subjects. Active follow-up of 52 568 individuals in the cohort was undertaken in 1997–98 and 97.6% were traced. Among these, 4358 deaths (293 368 person-years) were recorded. Among men, the overall relative risk (RR) for smoking was 1.63 (28 338 person-years). The age-adjusted relative risks were 1.39 for cigarette smoking and 1.78 for bidi smoking. The predominant habit among women was pan tobacco chewing, which was associated with a relative risk of 1.35 for mortality. Among men, the major smokeless tobacco use group was mishri plus others (relative risk 1.29). The results indicate that *bidi* smoking is no less hazardous than cigarette smoking and smokeless tobacco use may also result in high all-cause mortality.

Another cohort study in semi-urban areas of Trivandrum district in Kerala, southern India, initiated in December 1995, has recruited 125 000 subjects aged 35 years or more; another 100 000 male subjects will be

recruited. A case–control study within this cohort addressed risk factors for oral precancer. The adjusted odds ratios (OR) for erythroplakia were 19.8 for pan tobacco chewing, 3.0 for alcohol drinking and 1.6 for smoking. The adjusted ORs for oral leukoplakia were 7.6 for chewing, 2.8 for smoking and 1.5 for alcohol drinking. Information on death collected from the municipal death registration systems, cancer registries and by active follow-up is linked to both cohorts.

2.4.4

Tobacco use in Africa

A.J. Sasco; in collaboration with M. Bartal, Casablanca, Morocco; F. Ben Ayed, Tunis, Tunisia; M. Hamdi-Cherif, Setif, Algeria; and G. King, University Park, PA, USA

Surveys of tobacco use in several African countries are being carried out using a standardized data collection form. Preliminary analyses of data collected in the Wilaya of Setif in Algeria, among schoolchildren and their teachers in Senegal, among adolescents in Tunisia and in the general population of Uganda show a clear male preponderance. In an international case–control study of lung cancer, preliminary results from Morocco based on 118 cases and 236 controls indicate, besides active smoking, increased risks associated with passive smoking either in childhood or at the workplace and selected occupational exposures such as exposure to fumes or asbestos. A parallel study is being conducted in Algeria.

2.4.5

Dietary phenolics as anticarcinogenic substances in humans: a urinary bladder cancer case–control molecular epidemiological study

C. Malaveille and A. Hautefeuille; in collaboration with M. Peluso, Genoa, Italy; and P. Vineis, Turin, Italy

Our previous data strongly suggest that smokers ingesting dietary phenolics (e.g., flavonoids) are partially protected against the harmful effects of tobacco carcinogens within their bladder mucosal cells (Malaveille *et al.*, 1996, *Carcinogenesis*, **17**, 2193–2200). We have tested this hypothesis in a pilot molecular epidemiological study on bladder cancer with 114 cases and 46 controls. Consumption of fruit and vegetables was associated with lower bladder cancer risk (OR for four or more servings per day, 0.15; 95% CI, 0.03–0.6). A level of white blood cell DNA adducts greater than the median value was related to bladder cancer incidence (OR, 4.1; 95% CI, 1.9–9.0); furthermore, this relationship varied with the number of servings of fruit and vegetables per day. The level of DNA adduction was strongly associated with the *N*-acetyltransferase-2 slow genotype ($p = 0.0002$), indicating that the adducts were due mainly to aromatic and heterocyclic amines [365].

Catechol flavonoids can be metabolized by catechol-*O*-methyltransferase (COMT) into compounds that inhibit the activation of aromatic and heterocyclic amines by cytochrome P450 1A2 more strongly than the parent substances, and the mutated allele of COMT confers up to a four-fold decrease in enzyme activity. We found an association between a high level of DNA adducts in white blood cells and bladder cancer in subjects who ate four or more servings of fruit and vegetables per day and had COMT mutated genotypes (homo- and heterozygotes, together). These data show that catechol-*O*-methylation inhibits the formation of adducts which are critical for bladder carcinogenesis, and thus that certain dietary phenolics with a catechol moiety (e.g., quercetin) can decrease the carcinogenic activity of aromatic and heterocyclic amines in humans.

This conclusion was supported by measurements of the bacterial antimutagenicity of 135 plasma extracts, a putative biomarker of the protective effect of fruit and vegetables, using a representative heterocyclic amine as mutagen. Individuals having wild-type COMT alleles can efficiently methylate the catechol moiety of phenolics, thus

increasing their antigenotoxicity and/or determining the formation of antigenotoxic metabolites. Among such subjects, we observed an inverse relationship between the bacterial antimutagenicity and the level of DNA adduction in white blood cells.

In animals the liver and the colonic flora are two major sites of flavonoid metabolism. There is evidence of methylation, sulfation and glucuronidation of hydroxyl groups in the liver and bacterial scission in the colon. In the latter case, the subsequent degradation products (phenolic acids) can be absorbed and are found ultimately in the urine of animals and humans. In keeping with these metabolic considerations, we found that (*a*) the antimutagenic substances in plasma are not predominantly polyphenolics, and (*b*) the antimutagenicity of plasma extracts (per μg phenolics, measured spectrophotometrically) was inversely related to the amount of phenolics, suggesting that the metabolism leading ultimately to antimutagenic substances (probably derivatives of phenolic acids) is overloaded by inactive phenolic precursors. Work is in progress to characterize the antimutagenic metabolite(s) of flavonoids with a catechol moiety so as to determine the metabolic reactions that lead to formation of biologically active derivatives.

2.4.6 Polymorphisms in xeno(endo)biotic metabolism as modifiers of urinary bladder cancer risk: a case–control molecular epidemiological study

C. Malaveille and A. Hautefeuille; in collaboration with L. Airoldi, Milan, Italy; M. Peluso, Genoa, Italy; and P. Vineis, Turin, Italy

Tobacco smoking causes a major fraction of male urinary bladder cancers. The risk of this cancer can be modulated by genetically based metabolic polymorphisms (D'Errico *et al.*, 1996, *Biomarkers*, **1**, 149–173). Aromatic and possibly heterocyclic amines in tobacco smoke have been implicated as bladder carcinogens (Bartsch *et al.*, 1993, *Eur. J. Cancer*, **29A**, 1199–1207); [365]). In a molecular epidemiological study with 162 cases and 104 controls, we have assessed the relevance of genetic polymorphisms of *N*-acetyltransferase-2 (NAT-2), NAD(P)H quinone oxidoreductase-1, glutathione *S*-transferase M1, T1 and P1, catechol-*O*-methyltransferase, phenol sulfotransferase, myeloperoxidase and Mn-superoxide dismutase as bladder cancer risk factors and as modifiers of the protective effect of fruit and vegetable consumption or liquid intake. Among the polymorphisms investigated, only NAT-2 was clearly associated with the risk of bladder cancer, with a statistically significant odds ratio of 1.7. In keeping with previous studies, fruit/vegetable consumption and liquid intake were protective. The protective effect of fruit/vegetable consumption was related to the genetic polymorphism of NAT-2, GSTM1 and COMT: this effect was observed only in individuals with metabolic deficiencies. The association between NAT-2 and risk of bladder cancer was related to the level of liquid intake: the association (OR = 3.11, 95% CI 1.1–8.8) was observed with individuals drinking 1–3 glasses/day; for liquid intake of four or more glasses/day, slow acetylators were no longer at higher risk of bladder cancer. Overall, these findings support the role played by aromatic/heterocyclic amines as bladder carcinogens, and by catechol phenolics as bladder anticarcinogens.

2.5 Radiation and cancer

The main objective of research in this area is to provide answers to some outstanding questions in radiation protection and radiation carcinogenesis. Activities include

studies of the carcinogenic effects of ionizing radiation, in particular at low doses, in relation to the type of radiation, patterns of exposure and host and environmental factors. Studies of the effects of non-ionizing radiation (specifically radiofrequency (RF) radiation) are also being set up. The motivation for this work is twofold: to strengthen the scientific basis of radiation protection and to increase our understanding of biological mechanisms of carcinogenesis.

2.5.1

International collaborative study of cancer risk among radiation workers

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The International Collaborative Study of Cancer Risk among Radiation Workers is a retrospective cohort study of about 600 000 nuclear industry workers from seventeen countries; cohorts of 7000 subjects in Lithuania, 40 000 in Russia, 9000 in the Republic of Korea and over 40 000 nuclear power plant workers in the United States have recently been added. The objective of the study is to obtain precise direct estimates of the effect of low-dose protracted exposure to ionizing radiation in order to assess the adequacy of radiation protection standards for environmental and occupational exposures. Collection of entry data and follow-up are complete or virtually complete in all countries. Data from Canada, Finland, Spain and Slovakia have been received at IARC and are being validated. Data from most remaining countries should be received by early 2000.

The study of biases and random errors in the radiation dose estimates is continuing. The major sources of systematic and random errors in the dose estimates have been identified by facility, time period, dose level and, where relevant, activity. The approach for quantifying these errors has been defined and tested during a successful pilot study on the nuclear research and fuel cycle site of Saclay in France and in nuclear power plants in Switzerland. It is being extended to other countries. Experiments to provide necessary information on the energy and geometry response of old dosimeters have been carried out and the results are being analysed.

Various approaches for the analyses of data and risk estimation have been evaluated and implemented. The analyses will rely on fitting Cox proportional hazards model to individual data from each of the cohorts. Methods are being developed to fit random effects models in this framework and to take into account errors in dosimetry.

2.5.2

Health consequences of the Chernobyl accident

2.5.2.1

Chernobyl accident recovery workers

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Two case–control studies have been set up to estimate the risk of radiation-induced

leukaemia and non-Hodgkin lymphoma and of thyroid cancer among Chernobyl accident recovery workers ('liquidators') residing in Belarus or the Russian Federation, and, in particular, to study the effect of exposure rate.

The study population consists of approximately 40 000 Belarusian and 51 000 Russian liquidators who worked in the 30-km zone around the reactor. The study includes both retrospective and prospective cases diagnosed between 1 January 1993 and 30 June 1999 and four controls selected from the same study population for each case.

Information on all study subjects is obtained through the National Chernobyl Registries of Belarus and Russia and through face-to-face interview using a standardized questionnaire. Information is collected on demographic factors, on variables related to radiation dose and on exposure to potential confounding factors. In addition, a blood sample is obtained from each prospective case (before treatment) and relevant control for the purpose of biological dosimetry by techniques that may become available in the future.

Knowledge about dosimetry and dosimetric control practices in force in the 30 km zone around the Chernobyl reactor has been applied to develop a method of analytical dose reconstruction using the information collected by questionnaire together with dosimetric and environmental data. This method is being validated and optimized.

Interviews are in progress and data collection is expected to be complete in early 2000.

2.5.2.2

Thyroid cancer in young people

E. Cardis, A. Kesminiene and E. Amoros; in collaboration with V.K. Ivanov, M. Maksyoutov, E.P. Parshkov, E. Parshin, V.V. Shakhtarin, V.A. Stepanenko and V.A. Pitkevitch, Obninsk, Russian Federation; Yu. Gavrilyn, Moscow, Russian Federation; N.N. Piliptsevitch, I. Malakhova, S. Poliakov, E.P. Demidchik, L.N. Astakhova, E.D. Cherstvoy, E. Korotkevich and A. Mrochek, Minsk, Belarus; V. Masyakin, Gomel, Belarus; T. Krupnik, Mogilev, Belarus; G. Goulko, Munich, Germany; S. Yamashita, Y. Shibata and M Ito, Nagasaki, Japan, M. Hoshi, Hiroshima, Japan; D. Williams and G. Thomas, Cambridge, UK; and A. Pinchera, F. Pacini and R. Elisei, Pisa, Italy

A very early and large increase in the incidence of thyroid cancer in children and young adults in Belarus, and later in the Ukraine and Russia, following the Chernobyl accident has been reported. There is strong circumstantial evidence that this is due to radioactive fall-out from the accident.

A case–control study aimed at assessing the role of genetic predisposition, iodine status and very short-lived isotopes of iodine in radiation-induced thyroid cancer is being conducted in contaminated regions of Belarus and Russia. The source population consists of all persons in Gomel and Mogilev region of Belarus and in the regions of Bryansk, Kaluga, Orel and Tula in Russia who were children or adolescents at the time of the accident. The cases are all patients with a thyroid carcinoma occurring in this population during the study period (1 January 1990 until 30 June 1999) and operated in Belarus or Russia. All cases are independently verified by two pathologists. For each case, two controls are selected, matched on age (within one year), sex and village/city; two more are matched on age, sex and administrative region at the time of the accident.

A questionnaire, administered by a trained interviewer, includes questions about familial history of cancer, thyroid disorders, congenital malformation and mental retardation, about the behaviour of the subject during and after the accident and about stable iodine prophylaxis and thyroid hormone administration. Further information is obtained from medical and school records, results of current and past geographical surveys of iodine deficiency, surveys of countermeasures and analysis of biological samples and ultrasound evaluation of thyroid volume.

Estimates of radiation dose to the thyroid from ^{131}I and short-lived isotopes will be reconstructed using data from the questionnaire and information on environmental contamination and thyroid measurements.

If a subject reports a history of the diseases of interest among first- or second-degree relatives, an investigation is carried out and the pedigree drawn. In a second phase, once candidate genes have been identified under a parallel project (see Section 4.2.5), blood samples from the study subjects will be screened for mutations of these genes in order to evaluate the risk of radiation-induced thyroid cancer associated with the genetic predisposition.

Data collection is being carried out jointly (using a common questionnaire) with investigators of a collaborative Belarus/Russian/Japanese study with complementary objectives and overlapping populations.

Interviews of retrospective cases have been completed in Russia and are continuing in Belarus. Data collection is expected to be completed in early 2000.

2.5.2.3

European Childhood Leukaemia/ Lymphoma Incidence Study (ECLIS)

D.M. Parkin, R.J. Black, E. Kramarova and E.Masuyer; in collaboration with: *Austria,* B.G. Bennett and J. Langgaßner, Vienna; *Belarus,* E. Ivanov, Minsk; *Belgium,* J. Sinnaeve, Brussels; *Bulgaria* C.G. Tzvetansky, Sofia; *Czech Republic,* H. Hrstková, Prague; *Denmark,* H.H. Storm, Copenhagen; *Estonia,* M. Rahu, Tallinn; *Finland,* E. Pukkala, Helsinki; *France,* J.-L. Bernard, Marseille, P.-M. Carli, Dijon, B. Lacour, Nancy, F. Ménégoz, Grenoble, P. Schaffer, Strasbourg and S. Schraub, Besançon; *Germany,* J. Michaelis, Mainz; *Hungary,* E. Apjok, Budapest; *Italy,* P. Crosignani, Milan, C. Magnani and B. Terracini, Turin; *Latvia,* A. Stengrevics, Riga; *Lithuania,* R. Kriauciunas, Vilnius; *The Netherlands,* J.-W.W. Coebergh, Eindhoven; *Norway,* F. Langmark, Oslo; *Poland,* W. Zatonski, Warsaw; *Romania,* R. Tulbure, Bucharest; *Russian Federation,* A. Boukhny, Moscow, and V.M. Merabishvili, St Petersburg; *Slovakia,* I. Plesko, Bratislava; *Slovenia,* V. Pompe-Kirn, Ljubljana; *Sweden,* L. Barlow, Stockholm; *Switzerland,* T. Fisch, St Gallen, F.G. Levi, Lausanne, L. Raymond, Geneva, G. Schüler, Zurich and J. Torhorst, Basel; *Ukraine,* G. Moroz, Kiev; and *UK,* D. Brewster, Edinburgh, and C.A. Stiller, Oxford

The main aims of the European Childhood Leukaemia and Lymphoma Incidence Study (ECLIS) are to evaluate the incidence of childhood leukaemia in Europe since 1980, and to determine whether observed trends are related to exposure to radiation from the accident at the nuclear power plant at Chernobyl in April 1986.

The study began in 1988. Cancer registries throughout Europe provide annual listings of data on incident cases of childhood leukaemia (and, where possible, lymphomas) and denominators for the populations at risk, according to a standard protocol. Currently, 36 registries in 24 countries are participating.

Estimates of the excess radiation doses received as a result of the accident are provided by UNSCEAR. During the first five years of follow-up (1987–91), there was no evidence of an association between radiation doses received due to the accident and risk of childhood leukaemia in the study populations.

An analysis of incidence in children aged less than five years of age at diagnosis suggested that there was a small increase in leukaemia incidence in infants (less than one year) born soon after the accident. It seemed that this excess risk was confined to infants less than six months of age, and related to the estimated radiation dose received *in utero*, especially in the first trimester. Because of the interest of this finding, a careful verification exercise is being undertaken in the areas of highest exposure, to check the birth and diagnosis dates of the children concerned.

The collaborative framework of ECLIS has been used to undertake a study of possible effects of the Chernobyl accident on childhood and young adult thyroid cancer in European populations outside the former USSR. Participating registries were asked to provide data on thyroid cancers in the age group 0–19 years. There were 470 cases in all, but although there were geographical differences and temporal changes in risk, there was no suggestion that the relatively low exposure to radioactive iodine had played any role.

2.5.3
Health and environmental effects of static and time-varying electric and magnetic fields

2.5.3.1
International EMF project

E. Cardis; in collaboration with A. Ahlbom, Stockholm, Sweden; M. Linet, Bethesda, MD, USA; A. McKinlay, Didcot, UK; M. Repacholi, Geneva, Switzerland; D. Savitz, Los Angeles, USA; A. Swerdlow, London, UK; P. Vecchia and M. Grandolfo, Rome, Italy

The overall objective of this project is to assess health and environmental effects of exposure to static and time-varying electric and magnetic fields (EMF) in the frequency range 0–300 GHz (this range is divided into: static (0 Hz), extremely low-frequency (ELF, >0–300 Hz) and radiofrequency (RF, 300 Hz–300 GHz) fields).

Resources are being pooled through the establishment of the International EMF project, with an international advisory group. The project is run by WHO in collaboration with IARC, the International Commission on Non-Ionizing Radiation Protection, the United Nations Environment Programme, national governments, and other key institutions.

The specific involvement of IARC is to evaluate the carcinogenic risk associated with exposure to EMF and to identify gaps in scientific knowledge and recommend research protocols. Evaluations of the scientific literature on ELF and on the athermal effects of RF radiation have been made, as well as recommendations on research priorities for various types of electromagnetic radiation.

2.5.3.2
International case–control studies of cancer in relation to mobile telephone use (INTERPHONE)

E. Cardis, M. Kilkenny and M. Martuzzi; in collaboration with: *Australia*, B. Armstrong and K. Jong, Kings Cross; *Canada*: D. Krewski, Ottawa, and J. Siemiatycki, Montreal; *Denmark*: C. Johansen, Copenhagen; *Finland*: A. Auvinen, Helsinki; *France*: P. Guénel and J. Wiart, Paris, and M. Hours, Lyon; *Germany*: M. Blettner, Bielefeld, J. Michaelis, Mainz, and K. Schlaefer, Heidelberg; *Israel*: B. Modan and S. Sadetzki, Tel Hashomer; *Italy*: S. Lagorio and P. Vecchia, Rome; *New Zealand*: N. Pearce and A. Woodward, Wellington; *Norway*: T. Tynes, Oslo; *Sweden*: A. Ahlbom, M. Feychting and L. Hardell, Stockholm, and A. Hallqvist, Örebro; *Switzerland*: M. Repacholi, Geneva; *UK*: R. Cartwright, P. McKinney and R. Parslow, Leeds, A. Swerdlow, London, S. Mann, Didcot and M. van Tongeren, Birmingham; *USA*: S. Preston-Martin, Los Angeles, CA, F. Davis, Chicago, IL, M. Linet and P. Inskip, Bethesda, MD, J. Bowman, Cincinnati, OH, and Q. Balzano, Fort Lauderdale, FL

Several expert groups that recently reviewed the evidence concerning health effects of low-level exposures to radiofrequency (RF) electromagnetic fields (McKinlay *et al.*, 1997, *Rad. Protect. Bull.*, **187**, 9–16; Repacholi, 1998, *Bioelectromagnetics*, **19**, 1–19) recommended that research be carried out to determine whether radiotelephones could cause adverse health effects. One of the main recommendations was that epidemiological studies of the relationship between use of mobile telephones and the incidence of (*a*) brain tumours, (*b*) salivary gland tumours, acoustic neurinomas and other head and neck tumours and (*c*) leukaemia and lymphomas be carried out.

As a result of these recommendations, scientists from nine countries participated in a feasibility study co-ordinated by IARC. The study group met to review the results in September 1998 and, using criteria established in advance, concluded that an international study of the relation between mobile telephone use and brain cancer risk was feasible. The past prevalence of mobile telephone use and the expected number of cases are adequate to reveal a 1.5-fold increase in risk 5–10 years from the beginning of use, if it exists. Since it is unlikely that RF fields produce genotoxic effects, the most likely mechanism of any carcinogenicity is a promotion or progression effect, so that one would expect the latent period to be relatively short.

A series of case–control studies is therefore being set up, using a common core

protocol in thirteen countries: Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, New Zealand, Norway, Sweden, the United Kingdom and the United States. The aim is to establish whether mobile telephone use increases the risk of cancer and, specifically, whether the RF radiation emitted by mobile telephones is carcinogenic. The focus is on the tumours which, if RF fields are carcinogenic, would be most likely to be related (as they occur in the cells which receive the highest exposure) to mobile telephone use. Separate studies will be carried out for tumours of the acoustic nerve, tumours of the parotid gland, brain tumours (gliomas and meningiomas) and leukaemia. The study population will be mainly relatively young people (30–59 years), who had the highest prevalence of mobile phone use 5–10 years ago, in regions within the participating countries with the longest and highest use of mobile phones.

2.6 Viruses and cancer

The expected epidemic of HIV-related cancers in sub-Saharan Africa is being monitored in the two populations which have been continuously served by a cancer registry since the infection began to spread. Monitoring is performed by classical methods of descriptive and analytical epidemiology. The first aims at formulating hypotheses on interactions between the infection and other characteristics of the population and the second tests these hypotheses at the individual level.

Work is also in progress to identify genetic factors that may modify susceptibility to virally induced cancers.

Viruses also form a major focus of work on cervical cancer (see Sections 3.4 and 5.1.3) and the Gambia Hepatitis Intervention Study (Section 5.1.1) is examining the effect of vaccination against the hepatitis B virus in preventing liver cancer.

2.6.1 Monitoring of trends in incidence of cancers related to infection with HIV

D.M. Parkin; in collaboration with H. Wabinga, Kampala, Uganda; L. Levy and E. Chokunonga, Harare, Zimbabwe; and J.O. Thomas, Ibadan, Nigeria

The worldwide epidemic of AIDS is most severe in the African continent and, because the disease is known to influence the risk of several cancers in developed countries, monitoring of cancer incidence rates in African countries most affected by the epidemic is important. Few African cancer registries provide long enough time series to evaluate trends. An analysis of data from two (Kampala, Uganda and Harare, Zimbabwe) has been completed [111, 353]. Kaposi's sarcoma incidence has increased enormously, but this increase has now ceased in Uganda (Figure 17). There is evidence of an increase in recent years in incidence of squamous cell carcinomas of conjunctiva and of non-Hodgkin lymphomas, but not of Hodgkin's disease. There is no evidence for an increase in invasive carcinomas of the cervix or of hepatocellular carcinoma.

Figure 14. AIDS information for the general public, at a health centre in Côte d'Ivoire

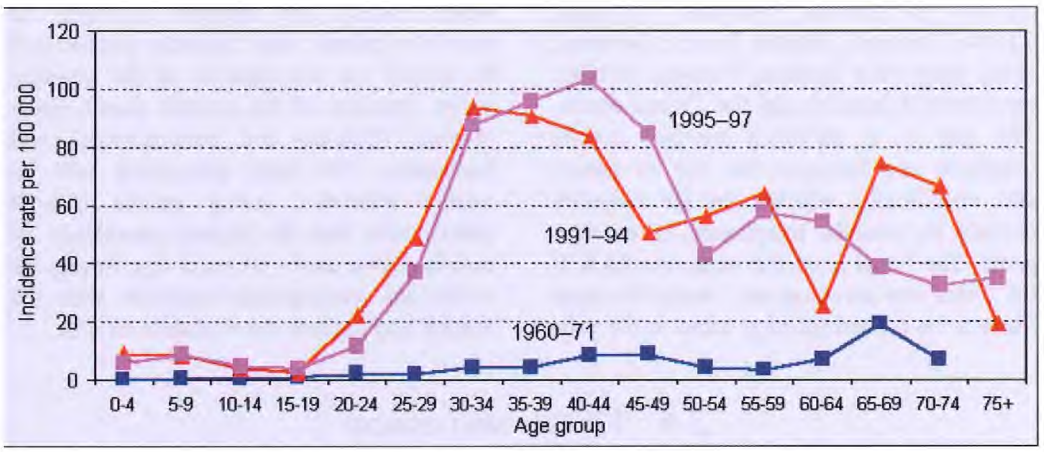

Figure 15. Age-specific incidence rates of Kaposi's sarcoma in Uganda among males for the years 1960–71, 1991–94 and 1995–97

2.6.2

Case–control studies of cancers related to HIV infection in Africa

D.M. Parkin and H. Garcia-Giannoli; in collaboration with V. Beral, R. Newton and R. Weiss, Oxford, UK; K. deCock, London, UK; H. Jaffe, Atlanta, GA, USA; E. Katangole Mbidde and H. Wabinga, Kampala, Uganda; M. Raphaël, Paris, France; J.O. Thomas, Ibadan, Nigeria; and J. Whitworth and L. Carpenter, Entebbe, Uganda

The data on HIV-negative Kaposi's sarcoma in Uganda have been analysed, but the results of serological testing for human herpesvirus type 8 (HHV-8) and other viruses are awaited. HIV-negative men with Kaposi's sarcoma show demographic factors related to relative affluence and mobility, and report more sexually transmitted diseases than the general population. Other data suggest that close interpersonal contact may also be important in the spread of HHV-8.

The study of non-Hodgkin lymphomas in children and adults was completed, and the results have been analysed. In children, the great majority of cases were Burkitt's lymphomas, and in all cases the genome of the Epstein–Barr virus was demonstrable. There was no association between HIV infection and risk of Burkitt's lymphoma in childhood. In adults, Burkitt's lymphoma and diffuse large B-cell lymphomas accounted for the majority of cases. There was an association with HIV infection, but it was not strong (about twofold).

For the other types of cancer, an analysis of the different prevalences of HIV infection (standardized for age, sex and other confounders) is in progress.

A new study of non-Hodgkin lymphomas in Ibadan, Nigeria, was initiated in 1999, focusing particularly on the role of viral infections.

2.6.3

Genetic–virus interaction in the etiology of cancer

G. Lenoir and D.E. Goldgar; in collaboration with M. Drira, Sfax, Tunisia; I. Ernberg and L.F. Hu, Stockholm, Sweden; and T.C. Yip, Hong Kong

Research at IARC on genetic factors in cancer has up to now focused mainly on syndromes due to a rare high-risk allele, such as multiple endocrine neoplasia and familial breast cancer. This project (which is an extension of the X-linked lymphoproliferative disease project; see Section 4.2.3) has as its objective the identification of genetic factors involved in the etiology of Epstein–Barr virus

(EBV)-associated cancers such as nasopharyngeal carcinoma and Hodgkin's disease.

2.6.3.1

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is an interesting model for genetic epidemiology studies of a complex cancer phenotype, because it has highly variable incidence worldwide, is an EBV-associated tumour, and is strongly associated with environmental factors, which may be population-specific. At least one study has shown a strong familial risk (~19-fold) indicating genetic susceptibility. There is clear HLA association and apparently some association with CYP2E1. The tumours show frequent loss of heterozygosity on chromosome 3p. A collaborative international study has been initiated to identify genes which may contribute to the strong familial clustering of NPC. In May 1999, a meeting of collaborators from Hong Kong, Tunisia and Sweden was held in order to plan a set of studies having a sufficient number of families to detect linkage to an NPC susceptibility locus. Our approach is to begin by testing candidate loci (HLA, regions of loss of heterozygosity (e.g., 3p), EBV receptor etc.), followed by an evaluation of the family set for power in a genome search; if there is sufficient power, we plan to test 400 random short tandem repeat markers throughout the genome. The first phase of the study began in late 1999 with representatives from the various groups coming to IARC with their familial samples to perform the candidate locus genotyping.

2.6.3.2

Hodgkin's disease

An evaluation has been carried out of the possibility of building upon the European Prospective Investigation into Cancer and Nutrition (EPIC; see Section 2.3.1) to analyse prospectively anti-EBV immune response in the context of specific HLA alleles. It was concluded that a study should be launched once material from EPIC becomes available.

2.7 Second malignancies following cancer treatment

Although cancer is still often a fatal disease, for which the use of aggressive therapies is justified, better and earlier diagnoses combined with more effective forms of treatment have led to the complete cure or at least much prolonged survival of many cancer cases. In these circumstances, it is essential to clearly understand the possible carcinogenic effects, as well as other toxicity, of the treatments available.

2.7.1

Prospective study on markers of DNA damage and risk of second malignancy in Hodgkin's disease patients

P. Boffetta and V. Gaborieau; in collaboration with S.A. Kyrtopoulos, Athens, Greece; M. Rajkumar, Madras, India; L. Simonato, Padua, Italy; and D.G. Zaridze, Moscow, Russian Federation

Hodgkin's disease patients treated with alkylating agents are at increased risk of second neoplasms, in particular leukaemia, non-Hodgkin lymphoma and lung cancer. Blood samples are being collected and stored from Hodgkin's disease patients treated at hospitals in India, Italy and the Russian Federation. The patients are being prospectively followed up for the occurrence of second malignancies. As each second malignancy arises, the therapy records for that case and several matched controls are examined, to try to identify carcinogenic therapeutic modalities as rapidly as possible. In parallel, blood samples are analysed for markers of DNA damage and repair, and comparisons made between the second malignancy cases and controls. A total of 300 patients have been enrolled. Follow-up will continue for a further three years.

2.7.2

DNA damage following chemotherapy for testicular cancer

P. Boffetta; in collaboration with D. Bron, Brussels, Belgium; A.M.J. Fichtinger-Schepman, Rijswijk, The Netherlands; and R. Somers, Amsterdam, The Netherlands

The reaction between alkylating chemotherapeutic agents and cellular DNA is probably the main pathway to both their cytotoxic and their carcinogenic effects. Blood samples from a series of testicular cancer patients enrolled in a clinical trial by the European Organization for Research and Treatment of Cancer (EORTC) have been analysed for DNA adducts formed by cisplatin. No relationship with response to chemotherapy was found, while there was a strong correlation between cisplatin–DNA adducts and total protein-bound platinum, suggesting that the latter might serve as a marker of biological effect of cisplatin [39].

2.7.3

Systematic analysis of cancer registry data

P. Brennan and P. Boffetta; in collaboration with B Armstrong, Sydney, Australia; R.J. Black, Edinburgh, UK; and J. Iscovich, Ra'anana, Israel

Previous studies of multiple primary cancers have helped to identify cancer sites which are likely to share a common etiology, and also to identify treatment strategies which influence the risk of subsequent cancers [38]. Recent collaborative efforts have concentrated on classic Kaposi's sarcoma and non-Hodgkin lymphoma in Israel. A fourfold excess of non-Hodgkin lymphoma and a sixfold excess of melanoma were detected among 1016 patients with an initial diagnosis of classic Kaposi's sarcoma in Israel [217]. A similar excess of classic Kaposi's sarcoma after an initial diagnosis of lymphoma or leukaemia was also detected, suggesting a common etiology [219].

A combined analysis of data on second cancers from large cancer registers which have at least 20 years of follow-up data is being organized. This should have sufficient power to reveal relationships between both rare and common tumours. The analysis will be conducted for each cancer site as a primary tumour and also for each cancer site as a secondary tumour. When available, information on the treatment of the primary cancer will also be analysed.

2.7.4

Case–control study of selected second primary cancers following breast cancer and tamoxifen use

A.J. Sasco, G. Le Mab and I. Gendre; in collaboration with C. Bouchardy, Geneva; T. Fisch, Saint Gallen, Switzerland; and P. Schaffer, Strasbourg, France; supported by the BioMed programme of the European Union, the French Institut national de la santé et de la recherche médicale (INSERM), the Fondation de France and the Federal Office of Public Health, Switzerland

A series of international case–control studies has been set up in order to evaluate the risk of occurrence of selected second primary cancers following breast cancer [433]. Cases of endometrial and ovarian cancers occurring among women who had previously developed breast cancer have been selected from population-based cancer registries in France (10 registries) and Switzerland (2 registries). So far, 127 cases of endometrial cancer and 86 cases of ovarian cancer have been recruited. They are matched to controls who had breast cancer at the same time and age as the case and who are still at risk of disease. The role of tamoxifen [431, 434, 438] and other treatment modalities in the occurrence of second cancers is being evaluated. Data collection in Denmark, Italy and Sweden is also envisaged. This study is important in the context of use of tamoxifen for cancer prevention, where the issue of its carcinogenicity is paramount [152, 437, 449, 563].

PART 3. CARCINOGENESIS BY ORGAN SITE

3.1 Cancer of the oesophagus

The two major forms of oesophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma (ADC). SCC is the most common, occurring at particularly high frequency in some areas of Asia, South America and western Europe. Epidemiological studies point to the involvement of exogenous risk factors, such as tobacco, alcohol and other dietary factors and cultural habits. ADC often occurs in the context of a precancerous lesion, Barrett's mucosa, in which the normal squamous epithelium is replaced by a metaplastic intestinal-type epithelium. Unlike gastric cancers, the frequency of ADC arising within the cardia at the gastro-oesophageal junction is increasing in western countries; this may represent a distinct pathological entity. Incidence trends for oesophageal cancers are being studied alongside those of stomach cancer (see Section 3.2.2).

We are investigating the cellular and molecular events that occur in the natural history of oesophageal cancers in relation to the etiology of these cancers. Our aims are to (1) analyse molecular alterations such as mutations in the *p53* gene, (2) determine the sequence of genetic events that occur during cancer development, and (3) identify molecular differences between SCC and ADC.

3.1.1 Cellular and molecular alterations in oesophageal cancer

P. Hainaut, C. Barnas, G. Martel-Planche, P. Taniere, A. Sepher, D. Peixoto-Guimaraes, S. Pomtosapon, O. Pluquet, K. Castren and R. Montesano; in collaboration with A. Casson, Toronto, Canada; A. Chanvitan, Songkhla, Thailand; C. Gallo, Porto Alegre, Brazil; O.A. Haas and T. Henn, Vienna, Austria; C. Lombard-Bohas, Lyon, France; and S.H. Lu, Beijing, China

Missense mutation in the *p53* gene is the most frequent genetic change in cancers of the oesophagus (48% in squamous cell carcinoma and 71% in adenocarcinoma). To examine whether the type and site of *p53* mutation are informative of the nature of the carcinogens involved, we are collecting samples of oesophageal lesions from high-risk and low-risk areas (western Europe, Brazil, China, Iran, Thailand). Mutations within the central portion of the *p53* gene (exons 4 to 9) are determined. In parallel, an immunohistochemical analysis of p53 protein is performed on paired tissue samples in order to correlate genetic alterations with protein expression.

We have found significant differences in the *p53* mutation profiles between SCC from Asia and those from Europe. In southern Thailand and in high-risk areas of China, there is higher proportion of G to A transversions and G to A transitions than in western Europe. In contrast, tumours from high-risk areas of Europe (Normandy, France and northern Italy) show a high prevalence of mutations at A or T bases that may correlate with exposure to alcohol and tobacco. Collaboration with several Iranian institutions is being established to allow collection of well characterized cases.

There are indications that infection with human papillomaviruses (HPV) is a risk factor in the pathogenesis of SCC in high-risk areas of China. It has been suggested that a polymorphism at codon 72 in p53 might be associated with an increased risk of HPV-associated cervical cancers. To determine whether such an association exists in areas of high risk for SCC, we have analysed DNA extracted from exfoliated oesophageal cells from 95 cancer cases and controls in Linxian, China. We detected no significant association between p53 polymorphic alleles

and cancer and failed to confirm the high prevalence of HPV reported by other groups.

We have also analysed p53 mutations in adenocarcinomas of the gastric cardia. In tumours lacking any evidence of pre-existing Barrett's metaplasia, we observed a p53 mutation pattern distinct from those of both Barrett's adenocarcinoma and gastric cancers. Tumours of the cardia show a relatively low prevalence of p53 mutations (25–30%), but frequently overexpress the product of the *MDM2* gene. These data suggest that, within the limits of the definition used, adenocarcinomas of the cardia represent a specific entity. This is supported by the observation that the age profile and sex ratio of patients with adenocarcinoma of the cardia differ from those of patients with Barrett's adenocarcinomas.

We have also used comparative genomic hybridization (CGH) to search for chromosomal areas of consistent alterations in both SCC and ADC. Multiple chromosomal modifications were detected in most cancers and the number of alterations was inversely correlated with tumour stage and patient survival. In addition to already known loci, chromosomes 1p and 1q, 4q and 20q were frequently altered. Deletion of 4q was detected in the majority of ADC. Further analysis of allele distribution on chromosome 4q, using 14 polymorphic markers in 22 ADC patients for whom DNA from both the tumour and adjacent normal mucosa was available, revealed two distinct areas of consistent losses within the chromosomes. One of these contains the FAT gene, encoding a cell-surface molecule involved in adhesion, which is a homologue of a gene important in the morphogenesis of epithelial tissues in *Drosophila*. We are now studying whether this locus is altered in oesophageal cancers.

In addition to primary tumour samples, we are using cell lines derived from oesophageal cancers to study alterations in cell-cycle regulatory genes and to functionally analyse signal transduction pathways involved in cell-cycle control and in apoptosis. We have examined the effects of non-steroidal anti-inflammatory drugs (NSAIDS) and of a differentiating agent, cholesterol sulfate, on the proliferation and survival of several SCC cell lines. Aspirin had strong anti-proliferative effects in all cell lines, but the molecular mechanisms involved may differ from one cell line to the other. In the TE-1 cell line, aspirin induced cell-cycle arrest in G1, correlated with an increase in levels of the cyclin kinase inhibitor $p27^{Kip1}$. However, in the TE-9 cell line, aspirin induced apoptosis, correlated with an increase in $p21^{WAF1}$ level. With cholesterol sulfate, inducing squamous differentiation increased the sensitivity of cultured cells to apoptosis induced by various drugs, including alkylating agents and cisplatin. Further work is warranted to relate these effects to clinical data suggesting a possible chemopreventive or therapeutic action of these substances in oesophageal cancer.

The TE-1 cell line expresses a temperature-sensitive mutant form of p53 and undergoes reversible cell cycle arrest upon switching the temperature to 32°C. In TE-6, the capacity of cells to grow as monolayers is dependent upon the presence of adhesion molecules. We are using gene array screening and differential display strategies to characterize genes differentially expressed in these two cell lines in the hope of identifying new genes of interest in oesophageal cancers.

3.1.2 Up-regulation of Fas (APO-1/CD95) ligand and down-regulation of Fas expression in oesophageal cancer

C. Gratas, Y. Tohma, C. Barnas, P. Taniere, P. Hainaut and H. Ohgaki

Fas (APO-1/CD95) is a cell surface receptor which mediates apoptosis when it reacts with Fas ligand (FasL) or Fas antibody. In this study, we analysed Fas and FasL expression in normal oesophageal mucosa and oesophageal squamous cell carcinomas.

Reverse transcriptase (RT) polymerase chain reaction (PCR) revealed that Fas, soluble Fas, and FasL were expressed in all of eight oesophageal SCC cell lines. Further, the FasL expressed in the carcinoma cells was functional, since co-culture with FasL-expressing TE-15 oesophageal carcinoma cells resulted in apoptosis of Jurkat T leukaemia cells, which are sensitive to Fas-mediated apoptosis. Immunohistochemical staining of Fas and FasL showed that they are constitutively expressed in normal oesophageal mucosa, FasL being seen predominantly in the basal and suprabasal layers and Fas in more differentiated layers, i.e., rows of polyhedral cells of the intermediate layers and squamous cells forming the outer layers. In 18 out of 19 invasive oesophageal SCCs, FasL was expressed in more than 50% of tumour cells. In contrast, in 15/19 tumours (79%) Fas was expressed in none or less than 5% of tumour cells. These alterations were already detected in dysplasia and carcinoma *in situ*. These results suggest that up-regulation of FasL and down-regulation of Fas expression are early and frequent events associated with the development of oesophageal SCC [177].

3.2 Cancer of the stomach

Cancer of the stomach remains the second most common cancer in the world, despite a steady decrease in incidence except for tumours of the gastric cardia. Among the possible causes of stomach cancer, dietary factors and *Helicobacter pylori* infection are being investigated in case–control studies in a high-risk population of Venezuela. Prevalence surveys of *H. pylori* strains and laboratory studies are also being carried out to determine why only a very small fraction of *H. pylori*-infected individuals develop stomach cancer.

A chemoprevention trial on precancerous lesions of the stomach is under way in Venezuela (Section 5.1.3).

Review articles on *H. pylori* and gastric cancer have been published [314, 315].

3.2.1 Case–control study of stomach cancer in Tachira, Venezuela

N. Muñoz, M. Plummer and C. Lavé; in collaboration with G. del Giudice and A. Ponzetto, Turin, Italy; J.L. Fauchère, Poitiers, France; G. Lopez, W. Oliver, S. Peraza and J. Vivas, San Cristobal, Venezuela; and V. Moreno, Barcelona, Spain

Gastric cancer is the leading cause of death from cancer in Venezuela. The mortality rate is particularly high in the Andean region, which includes the state of Tachira. A case–control study has been conducted with the dual aims of finding the causes of gastric cancer in this high-risk population and evaluating the protective efficacy of a gastric cancer screening programme which was set up in Tachira in the early 1980s.

Between January 1991 and August 1997, 303 new, histologically confirmed cases and 606 age- and sex-matched neighbourhood controls were recruited. Information on residential history, socioeconomic status, family history of gastric diseases, smoking, drinking and dietary habits was collected by personal interview. Habitual diet in the year before diagnosis was assessed using a food frequency questionnaire. Information on screening history was retrieved from the records of the cancer control centre in San Cristobal. Serum samples to measure selected micronutrients and antibodies to *H. pylori* were collected from all subjects and biopsies from tumoural and non-tumoural gastric mucosa were collected from cases.

Initially one hospital control and one neighbourhood control were recruited for each case. A preliminary analysis of the first 119 cases and their controls showed that the hospital controls had a substantially different

diet from the neighbourhood controls. Given the importance of diet to the study, the hospital controls were subsequently dropped from the protocol.

Estimates of *H. pylori* prevalence using assays of serum antibodies to various strains were in the range 72–92%. Levels of antibodies to French strains were lower in cases than controls, possibly due to loss of *H. pylori* from the gastric lumen in the precancerous stages of the disease or to reduced immune response in cases.

Antibodies to cagA were also investigated. This is a marker for the presence of a 40 kb pathogenicity island in *H. pylori* which encodes for virulence factors. The prevalence of cagA-positive *H. pylori* was 78% in cases and 79% in controls. Lower antibody levels were again found in cases, although the difference was not significant.

Preliminary analysis of other risk factors indicated a strong inverse association with social class, measured by education and by indicators of poverty. Farmers were at higher risk than other occupational groups. Alcohol drinkers and tobacco smokers were at higher risk, but when drinking and smoking were examined together, only drinking was an independent risk factor. There was some evidence of familial aggregation of gastric cancer. A monotonous diet, high in starch and low in meat, fish and fresh vegetables appeared to be associated with risk of gastric cancer. An inverse association with height may reflect nutritional status in childhood.

3.2.2

Prevalence surveys of *H. pylori* in high- and low-risk areas for stomach cancer

R. Herrero, N. Muñoz, B. Pignatelli and H. Ohshima; in collaboration with B. Appelmelk and E.J. Kuipers, Amsterdam, The Netherlands; L.E. Bravo, Cali, Colombia; R. Calderon and J. Rios-Dalenz, La Paz, Bolivia; A. Covacci, Siena, Italy; I.T. Gangaidzo, Harare, Zimbabwe; E. Kasamatsu and P.A. Rolon, Asunción, Paraguay; M. Matamoros, San José, Costa Rica; K. Miki and M. Ichinose, Tokyo, Japan; H. Posso, Bogotá, Colombia; D. Queiroz, Belo Horizonte, Brazil; E. Salazar, Cuernavaca, Mexico; C. Saul, Porto Alegre, Brazil; and J. Torrado, San Sebastian, Spain

Infection with *H. pylori* is extremely common in many populations, and the reported prevalences of serological markers of infection do not seem to explain the wide geographical variations in incidence of peptic ulcer disease and stomach cancer that are observed (see Figure 16). Individual clinical outcomes range from asymptomatic gastritis or peptic ulcer to chronic atrophic gastritis and invasive adenocarcinoma. This implies that bacterial, host or environmental cofactors of *H. pylori* infection are involved. Variations in the prevalence of *H. pylori* strains with different pathogenic potential might explain the geographical differences. Certain strains carry a 'pathogenicity island' in the genome, that encodes for a specialized secretion mechanism giving these strains enhanced virulence. Other cofactors under investigation include diet, food preparation practices, salt ingestion, smoking and individual inflammatory responses.

We have initiated an international survey of *H. pylori* infection in subjects attending gastroscopy clinics with a histological diagnosis of peptic ulcer disease, gastritis, gastric cancer precursors or invasive cancer in some 12 countries, mainly in Latin America, with high, intermediate or low incidence of stomach cancer. In each centre, approximately 400 subjects are being enrolled, to include a pre-defined number of subjects in each diagnostic category and age group. Specially trained interviewers administer a standard questionnaire on behavioural factors. From each subject, 12 gastric biopsies are obtained from six sites in the stomach, six for histological characterization of the lesions and six to be kept frozen for measurement of various biomarkers. Some of the biopsies are cultured for *H. pylori* at central laboratories, to genetically characterize the strains present. In addition, various markers of activation of inflammatory cells, oxidative stress, enzymatic antioxidant defence and cytokine

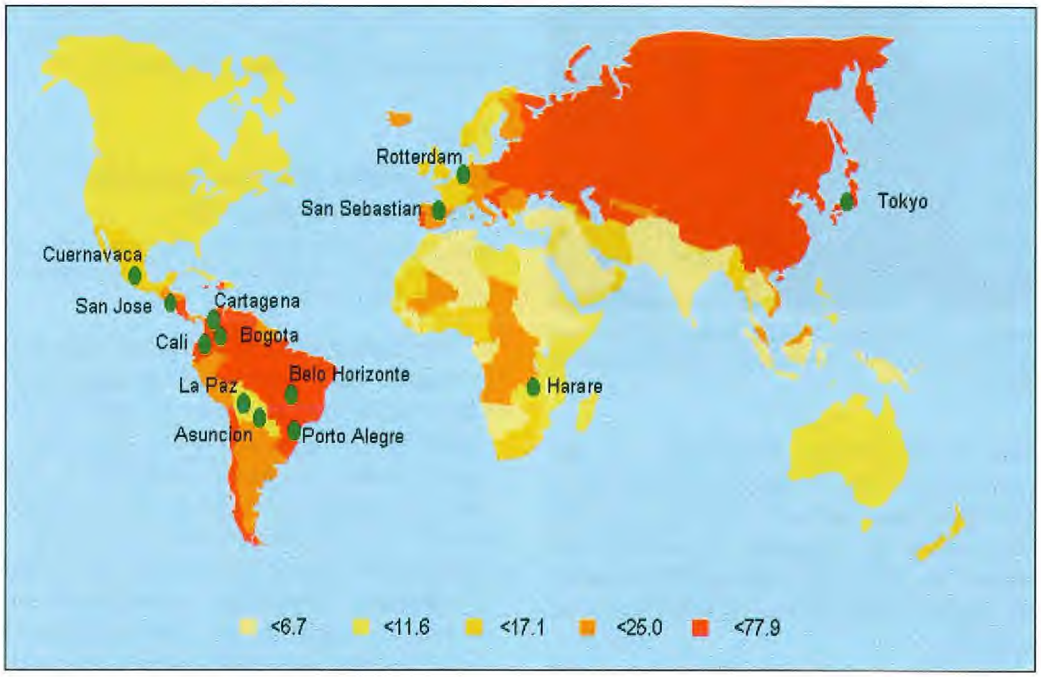

Figure 16. Age-adjusted incidence of stomach cancer among males in each participating centre.

induction in human gastric mucosa will be investigated in relation to *H. pylori* strains and individual susceptibility. A blood sample is also collected from each subject for measurement of serological markers of *H. pylori* infection, auto-immune responses to *H. pylori* and pepsinogen levels, which can be markers of chronic atrophic gastritis.

Site visits have been made to most of the participating centres. Pilot studies have been carried out in several centres to standardize study procedures and to refine the protocol (Figure 17). Great care is being taken to optimize and standardize the complex study procedures, and to ensure uniformity of diagnosis and availability of bacterial strains across all the collaborating clinical centres, in consultation with international experts.

The study has been initiated in most of the centres and data collection is expected to continue for two years. The relationship of prevalence of specific bacterial strains in defined lesions to stomach cancer incidence at each centre will be assessed, and a multicentre case–control study will be carried out for each pathological condition to determine the role of each exposure or biomarker.

3.2.3 Time trends of cancers of the oesophagus and of the stomach

A.P. Vizcaino, N. Muñoz, D.M. Parkin and R. Lambert; in collaboration with A. Kubik, Prague, Czech Republic; T. Hakulinen, Helsinki, Finland; and V. Moreno, Barcelona, Spain

Trends of oesophageal and stomach cancer incidence by histological type are being examined, using data for the period 1973–93 provided by 60 cancer registries from 32 defined populations in 25 countries. For a data-set to be included in the study, (*a*) the registry had to have had its data accepted for at least two consecutive volumes of *Cancer Incidence in Five Continents*; (*b*) the proportion of histologically confirmed cases

Figure 17. Dr Celso Oliveira explaining the study protocol to potental participants in Belo Horizonte, Brazil

had to be greater than 80%; (*c*) the proportion of cases identified through death certificate only had to be less than 5%; and (*d*) histological diagnosis compatible with the coding of the International Classification of Diseases for Oncology (ICD-O) had to be available.

Incidence rates of oesophageal and gastric cancer at specific subsites in men and women are being compared in the United States (SEER) (9 registries), Canada (8 registries), Japan (Osaka), England (8 registries), Scotland (5 registries), France (4 registries), Slovakia, the Netherlands (Eindhoven), Italy (Varese) and Switzerland (3 registries). For the oesophagus, tumours in the upper two thirds and in the lower third are being separately analysed. For the lower third, rates for adenocarcinoma and squamous cancer are being analysed. For the stomach, the cardia, antrum, pylorus and other sites are analysed separately. For each site and subsite, in each sex, cancer incidence is being calculated for five-year age groups and five-year time periods.

The preliminary results show an increasing incidence of adenocarcinoma at the gastro-oesophageal junction (lower third and gastric cardia) that is less marked in women than in men. This trend is observed in the registries from North America and in most registries from Europe (England, Scotland, Switzerland, Italy). In contrast, a decreasing trend is observed for distal gastric cancer. Oesophageal squamous cancer appears relatively stable in both sexes.

3.2.4

Case–control studies of stomach cancer in south-east Asia

D.M. Parkin and P. Pisani; in collaboration with S. Sriamporn and V. Vatanasapt, Khon Kaen, Thailand; and Pham Hoang Anh, Hanoi, Viet Nam

The highest incidence rates are observed in eastern Asia, particularly in Japan and China, while very low rates are reported in Thailand, Viet Nam and India. Two case–control studies are being conducted in the low-risk population of Khon Kaen, north-eastern Thailand, and in Hanoi, Viet Nam, where gastric cancer incidence is twice that in Thailand. Information is collected on socio-demographic factors, living hygienic conditions and home crowding at present and in childhood, sources of water supply, history of tobacco smoking and betel nut chewing, alcohol drinking and usual dietary habits. The dietary questionnaire, of the dietary history type, will allow estimation of the intake of major food groups and nutrients and discrimination of individuals who consume preferentially salty and fermented foods. Serum antibodies to *H. pylori* are assessed by an ELISA test. Data collection has been completed in Khon Kaen, where 131 incident cases and twice as many hospital controls have been interviewed and donated a sample of blood. Positivity for the infection, based on serum antibodies, is not associated with the risk of stomach cancer but it is associated with known risk factors for the infection such as number of siblings. The associations with cumulative exposure to tobacco in men (only one woman reported having ever smoked), chewing of betel nut or alcohol drinking were not statistically significant. Frequent consumption of fermented salted food was associated with a relative risk of 1.9 (95% CI, 1.1–3.3).

The same protocol has been adopted in the case–control study in Hanoi, with some differences in the dietary questionnaire to allow for local food items. Data collection is in progress.

3.3 *Cancer of the liver*

Hepatocellular carcinoma (HCC) is one of the most common fatal cancers worldwide. Hepatitis B virus and hepatitis C virus infections, exposure to aflatoxin and excessive intake of alcohol have been identified as major risk factors. Epidemiological studies are continuing to refine our understanding of the etiology of liver cancer in humans, while experimental studies address issues of mechanisms of hepatocarcinogenesis, genetic susceptibility to aflatoxins and the use of biomarkers in pilot intervention studies to assess how effective primary prevention measures may be in reducing exposure to these carcinogens. Liver cancer prevention is also the focus of the Gambia Hepatitis Intervention Study (Section 5.1.1).

3.3.1 Cohort study of HBsAg carriers in Thailand

M. Plummer, N. Muñoz and C. Lavé; in collaboration with P. Coursaget, Tours, France; H.R. Shin, Pusan, Republic of Korea; P. Srivatanakul and S. Purbahat, Bangkok, Thailand; and C.P. Wild, Leeds, UK

A cohort of 1800 male carriers of hepatitis B surface antigen (HBsAg) over the age of 30 years has been recruited in Bangkok, Thailand. All subjects are at high risk of developing hepatocellular carcinoma (HCC) and the purpose of the study is to identify cofactors which increase the rate of progression to cancer. The risk factors being investigated are diet, alcohol, tobacco and aflatoxin exposure. Active follow-up of the cohort was completed in June 1995 and accumulated 5800 person-years of observation. During follow-up, blood and urine samples were collected at regular intervals and stored. Environmental and behavioural risk factors were assessed through a questionnaire at recruitment.

A nested case–control study of HCC has been conducted. Forty-one cases have been diagnosed and two age-matched controls have been selected for each case. Aflatoxin exposure was assessed by measuring aflatoxin–albumin adducts in plasma by an immunoassay. In addition, genetic susceptibility to aflatoxin exposure was assessed by investigating genetic polymorphisms of the aflatoxin-metabolizing enzymes (glutathione *S*-transferases and epoxide hydrolase). Statistical analysis of diet, alcohol, smoking and socioeconomic status revealed no association with HCC. Likewise, analysis of the genetic polymorphisms and of aflatoxin exposure showed no association. HBV and HCV markers (HBeAg, HBV DNA, HBsAg titre, anti-HCV) are being assayed. A further nested case–control study of chronic liver disease (chronic active hepatitis or cirrhosis) is planned, using subjects with normal liver function as controls.

3.3.2 Cohort study of cholangiocarcinoma and other cancers in Thailand

P. Pisani and D.M. Parkin; in collaboration with V. Vatanasapt and S. Sriamporn, Khon Kaen, Thailand

A cohort study was set up in 1992 to investigate the causes of liver cancer in a province of north-east Thailand, where this disease is the most common malignancy in both sexes. The annual age-standardized incidence rates of liver cancer in the years 1988–91 reported by the Khon Kaen Cancer

Registry were 94.8 in men and 39.4 in women (a risk comparable to those of lung cancer in men and colorectal cancer in women in the USA). Cholangiocarcinoma represents 90% of all liver cancers occurring in this population, while HCC is the predominant type everywhere else in the world.

Over 12 800 individuals were enrolled by June 1996. Interview data are complemented with samples of blood and faeces; the first is separated and stored at –20°C for future analysis and the second provides evidence of current infection with *Opisthorchis viverrini*, a parasite of the biliary ducts endemic in the area. A nested case–control study of the first 50 incident cases observed within an average of two and a half years of follow-up confirmed a strong association between the infection and the risk of developing cholangiocarcinoma. This analysis also showed that serum antibody titres against the parasite are better markers of past infection than faecal egg-count.

A second phase of recruitment to double the size of the cohort started in 1998 and by June 1999, 5642 further subjects had been recruited, giving a total of over 18 000. The increased size of the cohort will allow study of other disease endpoints in relation to a variety of lifestyle factors, genetic factors and environmental exposures.

Figure 18. Liver cancer study in Khon Kaen, Thailand. Above, storage of specimens; below, dispatch of samples to IARC.

3.3.3

Liver cancer in Qidong, China

D.M. Parkin and R. Montesano; in collaboration with C.P. Wild, Leeds,UK; and Y.-R. Zhu, J.-G. Chen and Lu J.-H., Qidong,China; supported by a grant from the World Cancer Research Fund, UK

In 1989 a project was established in Qidong county, China, to screen the population of adult males aged 30–59 years for early liver cancer. About 45 000 subjects were screened for HBsAg. Approximately 20% proved to be positive. Blood specimens from 6000 HBsAg-positive and 10 000 HBsAg-negative subjects have been stored since that time. HBsAg-positive subjects entered the screening study proper, with details of each subject entered onto a computer file, and annual follow-up through the Qidong County Cancer Registry, and the death register.

A nested case–control study of subjects from this cohort who developed liver cancer was initiated in 1999. The objectives are (*a*) to determine the role of exposure to dietary aflatoxins in the etiology of liver cancer; (*b*) to investigate whether liver cancers bearing specific mutations (G:C to T:A transversions) at codon 249 of the *p53* gene are more frequent in individuals who had

measurably higher exposure to aflatoxin in the past; (*c*) to study the role of genetic polymorphisms in susceptibility to aflatoxins; and (*d*) to estimate the magnitude of the combined effects of aflatoxin and hepatitis viruses.

The computer file of cohort members who were HBsAg-negative at enrolment has been completed, followed by matching of the cohort members with the records of liver cancer cases and deaths. Specimens from identified liver cancer cases and matched controls are being analysed for albumin–aflatoxin adducts, for genetic polymorphisms and for p53 mutations.

3.3.4
Interaction between environmental exposures and viral infection in liver cancer

P. Boffetta; in collaboration with F. Donato, Brescia, Italy; D. Trichopoulos, Athens, Greece; S. Cordier, Paris, France; and J. Chen, Taipei, China

A meta-analysis addressing statistical interaction between hepatitis B and C viruses in liver carcinogenesis has provided evidence of an independent effect of the two viruses in increasing the risk of liver cancer [148]. A pooled analysis of case–control studies that have analysed infection from both viruses and collected a lifetime history of alcohol drinking has been initiated to provide information on the interaction between infection with either virus and elevated alcohol intake in liver carcinogenesis.

3.3.5
Experimental study on fumonisins

M. Castegnaro and L. Garren; in collaboration with W.C.A. Gelderblom, Cape Town, South Africa; and C.P. Wild, Leeds, UK

To investigate a possible synergistic interaction between HBV and fumonisin B_1, four groups of transgenic mice were set up, HBV-positive or -negative, with or without fumonisin B1. No fumonisin-related difference in the incidence of tumours was detected in the HBV-positive mice. The organs have been analysed for alterations of sphingolipid biosynthesis in the fumonisin-treated groups (see Section 6.1.3) and the results have shown that (1) the target organ in mice is the kidney (as in other species), (2) there is no significant difference in the other organs, and (3) there is a marginally significant difference in blood.

3.3.6
Genetic alterations in hepatocellular carcinoma

R. Montesano, P. Hainaut, A.-M. Camus, G. Kirk and D.M. Parkin; in collaboration with C. Brechot, Paris, France; J.J. Goedert, Bethesda, MD, USA; C. Trepo and P. Merle, Lyon, France; C.P. Wild, Leeds, UK; and Y.-R. Zhu, Qidong, China

The spectra of *p53* gene mutations in HCC differ considerably among different areas of the world, probably reflecting different etiologies. In particular, a high prevalence of mutation at codon 249 is found in HCC patients from regions of high exposure to aflatoxin B_1 (see Figure 19).

As part of the Gambia Hepatitis Intervention Study (see Section 5.1.1), cell-free DNA circulating in the plasma of patients with HCC and cirrhosis in The Gambia was analysed for the presence of the 249^{ser} p53 mutation. This mutation was detected in approximately 40% of HCC cases. No such mutation was detected in the plasma DNA of HCC patients from Europe [237]. A similar study in another population at high risk of HCC in Qidong (China) is in progress (see Section 3.3.3). The use of this and other genetic markers in DNA present in serum or plasma should facilitate the implementation of population-based molecular epidemiological studies of the etiology of HCC and in exploring the interaction between HBV infection and other risk factors.

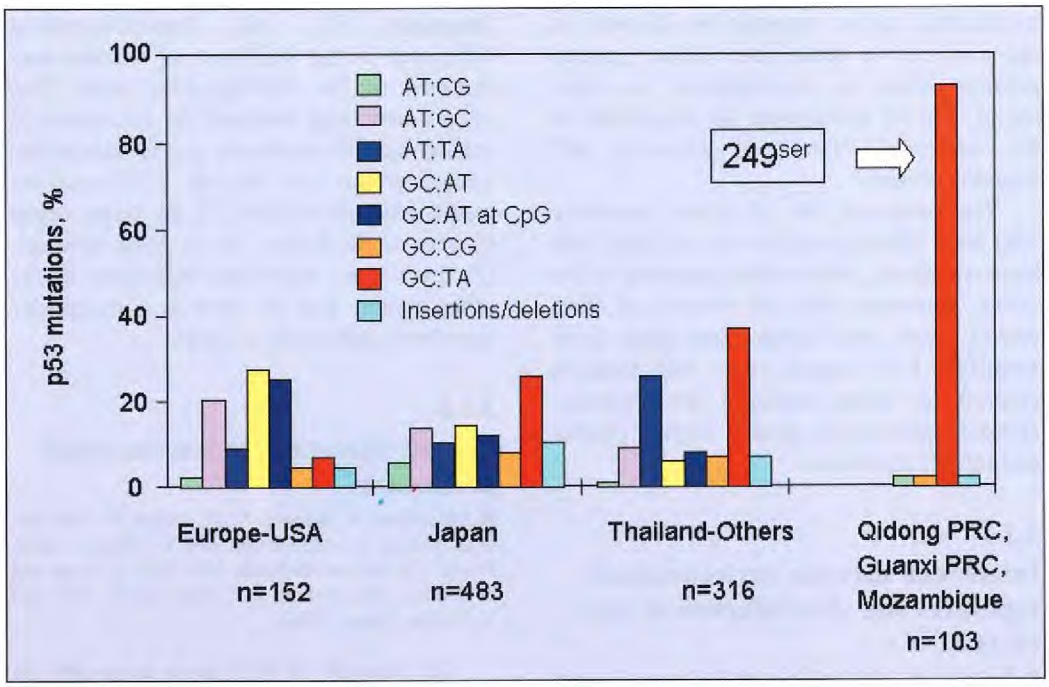

Figure 19. p53 mutation at codon 249 in HCC associated with exposure to hepatitis B virus and aflatoxin B_1

A selective G to T transversion mutation at codon 249 (AGG→AGT, arginine to serine) has been identified as a "hotspot" mutation for HCC. This mutation is absent in countries of low exposure to aflatoxin B_1 and its frequency increases with the level of exposure to aflatoxin B_1.
Adapted from Montesano *et al.* (1997) *J. Natl Cancer Inst.*, **89**, 1844–1851

3.3.7

β-Catenin mutations in human hepatocellular carcinomas associated with hepatitis C virus infection

H. Huang, A. Sankila, B.M. Mahler-Araujo, H. Ohgaki; in collaboration with H. Fujii and M. Matsuda, Yamanashi, Japan; and G. Cathomas, Zurich, Switzerland

The molecular mechanisms underlying the development of HCC remain poorly understood. Recently, β-catenin, one of the key components of the Wnt signalling pathway, was found to be mutated in about 20% of HCCs. In this study, we examined β-catenin and *APC* mutations in 22 HCCs associated with HCV infection, using single-strand conformational polymorphism (SSCP) analysis followed by direct DNA sequencing. β-Catenin mutations were found in nine (41%) cases, but no *APC* mutations were found. Immunohistochemistry revealed nuclear accumulation of β-catenin protein in all nine tumours with a β-catenin mutation and in two additional tumours without a mutation. These results suggest that activation of the Wnt signalling pathway by β-catenin mutation contributes significantly to hepatocellular carcinogenesis associated with HCV infection [202].

3.3.8

Expression of hepatic carcinogen-metabolizing enzymes in HBV transgenic mice with liver injury

I. Chemin and H. Ohgaki; in collaboration with F.V. Chisari, La Jolla, CA, USA; and C.P. Wild, Leeds, UK

To evaluate the possible modulation of carcinogen-metabolizing enzymes in relation

to chronic infection with HBV, we have investigated whether enzyme levels are altered in association with HBV gene expression *per se* or only when such expression is associated with induction of liver injury. We studied four different HBV transgenic mouse lineages that express the transgene encoding for the large envelope protein (HBsAg) at different levels. These lineages exhibit associated liver injury which progresses with age and is positively correlated with the degree of accumulation of HBsAg in the hepatocytes. The modulation of levels of cytochrome P450 and glutathione *S*-transferases (GSTα and π) involved in carcinogen metabolism was examined immunohistochemically. While we observed an increase in staining intensity of P450s 1a and 2a5 in lineages expressing cytopathic amounts of HBsAg, there were only minor or no changes at all for the other lineages. Staining with antibodies to cytosolic GSTπ revealed an increase in older mice, but no major alteration was observed for GSTα. These result suggest that liver cell injury induced by accumulation of HBV antigens can lead to induction of some carcinogen-metabolizing enzymes; this may be one mechanism of chemical–viral interactions in hepatocarcinogenesis [108].

3.4 Cancer of the cervix

Cancer of the cervix is the second most common cancer in women. The association of human papillomavirus (HPV) with cervical cancer is very strong, independent of other risk factors and consistent in several countries. This association is strong not only with the most common HPV types (HPV 16 and 18) but also with the less prevalent types (HPV 31, 33, 45, 52, 58, 59). Data on co-factors that influence progression from persistent HPV infection to invasive cervical cancer and on prevalence of HPV types in women with cervical cancer and in normal women are being collected that will provide essential background information for planning preventive strategies using HPV vaccines that are under development (Section 5.1.4).

Several review articles on HPV and cervical cancer have been published [60, 61, 194].

3.4.1 Case–control studies of cervical cancer in Spain and Colombia

N. Muñoz, J. Smith, R. Herrero and A. Arslan; in collaboration with N. Ascunce, Pamplona, Spain; F.X. Bosch, X. Castellsagué, S. de Sanjosé and P. Viladiu, Barcelona, Spain; K. Cho, Ann Arbor, Michigan, USA; M. Gili, Seville, Spain; L.C. Gonzalez, Salamanca, Spain; I. Izarzugaza, Vitoria-Gasteiz, Spain; C. Martos and P. Moreo, Zaragoza, Spain; C. Navarro and M.J. Tormo, Murcia, Spain; J. Schlehofer and K. Erles, Heidelberg, Germany; K.V. Shah and R. Daniel, Baltimore, MD, USA; and L. Tafur, Cali, Colombia

Adeno-associated viruses have been proposed as potential protective factors for cervical cancer because of their anti-oncogenic activity. To explore this hypothesis, adeno-associated virus type 2 (AAV-2) antibodies have been measured using an ELISA assay in randomly selected sera from 109 patients with invasive cervical cancer, 100 population-based controls age-matched to invasive cases, 77 patients with *in situ* cervical cancers (CIS) and 100 hospital-based controls age-matched to the *in situ* cases. The prevalence of AAV-2 IgG antibodies in these four groups was 74%, 80%, 87% and 89% respectively.

AAV-2 seropositivity was not significantly associated with the risk of carcinoma *in situ*. However, when invasive cancer cases were compared with controls or with CIS, a pattern of decreasing cervical cancer risk with increasing IgG titre was observed, supporting the notion that AAV-2 may be a potential protective factor for HPV-induced

cervical cancer. However, this finding requires confirmation.

HPV DNA detection in cervical cells collected during the follow-up of HPV-positive and HPV-negative control women and their husbands has been carried out. Only one third of the subjects could be traced 10 years after inclusion in the original study. Only 6% of the men and none of the women who were originally HPV DNA-positive were still HPV DNA-positive 10 years later.

Three women from Colombia (two originally positive for HPV 16 and one HPV-negative) were diagnosed with cervical intraepithelial neoplasia grade I (CIN-I) 10 years later, but none was diagnosed with high-grade lesions or cervical cancer.

A total of 200 frozen biopsies from invasive cancers from Spain and Colombia were analysed for alterations in the Fragile Histidine Triad (*Fhit*) gene, a candidate tumour-suppressor gene, and in other genes, to investigate their role in the pathogenesis and prognosis of cervical cancer. Half of the biopsies were considered suitable for the genetic studies. An immunohistochemical analysis is being performed to assess *Fhit* expression and to correlate this with clinical outcome.

High molecular weight genomic DNA was isolated from pooled frozen sections from 33 tumours. 26 tumours with sufficient DNA have been evaluated by Southern blot for increased copy numbers of c-*myc*, *HER2/neu* and *EGFR* genes. Only one tumour showed high copy numbers (i.e., amplification) of any of these genes (c-*myc*). The remainder showed changes suggesting low copy number gains.

3.4.2

Multi-centre case–control study of cervical cancer

N. Muñoz, R. Herrero, J. Smith and A. Arslan; in collaboration with M. Almonte and E. Caceres, Lima, Peru; R. Ashley, Seattle, WA, USA; F.X. Bosch and X. Castellsagué, Barcelona, Spain; N. Chaouki, Rabat, Morocco; S. Chichareon, Hat-Yai, Thailand; P. Coursaget, Tours, France; J. Eluf-Neto and C. Murta, São Paulo, Brazil; D. Hammouda, Alger, Algeria; C. Ngelangel, Manila, The Philippines; R. Peeling, Winnipeg, Canada; P.A. Rolón, Asunción, Paraguay; T. Rajkumar, Madras, India; M. Santamaria, Pamplona, Spain; and J. Walboomers, Amsterdam, The Netherlands

This study is investigating the role of specific HPV types and cofactors in the etiology of cervical cancer. Case–control studies have been completed in Algeria, Brazil, India, Mali, Morocco, Paraguay, Peru, the Philippines and Thailand, in addition to those conducted in Spain and Colombia (see above). The main results from Brazil, Colombia, Morocco [103], Paraguay [400], the Philippines [323] Spain and Thailand [110] have been published. For the studies in Algeria and India, each including 200 cases and 200 controls, the laboratory assays for HPV DNA detection have not yet been completed.

Sera from cases and controls in Brazil have been examined for antibodies to HPV 16 virus-like particles (VLPs) using an ELISA assay. The prevalence in cases was 47% and in controls 24%. This prevalence was higher in women positive for HPV 16 DNA (54%) than in those positive for other HPV types (37%) or negative for HPV (45%) but the differences were not statistically significant. Among cases and controls, HPV 16 VLP antibodies were associated with a greater number of lifetime sexual partners, and among controls, age was inversely associated with HPV 16 VLP reactivity [492].

In Mali, Paraguay and Peru, the overall HPV DNA prevalence in the cervical cancer cases was 92%, 97% and 95%, respectively, and among controls was 33%, 23% and 18%, respectively. The pattern of risk associations with HPV types and cofactors was similar to those observed in Brazil, Morocco, the Philippines and Thailand. HPV 16 was clearly the predominant type among cases, followed by HPV 18. In Mali and Paraguay,

HPV 45 was the third most common type, while in Peru it was HPV 31. Significant associations with the risk of cervical cancer were found for HPV 16, 18, 31, 33, 35, 39, 45, 52, 56 and 58.

In the study in Mali, sera from cases and controls have been tested for antibodies to HPV 16, 18 and 31 VLPs using an ELISA assay. The prevalence of antibodies to HPV 16 and 31 VLPs was slightly higher in cases (49% and 25%) than in controls (36% and 20%), but the prevalence of HPV 18 VLPs was the same in cases and controls (7.2% vs 7.3%). Positivity for any of the three HPV types was 60% in cases and 45% in controls.

In view of a previous report, the possible role of *p53* polymorphisms at codon 72 was investigated using DNA from plasma samples of about 120 cases and 120 controls in Peru. A non-significant increase in risk for cervical cancer was observed in women homozygous for the arginine allele as compared with women homozygous for the proline allele. A similar increase in risk was found when heterozygous women were compared with women homozygous for the proline allele. Results were similar when the analysis was restricted to HPV-positive women.

A pooled analysis including about 2000 cases and about 2000 controls from all studies, except those in Algeria and India, is being carried out. The overall HPV DNA prevalences in cases and controls are summarized in Figure 20. In cases, they range from 75% in Spain and Colombia to 90–97% in the other countries. The lower prevalences in Spain and Colombia are due to the lower sensitivity of the early versions of the assay. Specimens originally classified as HPV-negative or as carrying an uncharacterized HPV type are being re-tested. Among control women, there is a positive correlation between HPV prevalence and the risk of cervical cancer in the respective country. Thus, the control women from Latin American and African countries with the highest risk of cervical cancer have the highest HPV prevalence, while Spain shows the lowest HPV prevalence and risk of cervical cancer. The Philippines have an intermediate position for both incidence of cervical cancer and prevalence of HPV.

The most common HPV types among the 2000 cases of cervical cancer were: HPV 16 (59%), HPV 18 (12%), HPV 45 (5%) and HPV 31 (4%). In the four Latin American countries, the five most common types were HPVs 16, 18, 31, 45 and 33, in the two African countries, they were HPVs 16, 18, 45, 31 and 58 and in the two Asian countries they were HPVs 16, 18, 45, 52 and 58. Very strong associations (odds ratios of 16–200) were seen for squamous cell carcinoma and types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59.

In adenocarcinoma, HPVs 16, 18 and 45 were also the most common types, but HPV 18 was found as frequently as HPV 16.

Sera from the studies in Brazil and the Philippines have been tested for *Chlamydia. trachomatis* and herpes simplex virus type 2 (HSV-2) infection among 515 cases and 552 controls. The prevalence of *C. trachomatis* antibodies, by the micro-immunofluorescence test, was 45% among cases and 22% among

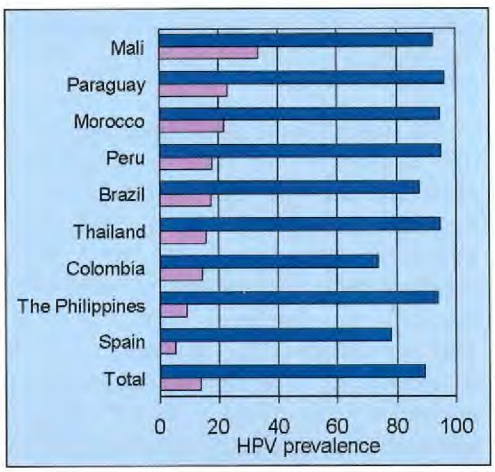

Figure 20. HPV prevalence in cervical cancer cases (■) and controls (■)

controls. Preliminary results, for all subjects and for HPV-positive cases and controls, indicate that *C. trachomatis* may be a cofactor with HPV in the etiology of cervical cancer. We are conducting further multivariate analyses to control for other potential confounding factors. The prevalence of type-specific HSV-2 antibodies was 37% among cases and 20% among controls. Preliminary results indicate that HSV-2 may be a significant HPV cofactor in the Philippines but not in Brazil.

3.4.3

International prevalence survey of HPV markers in cervical cancer tissue and sera

N. Muñoz, R. Herrero and A. Arslan; in collaboration with F.X. Bosch, V. Moreno, Ll. M. Puig Tintoré, Barcelona, Spain; A. Alihonou, Cotonou, Benin; S. Bayo, Bamako, Mali; H. Cherif Mokhtar, Sétif, Algeria; S. Chichareon, Hat-Yai, Thailand; A. Daudt, Porto Alegre, Brazil; E. de los Rios, Panama City, Panama; P. Ghadirian, Montreal, Canada; J.N. Kitinya, Dar es Salaam, Tanzania; M. Koulibaly, Conakry, Guinea; C. Ngelangel, Manila, the Philippines; J. Peto, London, UK; J. Rios-Dalenz, La Paz, Bolivia; Sarjadi, Semarang, Indonesia; M. Schiffman, Bethesda, USA; A. Schneider, Jena, Germany, L. Tafur, Cali, Colombia; A.R. Teyssie, Buenos Aires, Argentina; P.A. Rolón, Asunción, Paraguay; M. Torroella, Havana, Cuba; A. Vila Tapia, Concepción, Chile; H.R. Wabinga, Kampala, Uganda; W. Zatonski, Warsaw, Poland; K.V. Shah and R. Daniel, Baltimore, USA; M. Manos, Oakland, CA, USA; M. Jacobs and J. Walboomers, Amsterdam, The Netherlands; and C. Wheeler, Albuquerque, NM, USA

An international prevalence survey of HPV markers in over 1000 tissue specimens of invasive cervical cancer from 22 countries has been completed. Initial PCR-based analysis revealed an overall HPV DNA-positivity of 93% using primers which target the HPV L1 sequences (MY09/11 PCR). This prevalence was suspected to be an underestimate of the true prevalence due to integration events affecting the HPV L1 gene and specimen inadequacy. Serological assays for HPV 16 VLPs, E6 and E7 antibodies carried out on 49 cases of cervical cancer originally classified as HPV DNA-negative revealed 48 cases to be HPV DNA-positive. No significant difference was found in antibody prevalence to HPV 16 proteins between HPV DNA-positive cases and cases originally classified as HPV DNA-negative, supporting previous findings indicating that the latter cases were false negative for HPV DNA. Thus, PCR-based assays using more sensitive primers targeting the L1, E1 and E7 regions were carried out. Frozen biopsies from the specimens originally classified as HPV DNA-negative were subjected to histological assessment and HPV PCR assays. These new assays increased HPV DNA-positivity to 99.7%, suggesting that HPV-negative cervical cancer is extremely rare or perhaps non-existent [547].

The intratypical sequence variation of 13 HPV types (16, 18, 33, 35, 39, 45, 51, 52, 58, 59, 68, 73 and a novel type) has been investigated. The epidemiological correlates of these variants are being investigated.

To investigate prognostic factors of cervical cancer, a total of 1281 cases from this study and from some of the multi-centre case–control studies (Section 3.4.2) were followed up for survival. Preliminary results indicate that HPV type is not a predictor of tumour recurrence or survival; clinical stage and treatment modality are the main determinants. These findings confirm our previous observations in Spain and Colombia.

3.4.4

Comparison of two methods for sampling from the normal cervix in assessing HPV DNA prevalence

N. Muñoz; in collaboration with S. Chichareon, Hat-Yai, Thailand; S. de Sanjosé, F.X. Bosch, L. Balaguero, M.J. Pla, B. Lloveras and E. Condom, Barcelona, Spain; C. Ngelangel, Manila, The Philippines; and J. Walboomers, Amsterdam, The Netherlands

To assess the importance of the type of specimen in determinations of HPV prevalence, a validation study was performed. Cervical scrapes and biopsies were collected in the Philippines, Spain and Thailand from

331 women with normal cytology in whom hysterectomy was performed for reasons other than cervical cancer. These women, after giving informed consent, provided 992 cell samples and 1324 biopsy samples at the time of surgery; three consecutive cervical scrapes were taken as well as four biopsy specimens, one in each of the quadrants around the cervical os. All scrapes and 103 of the biopsy specimens were tested for HPV by PCR electroimmunoassay using a general primer (GP5+/bio6+). Type-specific tests were performed for 14 HPV types. The prevalence of HPV DNA was 6.3% in cervical cells. Of 19 HPV-positive samples in the scrapes, 17 were confirmed in the biopsy specimens. The agreement, as measured by the Kappa statistic, was 0.90 ($p < 0.001$). The concordance in detecting HPV infection between scrapes and biopsy specimens was 97.5%, and the concordance in categorizing the samples as negatives was 94.4%. These findings indicate that among women without cervical cancer, HPV DNA detection rates do not vary if exfoliated cells or random biopsy specimens are taken as the primary testing specimen. Screening programmes based on highly sensitive HPV DNA detection techniques in cell scrapes should expect a minimal underdetection [129].

3.4.5

Cohort study on HPV, hormonal contraception and cervical neoplasia

N. Muñoz, R. Herrero and A. Arslan; in collaboration with O. Meirik, Geneva, Switzerland; H. Posso, C. Camargo, C. Molina and O. Orozco, Bogotá, Colombia; K. Shah, Baltimore, MD, USA; and J. Walboomers, A. van den Brule and M. Molano, Amsterdam, The Netherlands

This cohort study was initiated in November 1993 to investigate the natural history of HPV infection and in particular to identify the determinants of progression to persistent HPV infection and cervical neoplasia. Special attention is being paid to the role of hormonal contraception as a predictor of progression in women with HPV infection. 2140 women attending several health centres in Bogotá, Colombia, have been enrolled. Personal interviews on risk factors and gynaecological examinations are performed at study entry and during follow-up examinations every 6–9 months. Cervical cells are collected for a Pap smear and HPV DNA detection by PCR-based assays at entry and during the follow-up examinations. Compliance with the follow-up visits ranges from 83% at the first follow-up visit to 40% at the fifth. A total of 10 400 cervical cell pellets had been collected by August 1999 and 900 (40%) of the women have completed five follow-up examinations. Follow-up will continue until December 2000.

Statistical analysis of the data collected at baseline indicates that the socioeconomic characteristics of the study women were similar to those reported in a demographic survey carried out in a random sample of the female population of Bogotá in 1995. 80% of the women reported use of any contraceptive method and 46% reported ever using oral contraceptives. Ever having smoked was reported by 27% of the women; 16% were current smokers and 11% ex-smokers. 90% reported ever having had a Pap smear taken.

The prevalence of squamous intraepithelial lesions at the baseline examination of 2122 women was 4.8% (3.8% low-grade, 0.8% high-grade). Invasive cervical cancer was diagnosed in five women (0.2%) at study entry.

HPV DNA detection in 1400 cell pellets collected at baseline has been carried out using PCR-based ELISA for 14 high-risk and 23 low-risk HPV types. A prevalence of 16% was found (14% high-risk and 2% low-risk types). HPV DNA detection in the remaining 9000 cell pellets, as well as HPV typing, is in progress. 1300 of the specimens have also been tested for *C. trachomatis* using a PCR-based ELISA; 8% were positive. No correlation was seen between positivity for HPV and positivity for *C. trachomatis*.

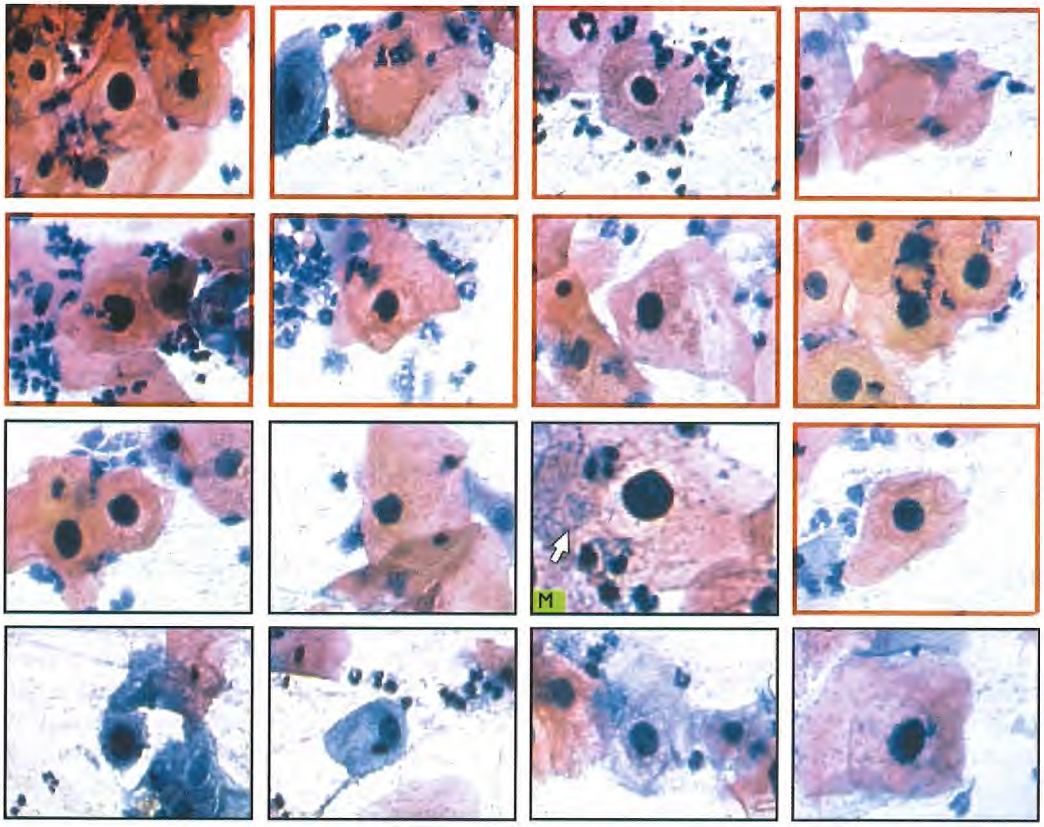

Figure 21. Computer-selected images from semi-automated PapNet cytological screening for cervical neoplasia.

3.4.6

Population-based natural history studies of cervical neoplasia in a high-incidence area of Latin America: the Guanacaste Project

R. Herrero, A. Arslan and M. Plummer; in collaboration with C. Bratti, A.C. Rodriguez, J. Morales and M. Alfaro, San José, Costa Rica; R. Burk, New York, NY, USA; M. Hutchinson, Boston, MA, USA; A. Lörincz, Silver Spring, MD, USA; and M. Schiffman, A. Hildesheim, M. Sherman and S. Wacholder, Bethesda, MD, USA

A population-based cohort study of 10 000 women in a high-incidence area of Costa Rica is being carried out, sponsored by the United States National Cancer Institute and the Costa Rican Bureau of Social Security. The aims are to investigate the natural history of HPV infection and cervical neoplasia and to evaluate new cervical cancer screening techniques (conventional cytology, liquid-based cytology, semi-automated cytology, cervicography, HPV testing). Women were invited to participate at local clinics and completed a questionnaire to provide information on risk-factors. A pelvic examination was carried out including determination of vaginal pH and collection of cells for the different screening techniques and HPV detection. Participation rates were over 90%.

A clear increase of vaginal pH was associated with increasing age and menopause. HPV infection and CIN were not associated with changes in pH [168]. Testing for more than 40 HPV types with an

MY09/MY11 PCR-based system has been completed. Overall prevalence of HPV infection was 16%. HPV DNA was detected in 11% of women with a normal cervix, 73% of women with low-grade CIN, 89% of high-grade CIN and 88% of cancers. Among women without significant cervical abnormalities, HPV detection showed a bimodal pattern, with an initial peak among women under 25 years of age and a second peak after age 55 years, indicating possible reactivation of HPV infections after menopause [193].

Evaluation of the performance of the semi-automated PapNet method for cytological screening among 7323 women indicated a sensitivity of 86% for high-grade CIN and cancer, with referral for colposcopy of 4.3% of subjects (those with a cytological diagnosis of atypical squamous cells of undetermined significance (ASCUS) or more severe) (Figure 21) [474]. Liquid-based cytology with the ThinPrep method among 8636 women showed a sensitivity for high-grade lesions and cancer of 93%, with referral of 12.7% of subjects for colposcopic evaluation [207].

A screening method based on HPV DNA detection, known as Hybrid Capture II, was evaluated to define the most suitable detection threshold. An analytical sensitivity of 1.0 pg/ml permitted detection of 89% of high-grade lesions and cancer, with referral of 12.3% of the women [459].

A similar evaluation of cervicography, a method in which two photographs of the cervix are taken after application of acetic acid and the images (cervigrams) are interpreted by expert colposcopists, showed a sensitivity of only 49% for high-grade lesions and cancer, although all of the small number of cancer cases were detected by this method [463].

In an effort to evaluate local mucosal immunity, samples of cervical mucus were collected from a sample of women. Initial evaluation indicates that the collection of mucus before collecting exfoliated cells for the Pap smear does not affect the quality of the smears [196]. Another study allowed the validation of the Weck-cell sponge as a reproducible method for measurement of immunological parameters in cervical secretions [197].

The potential role of the arg/arg polymorphism at codon 72 of the *p53* gene as a risk factor for cervical neoplasia was investigated, but no association was detected [198].

In order to investigate potential markers of immune response to HPV, plasma levels of soluble interleukin 2 receptor (SIL-2R), a known proxy for general immune activation, were measured among cases of low- and high-grade cervical intraepithelial lesions and compared with the levels in a control group. SIL-2R levels increased in the order controls < low-grade lesions ~ high-grade lesions < cancers, indicating that this marker increases in response to HPV infection or cancerous invasion, but is unrelated to disease progression among women with low-grade disease [514].

3.4.7 Prevalence surveys of HPV infection in high- and low-incidence areas for cervical cancer

R. Herrero and N. Muñoz; in collaboration with P.T.H. Ahn, Hanoi, Viet Nam; M. Almonte, Lima, Peru; P. Coursaget, Tours, France; S. de Sanjosé, Barcelona, Spain; N.T. Hieu, Ho Chi Minh City, Viet Nam; E. Lazcano, Cuernavaca, Mexico; E. Matos and G. Amestoy, Buenos Aires, Argentina; H. Posso, Bogotá, Colombia; R. Prado, Santiago, Chile; J.W. Sellors, Hamilton, Canada; K.V. Shah, Baltimore, MD, USA; H.R. Shin, Pusan, Republic of Korea; S. Sukvirach, Bangkok, Thailand; J.O. Thomas, Ibadan, Nigeria; and J. Walboomers, Amsterdam, The Netherlands

In preparation for phase III trials of HPV vaccines that are currently under development, we are investigating the age-specific prevalence of HPV infection and its immunological correlates in different geographical regions, by carrying out a series

of surveys in age-stratified random samples of the female population in areas with different incidence rates of cervical cancer. A series of life-style factors (e.g., sexual and reproductive behaviour, contraceptive use, smoking, alcohol, cervical cytological screening habits) and markers of past or current exposure to other sexually transmitted diseases are also being assessed. In each participating centre, approximately 1100 women are being recruited, to include 100 subjects in each of 11 age categories. Subjects who agree to participate are interviewed about behavioural factors; a pelvic examination is carried out and cervical cells are collected for cytological evaluation and HPV testing. The study has been completed in Hanoi and Ho Chi Minh City, Viet Nam; Lampang, Thailand; Concordia, Argentina; Morelos State, Mexico; and Barcelona, Spain. Field work is continuing in Hat-Yai, Thailand and in Ibadan, Nigeria, and plans have been made to extend the study to Pusan, Republic of Korea; Santiago, Chile and Peru (Figures 5–10). The baseline data from our cohort studies in Guanacaste, Costa Rica and Bogotá, Colombia (see above) are also available for this series.

Prevalence surveys among males with a similar design to that of females are being planned. A pilot study among recruits in Cuernavaca, Mexico, initially indicated that urine specimens could not be used for determination of the genital HPV status of male subjects, as most of the specimens collected were negative for β-globin, a marker of the adequacy of smears for PCR amplification. However, this may be explained by the presence of specific inhibitors of the PCR reaction in urine. Additional work is being carried out in an effort to eliminate such inhibitors.

HPV DNA testing of samples with PCR is in progress, and antibodies against L1 virus-like particles (VLPs) of HPV types 16, 18 and 31 are being measured.

In preliminary analyses of data for 1350 women in Morelos State, Mexico, overall HPV prevalence was 13% and was high among women aged under 25 years, declined with age up to 45 years but then increased with age in a pattern similar to that seen in the Guanacaste cohort (see Section 3.4.6). This suggests that latent HPV infection can be reactivated among older women.

For the survey in Concordia, Argentina, HPV DNA testing of 1037 cervical scrapes revealed an overall HPV prevalence of 19.5% (14% high-risk HPV types and 5.5% low-risk types). The prevalence of VLP antibodies shows a strong correlation with sexual behaviour for HPVs 16, 18 and 31 (Figure 22). Antibody levels initially increase with age, followed by a decline at later ages. In this centre, colposcopy was performed on all subjects. The extent of cervical ectopy was strongly and inversely correlated with age and also inversely correlated with the number of years since last birth and with current smoking. In addition, a strong correlation between ectopy and inflammatory Pap smears was observed. An analysis of determinants of participation in Pap smear and mammographic screening programs and of smoking is in progress.

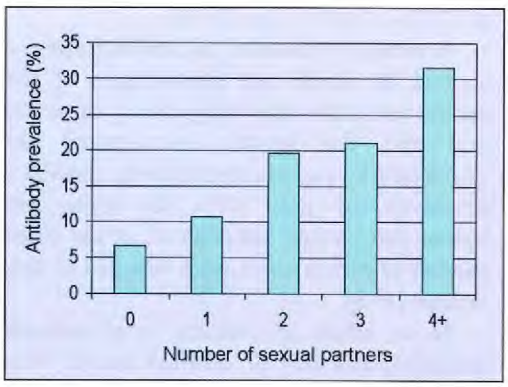

Figure 22. Levels of antibodies to HPV-16 VLPs by number of sexual partners, Concordia, Argentina

Figure 23. Prevalence surveys of HPV infection. (*a*) Planning the logistics of the HPV prevalence survey in Concordia, Argentina. (*b*) Selection of a random sample from clinical population lists in Lampang, Thailand. (*c*) Explaining the study to potential Nigerian participants. (*d*) Interviewing a participant in Hanoi, Viet Nam. (*e*) Blood collection from a participant in Nigeria. (*f*) Processing biological specimens in Thailand

In Nigeria, the study is being conducted in Idikan, a predominantly Muslim poor neighbourhood of Ibadan. The field work commenced in April 1999. 3500 women over 10 years of age were recruited and completed the initial part of the questionnaire on general and non-sensitive questions. By August 1999, about 800 of the recruited women had attended a local health clinic to complete the interview and undergo a gynaecological examination, during which cervical cells and blood samples are collected. Visual inspection with acetic acid is being evaluated as a simplified screening method for high-grade cervical neoplasia and cancer (see Section 5.4.2). The field work is expected to be completed in early 2000.

3.4.8

Time trends of cervical cancer

A.P. Vizcaino, N. Muñoz and D.M. Parkin; in collaboration with F.X. Bosch and V. Moreno, Barcelona, Spain

Trends in cervical cancer incidence by histological type have been examined, using data provided by 60 cancer registries for 32 defined populations in 25 countries during the period 1973–91 for at least two consecutive volumes of *Cancer Incidence in Five Continents*.

All cervical cancer cases were categorized by histological type according to the ICD-O codes, as assigned by each registry.

Three components of the incidence trend were studied: age, calendar period of diagnosis and birth cohort. Models were elaborated by smoothing the different effects with polynomials in a stepwise procedure. Two cumulative incidence rates for the age ranges 25–49 and 50–74 years were calculated from the model that best described the data.

The main finding was a significant increase in the incidence of adenocarcinoma among younger women in some populations in the United States (Whites), Australia, New Zealand (non-Maori), Denmark, Sweden, Slovenia, Slovakia and Japan (Osaka) and the Chinese population of Singapore, despite a concomitant decrease in squamous cell carcinoma[541, 542]. This is consistent with an underlying increase in risk of both histological types, but less efficient prevention of adenocarcinomas by conventional screening.

An increase in both histological types among younger women was observed in England, Scotland, Slovenia and Slovakia. However, for England and Scotland, in the cohort of youngest women (born around the 1960s), the incidence of squamous cell carcinomas appears to have started declining.

3.5 Brain tumours

Brain tumours are relatively rare, but pose a significant clinical challenge due their frequent occurrence in children and generally poor prognosis. Despite major epidemiological efforts, therapeutic X-irradiation has remained the only exposure unequivocally associated with the evolution of human brain tumours. Nervous system neoplasms also occur in various inherited cancer syndromes, including p53 germline mutations. In addition to epidemiological projects, studies at IARC are focused on the identification of sequentially acquired genetic alterations in the evolution and progression of astrocytic brain tumours and their relationship to histological phenotype and patients' survival.

3.5.1

Brain tumours in adults

J. Little and R. Saracci; in collaboration with A. Ahlbom, Stockholm, Sweden; M. Blettner, B. Schlehofer and J. Wahrendorf, Heidelberg, Germany; P. Boyle, Milan, Italy; N.W. Choi and E. Kliewer, Winnipeg, Canada; S. Cordier, Paris, France; R. Gurevicius, Vilnius, Lithuania; G. Howe, New York, USA; J. McNeil, Melbourne, Australia; F. Ménégoz, Meylan, France; B. Modan, Tel Hashomer, Israel; S. Preston-Martin, Los Angeles, CA, USA; and P. Ryan, Adelaide, Australia

Data have been collected on all cases of brain tumours newly diagnosed in nine centres in seven countries during the period 1984–92 and on population-based controls. Data were obtained on a total of 1238 cases of glioma, 412 cases of meningioma and more than 2500 controls. In combined analysis, there was an elevated risk of meningioma in men associated with a reported history of head injury. This was not statistically significant and the magnitude of the risk decreased when only serious head injuries were considered. There was little support for an association between glioma and head trauma, or between head trauma and meningioma in

women. No association between meningioma and previous medical history was found [461]. Inverse associations were apparent between gliomas and allergic diseases (either combined or asthma, eczema and others considered separately) and reported history of infectious diseases. As in some other studies, there was a positive association between epilepsy and glioma, but the possibility that epilepsy is an early symptom of glioma could not be excluded.

3.5.2
Brain tumours in children

J. Little and R. Saracci; in collaboration with P. Boyle, Milan, Italy; N.W. Choi and E. Kliewer, Winnipeg, Canada; S. Cordier, Paris, France; G. Filippini, Milan, Italy; R. Gurevicius, Vilnius, Lithuania; E.A. Holly. San Francisco, USA; M. McCredie, King's Cross, Australia; B. Modan, Tel Hashomer, Israel; B. Mueller, Seattle, USA; R. Peris-Bonet, Valencia, Spain; and S. Preston-Martin, Los Angeles, CA, USA

Data were collected on a total of 1218 cases and 2223 controls in nine centres in seven countries. Combined analysis suggests that maternal use of vitamin supplements for at least two trimesters during the index pregnancy is inversely associated with childhood brain tumours, with a trend of less risk with longer duration of treatment [383, 384]. The effect did not vary by histology and was observed for supplementation during pregnancy rather than during the month before pregnancy or while breast-feeding. This finding was largely attributable to the data from the centres in the USA, where most mothers took vitamin supplements during pregnancy. An increased risk of childhood brain tumours was associated with recalled use of inhaled anaesthetic gas during labour or delivery. No other aspect of the index pregnancy, delivery and early neonatal period or of maternal reproductive history was associated with childhood brain tumours [280]. An elevated risk associated with the index child's use of anticonvulsant drugs may be secondary to the use of these drugs for treatment of seizures before diagnosis of the tumour.

3.5.3
Genetics of glioma progression and the definition of primary and secondary glioblastoma

Y. Tohma, H. Fujisawa, R. Reis, C. Gratas, M. Fukuda, W. Biernat, K. Watanabe, A. Peraud, P. Kleihues and H. Ohgaki; in collaboration with M. Gazi Yasargil, Little Rock, AR, USA; M. Kurrer, Zürich, Switzerland; K. Schwechheimer, Essen, Germany; A. von Deimling, Berlin, Germany; S. Wakai, Mibu, Tochigi, Japan; and Y. Yonekawa, Zürich, Switzerland

Glioblastomas may develop *de novo* (primary glioblastomas) or by progression from low-grade or anaplastic astrocytoma (secondary glioblastomas). These subtypes constitute distinct disease entities which evolve through different genetic pathways, affect patients at different ages and are likely to differ in prognosis and response to therapy [240]. Primary glioblastomas develop in older patients (mean, 55 years) and typically show *EGFR* overexpression, *MDM2* amplification, homozygous *p16* deletion and LOH on chromosome 10p and 10q, while secondary glioblastomas occur in younger patients (mean, 40 years) and frequently contain *p53*

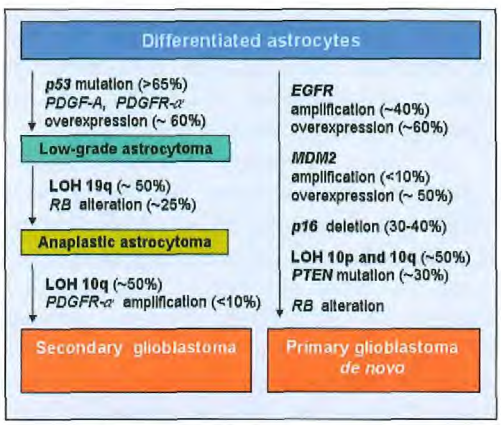

Figure 24. Genetic pathways operative in the development of primary and secondary glioblastomas

Table 3. Clinical and genetic data of glioblastoma subtypes

	Primary glioblastoma	Glio-sarcoma	Giant cell glioblastoma	Secondary glioblastoma
Clinical onset	*de novo*	*de novo*	*de novo*	Secondary
Preoperative clinical history	1.7 months	3 months	1.6 months	53 m. from low-grade astrocytoma, 25 m. from anaplastic astrocytoma
Sex ratio (M/F)	1.4	1.6	1.2	0.8
Age at diagnosis	56	55	44	40
p53 mutation	2/19 (11%)	8/35 (23%)	31/37 (84%)	20/30 (67%)
PTEN mutation	9/28 (32%)	8/21 (38%)	6/22(27%)	1/25 (4%)
p16 deletion	10/28 (36%)	7/19 (37%)	1/37(3%)	1/23 (4%)
MDM2 amplification	2/29 (7%)	1/19 (5%)	0/18 (0%)	0/27(0%)
EGFR amplification	11/28 (39%)	1/22 (4%)	2/37(5%)	0/22(0%)
CDK4 amplification	1/28 (4%)	2/19 (10%)	1/19 (5%)	3/23 (13%)

mutations and LOH on chromosome 10q [167, 239] (Figure 24 and Table 3).

Loss of heterozygosity on chromosome 10 is the most frequent genetic alteration associated with the evolution of malignant astrocytic tumours and may involve several loci. The tumour-suppressor gene *PTEN (MMAC1)* on chromosome 10q23 is mutated in approximately 30% of glioblastomas. Single-strand conformational polymorphism (SSCP) followed by direct sequencing has revealed that *PTEN* mutations are common in primary glioblastomas (32%) but rare in secondary glioblastomas (4%) [503].

In order to detect possible tumour-suppressor loci involved in the genetic pathway leading to secondary glioblastomas, we analysed loss of heterozygosity on chromosome 10, using polymorphic microsatellite markers in microdissected foci showing histologically an abrupt transition from low-grade or anaplastic astrocytoma to glioblastoma. Comparison with the respective low-grade or anaplastic astrocytoma of the same biopsy revealed deletions in seven of eight glioblastoma foci on 10q25-qter distal to D10S597, covering the *DMBT1* and *FGFR2* loci. Six of eight foci showed loss of heterozygosity at one or two flanking markers of *PTEN* but did not contain *PTEN* mutations. These data indicate that acquisition of a highly anaplastic glioblastoma phenotype with marked proliferative activity and lack of expression of glial fibrillary acidic protein (GFAP) is associated with loss of a putative tumour-suppressor gene on 10q25-qter [166].

3.5.4
Genetic alterations in low-grade astrocytomas

H. Ohgaki, W. Biernat, K. Watanabe, A. Peraud and P. Kleihues; in collaboration with M. Gazi Yasargil, Little Rock, AR, USA; A. von Deimling, Berlin, Germany; and Y. Yonekawa, Zürich, Switzerland

Low-grade diffuse astrocytomas have an intrinsic tendency for malignant progression, but the factors determining the kinetics of this process are still poorly understood.We analysed a case of a male patient who developed a fibrillary astrocytoma at the age of 33 years and who underwent six surgical

interventions over a period of 17 years without radiotherapy or chemotherapy. The first three biopsies spanned a period of 11 years and were diagnosed as low-grade, diffuse astrocytoma (WHO Grade II), and the fourth to sixth biopsies showed histological features of anaplastic astrocytoma (WHO Grade III). A *p53* mutation in codon 273 (CGT→TGT, Arg→Cys) was identified in the first biopsy and persisted throughout the course of the disease. However, the fraction of cells with p53 protein accumulation increased significantly during progression, from 3.2% in the first biopsy to 13.7% in the last. The absence of additional genetic alterations (*PTEN* mutations, loss of chromosome 10 and 19q) may be responsible for the slow progression and lack of glioblastoma features even after 17 years of disease [318, 327].

3.5.5
Genetic profile of giant-cell glioblastoma

A. Peraud, K. Watanabe, P. Kleihues and H. Ohgaki; in collaboration with K. Schwechheimer, Essen, Germany; and Y. Yonekawa, Zürich, Switzerland

Giant-cell glioblastoma is a rare glioblastoma variant characterized by the presence of large, bizarre, multinucleated giant cells. This subtype develops clinically *de novo* and contains a high frequency of *p53* mutations. We detected *PTEN* mutations in five of 15 (33%) tumours, but no homozygous deletion of *PTEN* or *p16*, or amplification of *MDM2*, and *EGFR* was amplified in only one of 17 (6%) tumours. These results indicate that giant-cell glioblastomas occupy a hybrid position, sharing with primary *(de novo)* glioblastomas a short clinical history, the absence of a less malignant precursor lesion and a 30% frequency of *PTEN* mutations. In common with secondary glioblastomas, they develop at a younger age and have a high frequency (>70%) of *p53* mutations (Table 3) [366].

3.5.6
Genetic profile of gliosarcoma

R.M. Reis, P. Kleihues and H. Ohgaki; in collaboration with D. Konu-Leblebicioglu, Zurich, Switzerland; and J.M. Lopes, Porto, Portugal

Gliosarcoma is an another glioblastoma variant characterized by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation. Analysis of 19 gliosarcomas showed that gliosarcomas exhibit a genetic profile similar to that of primary glioblastomas, except for the absence of *EGFR* amplification or overexpression. Identical genetic alterations (*PTEN* and *p53* mutations, *p16* deletion, *MDM2* and *CDK4* amplification) were observed in the gliomatous and sarcomatous tumour components, supporting the concept of a monoclonal origin of gliosarcomas [395] (Table 3, Figure 25).

3.5.7
Genetic alterations in gemistocytic astrocytomas

K. Watanabe, C. Gratas, P. Kleihues and H. Ohgaki; in collaboration with S. Wakai, Mibu, Tochigi, Japan

The gemistocytic astrocytoma is a histological variant of diffuse astrocytomas and is characterized by the presence of large, GFAP-expressing neoplastic astrocytes (gemistocytes) and a tendency for rapid progression to glioblastoma. Using SSCP followed by direct DNA sequencing of *p53* exons 5–8, we detected a mutation in 23 of 28 (82%) cases. Regional analysis of four tumours revealed identical *p53* mutations in gemistocytic and fibrillary tumour areas. In contrast, none of 15 gemistocytic astrocytomas (WHO Grade II) and only 2 of 11 (18%) anaplastic gemistocytic astrocytomas (WHO Grade III) contained a *PTEN* mutation. Of these, one was a 1-bp deletion in codon 345, the other a 1-bp insertion in intron 4. No homozygous *PTEN* deletion was detected in any of the tumours. These results indicate that *p53* mutations are a genetic

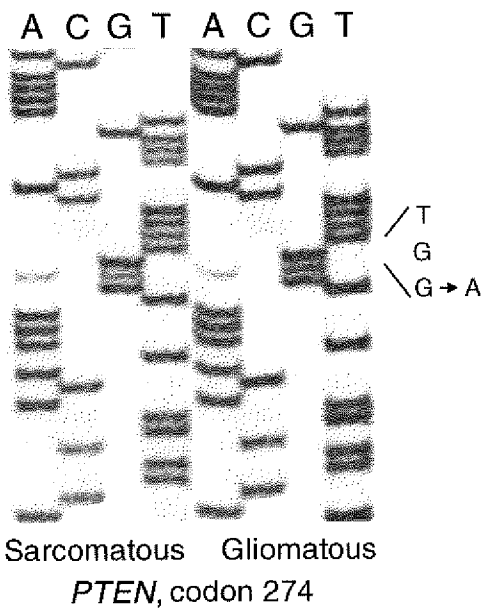

Figure 25. Sequencing gel showing an identical *PTEN* mutation in codon 274 (TGG→TGA, Trp→Stop) in microdissected sarcomatous and gliomatous areas of a gliosarcoma.

hallmark of gemistocytic astrocytomas, and that *PTEN* mutations are absent in low-grade and rare in anaplastic gemistocytic astrocytomas [548].

3.5.8
APC mutations in sporadic medulloblastomas

H. Huang, B.M. Mahler-Araujo, A. Sankila, P. Kleihues and H. Ohgaki; in collaboration with L. Chimelli, Rio de Janeiro, Brazil; and Y. Yonekawa, Zurich, Switzerland

The cerebellar medulloblastoma (WHO Grade IV) is a highly malignant, invasive embryonal tumour with preferential manifestation in children. Several molecular alterations appear to be involved, including isochromosome 17q, and *p53*, *PTCH* and β-catenin gene mutations. In this study, 46 sporadic medulloblastomas were screened for the presence of mutations in genes of the Wnt signalling pathway (*APC* and β-catenin). SSCP followed by direct DNA sequencing revealed three miscoding *APC* mutations in two (4.3%) medulloblastomas. One case contained a GCA→GTA mutation at codon 1296 (Ala→Val) and another had double point mutations at codons 1472 (GTA→ATA, Val→Ile) and 1495 (AGT→GGT, Ser→Gly). Miscoding β-catenin mutations were detected in four tumors (8.7%). Three of these were located at codon 33 (TCT→TTT, Ser→Phe) and another at codon 37 (TCT→GCT, Ser→Ala). *APC* and β-catenin mutations were mutually exclusive and occurred in a total of six of 46 cases (13%). While germline *APC* mutations are a well established cause of familial colon and brain tumours (Turcot syndrome), this study provides the first evidence that *APC* mutations are also operative in a subset of sporadic medulloblastomas [203].

3.5.9
Identification of DNA sequences specific for SV40 large T antigen in human brain tumours

H. Huang, R. Reis, P. Kleihues and H. Ohgaki; in collaboration with J.M. Lopes, Porto, Portugal, and Y. Yonekawa, Zurich, Switzerland

Simian virus 40 (SV40) induces a variety of tumours including brain tumours in animals [241]. SV40 sequences have recently been identified in a variety of human neoplasms, including mesothelioma, osteosarcoma and brain tumours, but at differing frequencies. The SV40 genome is 70% homologous to the related JC and BK polyomaviruses that are highly prevalent in humans and which may cause progressive multifocal leukoencephalopathy (PML) and cystitis, respectively, in immune-compromised patients. We have established a specific and sensitive method to identify SV40 sequences in DNA extracted from histological sections, using PCR followed by Southern hybridization to probes specific to the large T region. We found SV40 large T

antigen sequences in all brain tumour types investigated. High frequencies were found in low-grade astrocytomas, anaplastic astrocytomas and secondary glioblastomas derived from them (13/22, 59%), while somewhat lower frequencies were found in gemistocytic astrocytomas (9/28, 32%) and oligodendrogliomas (3/12, 25%). Primary glioblastomas, giant cell glioblastomas and gliosarcomas, which clinically develop *de novo*, contained SV40 sequences in 11–25% of cases. Viral DNA was also detected in paediatric brain tumours, including ependymomas (9/16, 56%), choroid plexus papillomas (6/16, 38%), and medulloblastomas (5/17, 29%). In eight tumour biopsies with SV40 sequences, the adjacent normal brain tissue was also analysed but was devoid of viral DNA in all but one case. BK and JC virus sequences were rarely detected, the overall frequencies being 3% and 2%, respectively. It remains to be shown whether the presence of SV40 contributes significantly to malignant transformation or whether certain human neoplasms provide a microenvironment that favours viral replication in humans with latent SV40 infection [204].

3.5.8
Mechanisms of apoptosis and necrosis in glioblastomas

Y. Tohma, C. Gratas, O. Tachibana, P. Kleihues, H. Ohgaki; in collaboration with E.G. Van Meir, Lausanne, Switzerland; and M. Weller and J. Dichgans, Tübingen, Germany

Fas (Fas/APO-1) and its ligand (FasL) belong to a growing cytokine and cytokine receptor family that includes nerve growth factor (NGF) and tumour necrosis factor (TNF) and their corresponding receptors. The possible use of this system in therapy of human brain tumours has been extensively investigated [553].

We assessed the expression of Fas, an apoptosis-mediating cell membrane protein, and its relationship to necrosis phenotype in primary and secondary glioblastomas. Large areas of ischaemic necrosis were observed in all primary glioblastomas but were significantly less frequent in secondary glioblastomas (10/20, 50%). Fas expression was predominantly observed in glioma cells surrounding large areas of necrosis and was thus significantly more frequent in primary (100%) than in secondary glioblastomas (20%), suggesting that these clinically and genetically defined subtypes of glioblastoma differ in the extent and mechanism of necrogenesis [504].

Necrosis and microvascular proliferation are histological hallmarks of the glioblastoma. Following incubation of glioblastoma cell lines under hypoxic or anoxic conditions for 24–48 hours, Fas mRNA levels remained unchanged. This suggests that, in contrast to vascular endothelial growth factor (VEGF), Fas expression is not induced by ischaemia or hypoxia. Analysis of Fas mRNA levels in a glioblastoma cell line containing a *p53* mutation and an inducible wild-type *p53* gene showed little difference under induced and non-induced conditions, suggesting that in glioblastomas, Fas expression is not directly linked to *p53* status [504].

APO2 ligand (APO2L) is a FasL-related cytokine of the TNF family that interacts with agonistic (DR4, DR5) and antagonistic (DcR1, DcR2) receptors. Cultured malignant glioma cells preferentially express agonistic receptors and are susceptible to APO2L-induced apoptosis. We showed that all of eight human glioma cell lines expressed APO2L mRNA and protein *in vitro*. Immunohistochemistry using a monoclonal antibody to APO2L revealed that all 23 primary astrocytic brain tumours analysed, including low-grade astrocytomas and glioblastomas, expressed APO2L *in vivo*. With the exception of reactive astrocytes, non-neoplastic glia and neurons in the cerebrum lacked immunoreactivity for APO2L. Thus, in addition to the Fas/FasL

system, a second death ligand/death receptor pair may regulate susceptibility to apoptosis in human glial neoplasms [399].

3.5.9
Hereditary factors in development of human brain tumours

H. Ohgaki, P.P. Bringuier, H. Huang and P. Kleihues; in collaboration with A. Sarasin, Villejuif, France; and A. Vital, Bordeaux, France

Xeroderma pigmentosum (XP) is a rare hereditary disease characterized by a very high frequency of skin tumours due to a defect in the nucleotide-excision repair process. Internal tumours have also been reported to develop with higher frequency than in the normal population. We have carried out genetic analyses of multiple skin cancers as well as a thalamic glioma in an XP patient. Characterization of *p53* mutations in the two tumours indicates that the skin tumour was clearly induced by the presence of unrepaired UVB-induced DNA damage on the non-transcribed strand of the *p53* gene, while the glioma may have been induced by unrepaired DNA lesions produced by free radicals [173].

Germline *p53* mutations confer an increased risk of development of breast cancer, soft-tissue and osteosarcomas, brain tumours, leukaemia and adrenocortical carcinomas [326]. Cerebral neoplasms are usually of astrocytic lineage and occur in 40% of affected families. We found two families in France with an identical *p53* germline mutation in codon 248 (CGG→TGG; Arg→Trp) and a clustering of central nervous system tumours. The youngest patient in each family developed a malignant choroid plexus tumour, while several young adults of both kindreds succumbed to low-grade astrocytoma, anaplastic astrocytoma or glioblastoma. The only non-neural neoplasm was an adrenocortical carcinoma in a boy aged four years who developed an anaplastic choroid plexus papilloma two years later. Of two previously reported inherited choroid plexus tumours, one occurred in a family which also carried a germline mutation in codon 248. It remains to be shown whether this unusual pattern of tumours is due to an organ-specific effect of this particular *p53* mutation or whether it reflects the genetic background of the affected families [539].

3.6 Cancer of the urinary tract

Tobacco smoking and diet are the major known risk factors for cancers of urinary tract, which comprise mainly neoplasms of the kidney and the bladder. The studies in progress at IARC on these cancers address three broad questions: the etiological role and the mechanism of less investigated risk factors that are of particular importance in developing countries, such as ochratoxin A in kidney cancer, the detailed aspects of the carcinogenic effect of tobacco smoking and the modification of risk due to polymorphism of metabolic enzymes.

3.6.1
Environmental risk factors and genetic susceptibility to bladder cancer in northern Italy

P. Boffetta and C. Malaveille; in collaboration with S. Porru and F. Donato, Brescia, Italy

Cases of bladder cancer and matched controls at two hospitals in Brescia are being enrolled, to assess the interaction between environmental and occupational exposure to bladder carcinogens and polymorphisms of metabolic enzymes. Data collection was completed in 1999; the laboratory and statistical analyses will be completed in 2000.

3.6.2

Combined analysis of case–control studies of bladder cancer in western Europe

P. Boffetta, P. Brennan, O. Bogillot and A. 't Mannetje; in collaboration with U. Bolm-Audorff, Wiesbaden, Germany; J. Chang-Claude and J. Wahrendorf, Heidelberg, Germany; S. Cordier, Paris, France; F. Donato, Brescia, Italy; E. Greiser, Bremen, Germany; M. Hours, Lyon, France, K.H. Jöckel, Essen, Germany; M. Kogevinas, Barcelona, Spain; G. Lopez-Abente, Madrid, Spain; W. Schill, Bremen, Germany; C. Serra, Sabadell, Spain; A. Tzonou, Athens, Greece; and P. Vineis, Turin, Italy

A total of 2600 cases of bladder cancer and 5500 controls have been enrolled in a series of 11 studies in western Europe and comparable information on tobacco smoking has been collected. A common database with information on tobacco has been established, and the analysis is focusing on detailed aspects of tobacco carcinogenesis that cannot be addressed in smaller studies. Among men, the risk of bladder cancer was found to increase linearly with increasing duration of smoking (Figure 26), and an immediate decrease in risk of bladder cancer was observed in those who gave up smoking. However, even after 25 years, the decrease in risk did not reach the level of the never-smokers. Furthermore, two out of three bladder cancer cases were found to be attributable to having ever smoked [66]. Comparative analyses of the risk of bladder cancer from cigarette smoking in women and of the effect on bladder cancer of smoking cigars and pipe tobacco are being carried out.

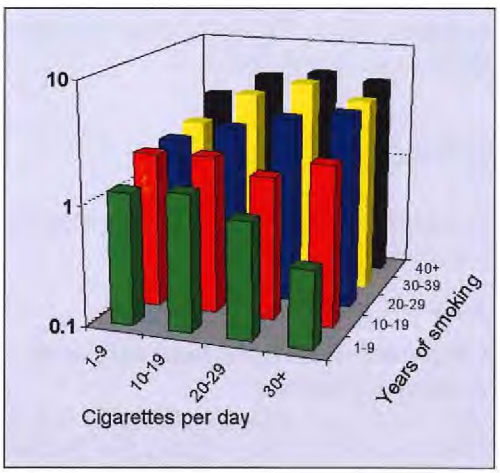

Figure 26. Effect of duration of smoking and average consumption on the risk of bladder cancer. Reference category: non-smokers

3.6.3

Ochratoxin A in relation to urinary tract tumours

M. Castegnaro and L. Garren; in collaboration with H. Bartsch, Heidelberg, Germany; I.N. Chernozemsky, T. Petkova-Bocharova, I. Nicolov and T. Vrabcheva, Sofia, Bulgaria; S. Dragacci, Paris, France; and A. Pfohl-Leszkowicz and E. Pinelli, Toulouse, France

3.6.3.1

Mechanism of action of ochratoxin A

A carcinogenicity study performed in two rat strains has shown that CYP2C, 1A1/2 and 2A, but not CYP2D, are implicated in the mechanism of ochratoxin A (OTA) carcinogenicity, and that OTA modifies expression of CYPs [94, 372]. Further work is in progress to elucidate the implication of glutathione *S*-transferase and other metabolic pathways.

A study of genotoxic effects in the progeny of mice after administration of a single dose of OTA during late pregnancy has provided evidence for a direct action of OTA through transplacental contamination [367]. This constitutes a new serious health hazard of exposure to this toxin. Some of the progeny have been kept alive and fed an OTA-free diet to determine whether the animals will suffer from tumours or pre-tumourous lesions.

3.6.3.2

Serum and urinary OTA levels as a biomarker of exposure

A controlled duplicate diet study involving 19 volunteers consuming their free-choice diet has been set up to validate

the use of measurements of serum and/or urinary OTA as biomarkers of exposure to OTA-contaminated food at the individual level. Samples of daily food during a period of four weeks and of urine and blood collected from each volunteer at the beginning of the study and the end of each week have been analysed by immunoaffinity purification and HPLC–spectrofluorimetry detection. The data are being analysed. A questionnaire has been validated for a study in a population exposed to natural environmental levels of OTA, who will be followed after transfer to an OTA-free controlled diet, in order to measure the half-life of the toxin in the blood.

3.6.4

Renal pelvis carcinomas associated with smoking and phenacetin: p53 mutations and polymorphism of carcinogen-metabolizing enzymes

P.-P. Bringuier, H. Ohgaki and P. Kleihues; in collaboration with M. Bilous, Westmead, Australia; M. McCredie, Sydney, Australia; and G. Sauter and M.J. Mihachi, Basel, Switzerland

Phenacetin abuse and smoking are established risk factors for transitional cell carcinomas in the urinary tract. We analysed exposure and the clinical course of patients who underwent nephrectomy for transitional cell carcinoma of the renal pelvis. PCR-SSCP followed by direct DNA sequencing revealed that 29 of 89 renal pelvic carcinomas (33%) contained a *p53* mutation. The incidence of *p53* mutations was significantly higher in tumours of grades 3 and 4 (46%) than in those of grades 1 and 2 (21%; $P<0.05$) and higher in invasive (51%) than in non-invasive tumours (15%; $P<0.001$). Furthermore, patients with carcinomas carrying a *p53* mutation showed poorer survival than those without mutation ($P<0.001$). The types of *p53* mutation in renal pelvic carcinomas were similar to those reported for bladder cancer, G:C→A:T transition mutations (33% at CpG sites) being most frequent, followed by G:C→T:A and G:C→C:G transversions. The incidence and type of *p53* mutations did not differ significantly in patients with a history of phenacetin abuse, smoking or neither of these habits. The frequency of genetic polymorphism in genes coding for carcinogen-metabolizing enzymes (CYP1A1, NAT1, GSTT1 and GSTM1) was also unrelated to exposure. Although the sample was too small to allow definite conclusions, these data are compatible with chronic tissue damage being a causative factor in the evolution of urothelial carcinomas, rather than a direct mutagenic effect of phenacetin and tobacco-specific carcinogens [69].

3.7 Cancer of the lung

Lung cancer is the most frequent malignant neoplasm worldwide: tobacco smoking is responsible for most cases, and the control of smoking represents the most important approach to prevent lung cancer (see Section 2.4). Among the important research questions still to be answered are the contributions of other risk factors (occupation, diet, environmental pollution) in both smokers and non-smokers and the role of genetic predisposition: these questions are being addressed in a series of studies conducted in areas of high and low risk for lung cancer.

3.7.1

Case–control study of lung cancer in northern Thailand

D.M. Parkin and P. Pisani; in collaboration with T. Bishop, Leeds, UK; N. Martin, Chiang Mai, Thailand; V. Saensingkaew, Bangkok, Thailand; and P. Srivatanakul, Bangkok, Thailand

This study has investigated the reasons for the relatively high incidence of lung

cancer, particularly in women, in northern Thailand. Age-standardized incidence rates in Lampang province, where the study was conducted, are 41.8 per 10 000 in men and 20.1 per 10 000 in women.

A case–control study comparing 196 cases of lung cancer with two groups of controls (217 hospital controls and 156 community controls drawn at random from the population of the province) was carried out from 1993 to 1995. The results confirm the major role of tobacco smoking in the incidence of lung cancer in this population, 53% of cases being attributable to this cause. The role of air pollution from numerous coal-fired electricity-generating plants was assessed by linking individual histories of place of residence to corresponding environmental measurements of arsenic and cadmium. No excess risk was detected in subjects who had long been resident in the area, after accounting for tobacco smoking.

No difference was detected between 76 cases and 74 hospital controls in cadmium and lead levels in blood samples. DNA extracted from white blood cells of cases and controls was analysed for polymorphisms of GSTM1, CYP1A1-spml and CYP1A1-E7; the effect of exposure to tobacco was not modified by genetic status with respect to polymorphisms at these loci.

3.7.2

Lung cancer and exposure to environmental tobacco smoke

P. Boffetta, P. Brennan, F. Nyberg and G. Ferro; in collaboration with A. Agudo, Barcelona, Spain; W. Ahrens, Bremen, Germany; E. Benhamou and S. Benhamou, Villejuif, France; S.C. Darby, Oxford, UK; F. Forastiere, C. Fortes and E. Rapiti, Rome, Italy; S.K. Jindal, Chandigarh, India; K.H. Jöckel, Essen, Germany; A. Mendes, Lisbon, Portugal; F. Merletti, Turin, Italy; G. Pershagen, Stockholm, Sweden; R. Saracci, Pisa, Italy; L. Simonato, Padua, Italy; H. Wichmann, Munich, Germany; and C. Winck, Porto, Portugal

An international collaborative case–control study coordinated by IARC was aimed at investigating the relationship between exposure to environmental tobacco smoke (ETS) and other environmental and occupational risk factors and the risk of lung cancer in subjects who have never smoked tobacco. Information on exposure to occupational carcinogens, urban air pollution, background radiation and dietary habits, as well as lifelong exposure to ETS, was collected for a total of 650 cases and 1542 controls in 12 centres in seven European countries. The relative risk (RR) of lung cancer was 1.16 (95% CI 0.93–1.44) for exposure to ETS from the spouse, 1.17 (0.94–1.45) for workplace ETS exposure and 1.14 (0.88–1.47) for combined spousal and workplace exposure. Several quantitative indicators of ETS showed a dose–response with lung cancer risk; RRs were higher for squamous cell carcinoma and small cell carcinoma than for adenocarcinoma. There was no association between lung cancer risk and ETS exposure during childhood [33, 34]. Self-reported (non-)smoking status was confirmed by interviews of relatives conducted in four centres: the number of self-reported non-smokers who were reported by the relatives to have ever smoked was around 1% [324]. Further analyses suggested a small increase in risk of lung cancer following heavy exposure to ETS from cigars and pipe (RR 1.60, 95% CI 0.80–3.24 for ≥ 260 g tobacco-years) [43].

An analysis of the dietary data of 506 cases and 1045 controls from eight of the centres in this study showed a strong protective effect of fruits and vegetables, that was of the same magnitude as that exerted among smokers (Figure 27) [68]. No protection was exerted by foods of animal origin. An additional analysis of the interaction between low fruit and vegetable intake and ETS exposure suggested an independent effect of the two exposures. Furthermore, low consumption of fruits and vegetables combined with high exposure to ETS was found to approximately double the risk of lung cancer among non-smokers.

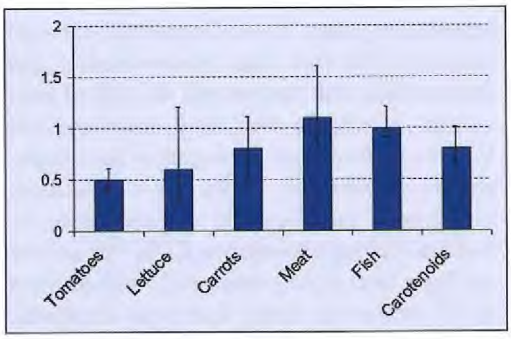

Figure 27. Risk of lung cancer among nonsmokers according to intake of selected fruits and nutrients

Risk in the highest tertile of consumption relative to lowest tertile [68].

A parallel study was conducted in Chandigarh, India, where ETS exposure comes mainly from bidi smoking. No effect was seen from exposure to ETS from bidis, while ETS from cigarettes and exposure to ETS during childhood were associated with increased risk [394].

A meta-analysis of studies of cancer risk following childhood exposure to ETS revealed no increased risk of lung cancer, while there was a small excess of all childhood neoplasms associated with exposure to mother's smoke (RR 1.10, 95% CI 1.03–1.19, based on 12 studies) and of brain tumours associated with father's smoke (RR 1.22, 95% CI 1.05–1.40, based on 10 studies) [51].

3.7.3
Combined analysis of case–control studies of lung cancer in western Europe

P. Boffetta, P. Brennan, F. Nyberg and V. Gaborieau; in collaboration with W. Ahrens and H. Pohlabeln, Bremen, Germany; E. Benhamou and S. Benhamou, Villejuif, France; S.C. Darby, Oxford, UK; F. Forastiere and C. Fortes, Rome, Italy; C.A. González and A. Agudo, Barcelona, Spain; K.H. Jöckel, Essen, Germany; F. Merletti, Turin, Italy; G. Pershagen, Stockholm, Sweden; R. Saracci, Pisa, Italy; J. Siemiatycki, Montreal, Canada; L. Simonato, Padua, Italy; and H. Wichmann, Munich, Germany

In parallel to the study on non-smokers described above (Section 3.7.2), cases of lung cancer and controls have been enrolled in a series of studies in 10 centres in western Europe, irrespective of their smoking habits. Comparable information on tobacco smoking, exposure to occupational carcinogens and urban air pollution has been collected from about 9000 cases and 10 000 controls. A common database with the information on tobacco has been established, and the analysis is focusing on detailed aspects of tobacco carcinogenesis that cannot be addressed in smaller studies. Smoking of cigars or a pipe was shown to exert a carcinogenic effect in the lung comparable to the effect of cigarette smoking, the small overall risk of lung cancer among cigar and pipe smokers being largely due to their lower average consumption (Figure 28(*a*)) [47]. A comparative analysis of the risk of lung cancer from cigarette smoking in men and women showed similar effects, suggesting that gender does not influence susceptibility to lung cancer from tobacco smoke (Figure 28(*b*)) [249]. Additional analyses will address the relative contributions of time-related variables such as age at start, duration of smoking and time since quitting.

3.7.4
Multicentric case–control study of lung cancer in central and eastern Europe

P. Brennan and P. Boffetta; in collaboration with E. Fabianova, Banska Bystrica, Slovakia; J. Fevotte, Lyon, France; A. Fletcher, London, United Kingdom; D. Mates, Bucharest, Romania; P. Rudnai, Budapest, Hungary; N. Szeszenia-Dabrowska, Lodz, Poland; D.G. Zaridze, Moscow, Russian Federation; and W. Zatonski, Warsaw, Poland

Countries of central and eastern Europe experience the highest incidence and mortality of lung cancer ever recorded. Air pollution is often blamed as the main contributor to the excess, but the evidence for its role is limited. A study is in progress in six areas of Hungary, Poland, Romania,

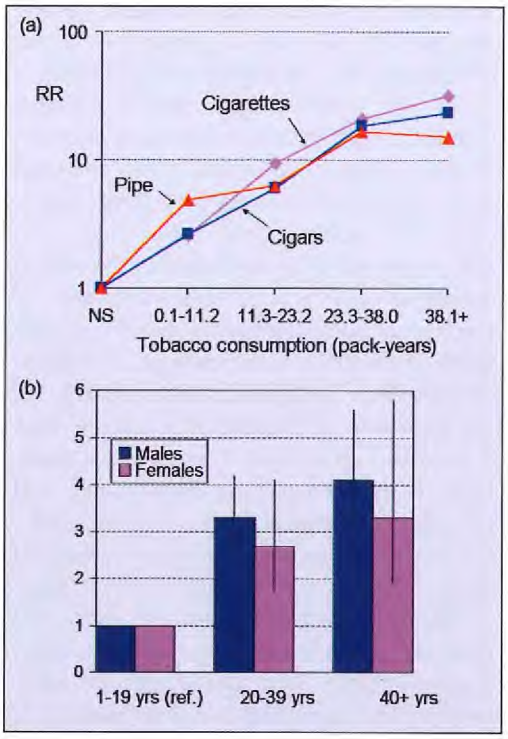

Figure 28. Relative risk of lung cancer (*a*) by cumulative consumption of different tobacco products, (*b*) according to duration of cigarette smoking.

Relative risks adjusted for average consumption and time since quitting smoking [249].

the Russian Federation and Slovakia to assess the relative contributions of tobacco smoking, occupational exposures and outdoor air pollution in lung carcinogenesis. A total of 2500 cases and a comparable number of controls are being enrolled; special efforts are being made to assess past occupational exposures via evaluations of detailed employment histories by panels of local experts. Blood samples are also being collected, to investigate polymorphisms of metabolic enzymes. In parallel to the series of lung cancer cases, cases of oral, pharyngeal and laryngeal cancers are also being enrolled (see Section 3.8.3).

3.7.5

Case–control studies of lung cancer in Brazil, Uruguay and Argentina

P. Boffetta; in collaboration with E. De Stefani, Montevideo, Uruguay; E. Matos, Buenos Aires, Argentina; and V. Wunsch, São Paulo, Brazil

Urban areas of Brazil and Argentina have among the highest death rates in the Americas for cancer of all sites and of the lung in particular. Following a similar study in São Paulo, Brazil [562], a study has been conducted in Buenos Aires to identify associations between environmental and occupational exposures and risk of lung cancer and examine the synergistic effect of selected occupational exposures and tobacco smoking. This study revealed an increased risk of lung cancer in the food, metal, leather and chemical industries [277, 278, 562]. Analyses based on a job–exposure matrix are in progress. A parallel study in Uruguay included cases of lung cancer and of other epithelial tumours. A protective effect of dietary antioxidants was seen for lung cancer [132]. Further analyses showed a higher risk of cancer of the oral cavity and the pharynx among smokers of black cigarettes [134] and drinkers of hard liquor [135] compared with other groups of smokers and drinkers. An analysis of occupational risk factors for laryngeal cancer suggested an effect of asbestos and an increased risk among meat workers [136]. An increased risk of stomach cancer was associated with tobacco smoking, alcohol drinking and high intake of heterocyclic amines and carbohydrates [130, 131, 133]. High meat intake was suggested as a risk factor for oesophageal cancer [137].

3.7.6

Multicentric case–control study of lung cancer in India

P. Boffetta, P. Brennan and R. Sankaranarayanan; in collaboration with M.K. Nair, Trivandrum, India; D.N. Rao, Bombay, India; and V. Shanta, Madras, India

Although the industrial population in India is very large and many hazardous

industries are present, virtually no information exists on occupational cancer risk factors. The presence of a network of well organized cancer registries is a favourable condition for conducting multicentric case–control studies. Such a study is in progress in Bombay, Trivandrum and Madras, to investigate occupational and environmental factors for lung cancer. A series of cases of lymphatic and haematopoietic neoplasms has also been included. Data collection has been completed for 1200 lung cancer cases, 1000 lymphoma cases, 600 leukaemia cases and over 11 000 controls and analysis will be completed in 2000.

3.7.7

Case–control study of environmental tobacco smoke and genetic susceptibility to lung cancer

P. Boffetta, M. Friesen and J. Hall; in collaboration with W. Ahrens, Bremen, Germany; H. Batura-Gabryel, Poznan, Poland; S. Benhamou, Villejuif, France; I. Brüske-Hohlfeld, Munich, Germany; V. Constantinescu, Bucharest, Romania; C. Fortes, Rome, Italy; K. Husgafvel-Pursiainen, Helsinki, Finland; M. Lang, Uppsala, Sweden; N. Malats, Barcelona, Spain; A. Menezes, Pelotas, Brazil; G. Pershagen and F. Nyberg, Stockholm, Sweden; L. Simonato, Padua, Italy; and D.G. Zaridze, Moscow, Russian Federation

Among lung cancer cases, non-smokers have been exposed on average to lower levels of carcinogens than smokers; genetic susceptibility may play a greater role in risk of lung cancer in the former group of cases.

In ten centres from Brazil, France, Germany, Italy, Poland, Romania, Russia and Sweden, blood samples have been collected from about 200 non-smoking lung cancer cases, 200 smoking lung cancer cases and 200 non-smoking control subjects, in order to determine (*a*) genetic polymorphism of glutathione *S*-transferase M1 and T1, (*b*) the levels of the DNA repair enzyme, O^6-methylguanine-DNA methyltransferase (AGT), (*c*) the formation of haemoglobin adducts with 4-hydroxy-1-(3-pyridyl)-1-butanone, a metabolite of tobacco-specific nitrosamines, and (*d*) genetic alterations in the *p53* gene and K-*ras* mutations in lung neoplastic tissue of cases. Cases and controls have been interviewed about their smoking habits and exposure to environmental tobacco smoke. Analyses have been conducted on nitrotyrosine and oxidized proteins as markers of oxidative stress (see Section 4.3.6.4). The analysis of AGT activity showed that the risk of lung cancer increased, although not significantly, with decreasing activity. Additional analyses are being carried out on genetic polymorphisms of metabolic enzymes and on *p53* mutational patterns.

3.8 Head and neck cancer

Tobacco, alcohol and a diet poor in certain micronutrients have been clearly identified as the main etiological factors for cancer of the oral cavity and pharynx. However, only a small proportion of smokers and drinkers ever develop significant disease, suggesting the existence of genetic or environmental cofactors. The association of human papillomavirus (HPV) with cervical cancer and other anogenital malignancies suggests that some HPV types could be involved in the etiology of yet other epithelial tumours. Some studies have indicated a possible role of HPV in the etiology of oropharyngeal cancer, particularly for certain tumour sites, notably the tonsils.

Genetic studies of head and neck cancers are described in Section 4.2.6. Studies of chemoprevention and of screening for oral cancer are covered in Sections 5.1.4 and 5.4.3, respectively.

3.8.1

Multicentric case–control study of laryngeal cancer in Brazil and Argentina

P. Boffetta, P. Brennan and R. Herrero; in collaboration with M.P. Curado, Goiania, Brazil; A. Daudt, Porto Alegre, Brazil; M. Kogevinas, Barcelona, Spain; S. Koifman, Rio de Janeiro, Brazil; E. Matos, Buenos Aires, Argentina; A. Menezes, Pelotas, Brazil; V. Wunsch, São Paulo, Brazil

Argentina and southern Brazil experience high incidence rates of laryngeal cancer, that do not seem to be explained only by exposure to known carcinogens such as tobacco smoking and alcohol drinking. In conjunction with studies of lung cancer (see Section 3.7.5), a multicentric study of laryngeal cancer is being conducted in five areas of Brazil (Rio de Janeiro, São Paulo, Pelotas, Porto Alegre and Goiania), and in Buenos Aires. The aims are to identify occupational risk factors of this disease, to assess the role of HPV infection, to quantify the contributions of tobacco smoking and alcohol drinking, and to clarify the role of other possible lifestyle risk factors, such as diet and mate drinking. Collection of interview data and biological samples started in 1998 and will be completed in 2000. In all of the centres, the study is being conducted in parallel with an investigation of the role of HPV infection in oral cancer (see Section 3.8.3).

3.8.2

Survival and occurrence of second primaries among laryngeal and hypopharyngeal cancer patients

P. Boffetta and P. Brennan; in collaboration with C. Bouchardy, Geneva, Switzerland; P. Crosignani, Milan, Italy; J. Estève and A. Tuyns, Lyon, France; and F. Merletti, Turin, Italy

During the 1980s, IARC conducted a multicentric case–control study of cancer of the larynx and the hypopharynx in relation to tobacco smoking, alcohol drinking, occupational exposures and diet. The study included over 1100 cases and 3000 controls from areas of Italy, Spain, Switzerland and France covered by cancer registration. The occurrence of second primary tumours in the series of cases is now being investigated for an analysis with respect to exposure to risk factors. In parallel, occurrence of cancer will be studied in the series of population controls.

3.8.3

Molecular epidemiology of cancer of the oral cavity and oropharynx

R. Herrero, N. Muñoz, P. Hainaut and R. Sankaranarayanan; in collaboration with P. Balaram, Trivandrum, India; F. Barbone, Udine, Italy; X. Castellsagué, Barcelona, Spain; S. Dicht, Bethesda, MD, USA; L. Fernandez, Havana, Cuba; S. Franceschi, Aviano, Italy; A. Idris, Khartoum, Sudan; F. Kee, Belfast, UK; J. Lissowska, Warsaw, Poland; C. Martinez, Granada, Spain; A. Nieto, Sevilla, Spain; M. Pawlita and U. Nair, Heidelberg, Germany; J. Pintos and E. Franco, Montreal, Canada; T. Rajkumar, Madras, India; K.B. Rose, Sydney, Australia; V. Shah and R. Viscidi, Baltimore, MD, USA; H. Sridhar, Bangalore, India; and A. Tavani, Milan, Italy

We are conducting a hospital-based case–control study of incident cancers of the oral cavity and pharynx in Montreal, Havana, Belfast, Barcelona, Seville, Granada, Aviano, Milan, Warsaw, Khartoum, Trivandrum, Bangalore, Madras and Sydney. The main objectives are to assess the roles of HPV, other infectious agents and genetic polymorphisms of carcinogen-metabolizing enzymes in the etiology of these cancers, and their interactions with tobacco (smoking or chewing) and alcohol consumption, dietary habits, oral hygiene, sexual behaviour and medical and family history. In the context of the multi-site case–control study described in Sections 3.7.4 and 3.8.1), additional centres have started data collection in Brazil (Rio de Janeiro, São Paulo, Goiania, Porto Alegre and Pelotas), Argentina (Buenos Aires), Poland (Lodz), Hungary (Budapest), Slovakia (Banka Bystrica), Romania (Bucharest)

Figure 29. Components of betel quid for sale in a market in Bangalore, India.

and the Russian Federation (Moscow). Subjects are interviewed on risk factors, and exfoliated cells are collected by brushing and washing of the entire oral cavity. In addition, fresh biopsies are taken from lesions and immediately frozen. A blood specimen is also collected, and plasma, buffy coat and red blood cell aliquots are prepared and frozen. More than 1500 cases and a similar number of controls have been recruited in the first 14 centres for the initial analysis. HPV testing of exfoliated cells with the GP5+/6+ PCR method was carried out in approximately 800 cases and 800 controls. The overall prevalence of HPV detection was about 4%, with no major difference between cases and controls. A sample of subjects was tested with specific primers for skin-related HPV types, increasing the prevalence to about 15%, again without case–control differences. The PCR signals detected in exfoliated cells are, however, weak and not indicative of clonal expansion. Therefore, we are now analysing more than 1000 biopsy specimens by PCR, with verification of the presence of tumour cells. Data for the specimens tested to date indicate an overall HPV prevalence under 10%, with more frequent detection of the virus in tonsils and other pharyngeal locations [98]. The prevalence of specific HPV types will be investigated in relation to the tumour location, histological type, exposure to specific risk factors and *p53* mutations. The presence of antibodies against L1 VLPs of HPV types 16, 18, 31, 33, 45 and 11, as well as of antibodies against the E6 and E7 proteins of HPV 16, which have been linked to invasive HPV-related disease, is under investigation. GST polymorphisms are being analysed in a group of approximately 400 cases and controls from India.

3.9 Skin cancer

Skin cancer incidence is the highest among all cancers and solar radiation, especially ultraviolet radiation, is considered to be the major risk factor for both melanocytic and non-melanocytic cancers. The molecular epidemiology and molecular mechanisms of skin cancers are being studied at IARC.

3.9.1 Molecular biomarkers to measure cumulative ultraviolet exposure and to predict skin cancer

T. Suzuki, K. Kawasaki, N. Martel, G. Reguer and H. Yamasaki; in collaboration with H. Ichihara and M. Ueda, Kobe, Japan

We have established that CC to TT tandem mutations in the *p53* gene are UV-specific molecular signatures and that their presence in normal skin can be used to predict risk of basal cell carcinoma [344]. However, they cannot yield an accurate measure of total UV exposure, since they provide the cells with a growth advantage. Moreover, a large skin biopsy is necessary for each assay. To circumvent these problems, we have measured mitochondrial (Mt) DNA mutations; there are more than 1000 copies of the Mt genome per cell, and Mt genes are not directly involved in cell growth. Using a sensitive assay capable of detecting one CC to TT mutation in Mt DNA

among 10^7 wild-type genes, we found no mutation-positive samples from non-exposed tissue (0/50). In normal skin tissue, the prevalence of positive samples was higher in sunlight-exposed samples (13/51) than in non-exposed samples (1/26) ($p<0.05$). However, no quantitative correlation between sunlight exposure and the accumulation of mutations was seen. Thus, although the UV exposure-associated CC to TT mutation can be detected in Mt DNA from normal skin, further studies are required if it is to be usable as a quantitative marker for UV exposure.

3.9.2
Functional role of *cdc27Hs/h-nuc* overexpression in basal-cell and squamous-cell carcinomas of the skin

H. Nakazawa and M. Kallassy

The commonest human cancers, basal-cell and squamous-cell carcinomas of the skin, both originate from epidermal keratinocytes, but a unified concept of their molecular genesis is lacking. We have identified a gene that is overexpressed in cases of Bowen's disease (100%), squamous-cell carcinoma (90%) and basal-cell carcinoma (78%), but not in normal skin or proliferating keratinocytes. This gene is identical to *cdc27Hs/h-nuc*, the human homologue of the yeast genes *CDC27* and *nuc2*, which encode a protein that binds to the retinoblastoma (pRB)-binding protein and is a component of anaphase-promoting complex. The major role of *cdc27Hs/h-nuc* overexpression in carcinogenesis is to prevent pRB–E2F complex formation and, after transactivation of E2F-effector genes, stimulation of cell growth. Expression of anti-sense *cdc27Hs/h-nuc* in HaCaT cells strongly reduced their growth. Preliminary experiments in athymic mice indicate the possibility of a novel *cdc27Hs/h-nuc*-mediated strategy to inhibit the growth of human skin cancers. We believe that overexpression of *cdc27Hs/h-nuc* is an essential pathway in human skin carcinogenesis.

3.9.3
p21^{WAF1} gene expression suppresses telomerase activity of human immortalized keratinocytes

H. Nakazawa and M. Kallassy

Since most non-melanocytic human skin cancer cells carry *p53* mutation(s), their aberrant growth could be simply a result of the loss of the *p53*-downstream mediator, universal cyclin-dependent kinase inhibitor, p21^{WAF1}. To investigate the role of this protein in human skin carcinogenesis, we have studied its regulation in normal and *p53*-mutated immortalized human keratinocytes. Our results are consistent with the idea that p21^{WAF1} universally inhibits the growth of non-melanocytic skin cancers, even those which have alterations in p53, p21^{ras} and/or pRB [231]. Our findings further indicate that retrovirus-mediated expression of exogenous p21^{WAF1} in immortalized and transformed keratinocytes prevents *p53* mutation-, *ras* mutation- and *pRB* alteration-mediated keratinocyte proliferation. This suggests that introducing exogenous p21^{WAF1} into skin tumours containing these genetic alterations might be a universal strategy for controlling growth of skin tumours *in vivo*.

3.9.4
p53 Mutations in sweat gland carcinomas

W. Biernat, A. Peraud and H. Ohgaki; in collaboration with L. Wozniak, Lodz, Poland

Sweat gland carcinomas are rare skin tumours and little is known about their etiology and molecular basis. We have analysed *p53* mutations in 16 sweat gland carcinomas of different histological types. SSCP followed by direct DNA sequencing revealed that five carcinomas (31%) contained a *p53* mutation, four of which were

G:C→A:T transition mutations and one was a deletion. Three G:C→A:T mutations were located at dipyrimidine sequences on the antisense strand (two spiradenocarcinomas, one eccrine hidradenocarcinoma), suggesting that UV light may play a role in the development of sweat gland carcinomas. In the two spiradenocarcinomas, *p53* mutations were present in the carcinoma but not in the adenoma portions, suggesting that *p53* mutations may be associated with malignant progression in these rare adnexal tumours [19].

3.10 Soft-tissue tumours and lymphomas

3.10.1

Case–control study of soft-tissue sarcoma and non-Hodgkin lymphoma in relation to exposure to herbicides in Viet Nam

D.M. Parkin, E. Kramárová and E. Démaret; in collaboration with Nguyen Chan Hung and Cung Tuyet Anh, Ho Chi Minh City, Viet Nam; Hoang Dinh Cau and Vu Ngoc Phan, Hanoi, Viet Nam; S. Cordier, Villejuif, France; M. Kogevinas, Barcelona, Spain; M. Raphaël, Paris, France; J.M. Rivera-Pomar, Vizcaya, Spain; and S. Stellman, New York, NY, USA; supported by the French Ministry of the Environment, the Ligue Contre le Cancer, France, the NAS Committee, USA, and the Association pour la Recherche sur le Cancer, France

It has been estimated that during the Second Indochina War, 230 kilograms of the most toxic dioxin congener, TCDD, were deposited in contaminated herbicides onto the territory of south Viet Nam. TCDD was evaluated in 1996 as a human carcinogen. This study is investigating whether any excess risk for two cancers—soft-tissue sarcoma and non-Hodgkin lymphoma—can be detected. Due to the long biological half-life of dioxin, it is still possible to detect it in human fat tissues 30 years after exposure.

Overall, 150 cases of each disease and two hospital controls per case have been interviewed and samples of blood and adipose tissue stored. Estimation of exposure is expressed by an index based on detailed residential history, matched with the records of the US air forces (HERBS tape), containing the time, location, type and quantity of herbicide sprayed. Direct measurement of dioxins in a sample of 200 subjects will be conducted in a laboratory in the United States.

A validation study of the exposure index based on residential histories using the tissue measurements of dioxin levels has been initiated. A preliminary analysis of the partial results in 1999 showed no association of the exposure index with soft-tissue sarcomas or non-Hodgkin lymphomas [248].

3.10.2

Multicentric case–control study of lymphomas in Europe

P. Boffetta, P. Brennan and A. 't Mannetje; in collaboration with N. Becker, Heidelberg, Germany; J. Clavel, Paris, France; P.L. Cocco, Cagliari, Italy; S. de Sanjose, Barcelona, Spain; J. Iscovich, Ra'anana, Israel; M. Meynadie, Dijon, France; A. Staines; Dublin, Ireland; and P. Vineis, Turin, Italy

The incidence of lymphoid neoplasms is increasing in most parts of the world, for reasons that remain unclear. A case–control study is being undertaken in five European countries in order to test several hypotheses about this increase. The aim is to recruit over 1500 cases of lymphoid neoplasms and a group of comparable controls. All participants complete a questionnaire including information on sources of UV radiation, use of hair dyes, previous medical history of autoimmune disease, previous infections, allergies and previous cancers. A detailed job history from all cases and controls is also obtained in order to assess the relationship

between lymphoid neoplasms and specific pesticides and solvents, as well as other occupational exposures including ionizing radiation, zoonotic viruses, ethylene oxide and organic dusts. A bank of serum samples will be established to test current hypotheses regarding particular infectious agents (e.g., human herpes virus 8, Epstein–Barr virus, hepatitis C virus). Collection of interview data and biological samples started in 1999 and will be completed in 2001. Extension of the project to other countries, in particular in western and eastern Asia, is being considered.

3.10.3
Classic Kaposi's sarcoma in Israel

P. Boffetta, P. Brennan and R. Winkelmann; in collaboration with J. Iscovich, Ra'anana, Israel

The incidence of classic Kaposi's sarcoma has been reported to be high in Jewish populations living in Israel and in immigrants originating from the Mediterranean basin, but no population-based reports are available for Israeli Arabs [216]. We have analysed the incidence of classic Kaposi's sarcoma between 1970 and 1993 among Jews and Arabs living in Israel. Reporting systems were the Israel Cancer Registry, the medical documentation of all Kaposi's sarcoma cases and the registry of human immunodeficiency virus (HIV)-seropositive patients. Age-standardized incidence rates (ASR) for Jews were 16.9 per million in men and 6.3 per million in women, and in Arabs 6.87 per million in men and 2.18 per million in women [216, 220]. The ASR did not increase between 1970 and 1993 in either men or women. Among Jews, immigrants from Morocco, Algeria and Tunisia had the highest incidence compared with Jews born in Israel (RR 2.01, 95%CI 1.52–2.65). The incidence of classic Kaposi's sarcoma in Israel-born Arabs, while lower than that of Israel-born Jews, was still higher than in other populations around the Mediterranean basin. A population-based case–control study and a seroprevalence survey are now being planned.

3.11 Gall bladder cancer

3.11.1
Gall bladder cancer in northern India

R. Sankaranarayanan and D.M. Parkin; in collaboration with V.K. Shukla, Varanasi, India; and R. Tandon, New Delhi, India

A high incidence of gall bladder cancer is observed in females in northern India. The risk factors for this cancer are not well established. An exploratory case–control study to address dietary and inflammation related factors, and the role biliary lipid peroxidation products in the etiology of this cancer in Varanasi was unsuccessful due to difficulties in collecting bile from healthy controls. A multi-centre study is now being planned.

3.12 Breast cancer

Breast cancer is the most common cancer among women in the world. Questions remain unsolved regarding its etiology, including the role of the environment [126], the interaction between genetics and other factors [157] and the role of diet [393]. Detailed studies of cancer trends may

provide some evidence for identification of environmental risk factors [145].

The role of gene mutations in breast cancer etiology is being intensively studied (Sections 1.2.7 and 4.2.1–4.2.3). A trial of breast cancer screening by physical examination is described in Section 5.4.1.

3.12.1

Natural history of breast cancer

A.J. Sasco; in collaboration with M. Abrahamowicz, Montreal, Canada; J.Y. Bobin, J. André and F. Descotes, Lyon, France; D.L. Davis, Washington, DC, USA; and P.M. Martin and P. Bonnier, Marseille, France

Several factors affect breast cancer prognosis, including the use of hormonal treatment at the time of diagnosis. For example, in a recent study in a cohort of 1379 breast cancer cases diagnosed in one hospital in Marseille, women who were users of hormone replacement therapy at the time of diagnosis were compared with non-users. Tumours were smaller, with less frequent nodal involvement but were more often estrogen-receptor negative among users than non-users. No significant differences were found for recurrence or survival [58].

Studies are in progress focusing on the identification of predictive tumour markers. We are also developing new methodological tools to study risk factors for survival, as was previously done for nasopharyngeal carcinoma [392], as well as for the occurrence of second events, be they recurrences or second cancers. Currently used models are often inadequate to correctly estimate the evolution of risk over time, without undue assumptions such as the proportionality of hazards. New approaches are being tested on a cohort of 801 cases from the Rhône diagnosed in 1985 and followed since then.

3.12.2

Polymorphisms in xeno(endo)biotic metabolism, environmental exposures and breast cancer

C. Malaveille, A. Hautefeuille; in collaboration with M. Gerber, Montpellier, France

Circumstantial evidence suggests that environmental exposures are breast cancer risk factors. We have initiated a molecular epidemiological study to analyse the role of metabolic polymorphisms as cancer risk factors which may affect the response to environmental exposures and influence endogenous processes. Cases and controls are being recruited at the Centre Régional de Lutte contre le Cancer, Val d'Aurelle, Montpellier, France.

PART 4. MECHANISMS OF CARCINOGENESIS

4.1 Regulation of the mammalian cellular response to DNA damage

Mammalian cells respond to DNA damage with a transient inhibition of DNA synthesis, induction of expression of several genes and a delay in cell cycle progression. Such delays could be considered as a surveillance mechanism allowing time for detection and repair of DNA damage. The objective of the studies presented here is to investigate the role of various gene products in signal-transduction pathways resulting in cell-cycle arrest, with particular emphasis on those involved in the detection of DNA damage produced by ionizing radiation.

Cell lines established from patients with the rare autosomal cancer-prone diseases ataxia telangiectasia (AT) and Nijmegen breakage syndrome (NBS), which both show considerable radiation sensitivity and abnormal cellular responses to DNA damage, are being used as model systems and the potential contribution of the products of the associated genes (*ATM* and *NBS*) to other forms of cancer in which radiation sensitivity is observed is being assessed.

4.1.1
Role of the Nijmegen breakage syndrome gene product in DNA damage recognition

S. Angèle, M. Vuillaume and J. Hall; in collaboration with K. Chrzanowska, Warsaw, Poland; and K. Sperling, Berlin, Germany; with support from the Programme de Cooperation Scientifique entre la France et la Pologne

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disease characterized by microcephaly, chromosomal instability, radiosensitivity, immunodeficiency and lymphoreticular malignancies. Studies in our laboratory have shown that the functionality of the p53-mediated pathway activated in response to DNA damage, in which the ataxia telangiectasia gene product is also involved, is sub-optimal in NBS cell cultures specifically after exposure to ionizing radiation. In agreement with loss of p53 function, NBS cells exposed to ionizing radiation show an abnormal cell cycle arrest at G1-S and a prolonged accumulation in the G2 phase, a response very similar to that observed in AT cells after exposure to ionizing radiation. The *NBS1* gene has recently been cloned and its protein product shown to be involved in a double-strand break repair complex with the *hMre11* and *hRad50* gene products. These results are consistent with the hypothesis that mutations in *NBS* and *ATM* affect proximate functions in the response to DNA damage and demonstrate a direct molecular link between proteins involved in double-strand break repair and the activation of cellular DNA damage responses. We observed no significant change in *NBS*1 mRNA in NBS, AT and normal cell lines after exposure to ionizing radiation.

4.1.2
Characterization of *ATM* mutations in children with ataxia telangiectasia

S. Angèle, M. Vuillaume and J. Hall; in collaboration with J.-O. Bay and Y.-J Bignon, Clermont Ferrand, France; G. Lenoir, Lyon, France; and D. Stoppa-Lyonnet, Paris, France; with support from the French Ministère de l'Education Nationale, de la Recherche et de la Technologie

A collaborative project has been established to examine the mutation profile of the ataxia telangiectasia gene (*ATM*) in children with AT living in France over the period 1977–99. 54 AT families have been identified with a well defined clinical phenotype.

In most cases, lymphoblastoid cell lines have been established from peripheral blood lymphocytes of the affected individual or their family members, thus allowing the isolation of both genomic DNA and RNA for analysis. Mutation analysis of the *ATM* gene is being carried out using either cDNA-based techniques or, where only genomic DNA was available, by SSCP analysis; all alterations were confirmed by direct sequencing. The mutations detected so far appear to be scattered throughout the whole *ATM* gene and demonstrate the extensive allelic heterogeneity of AT in French patients.

4.1.3

Role of the *ATM* gene in breast cancer

S. Angèle, M. Vuillaume, P. Tanière, G. Martel-Planche and J. Hall; in collaboration with A. Brémond, J.P. Gérard, P. Romestaing and I. Treilleux, Lyon, France; and Y Shiloh, Tel Aviv, Israel; with support from the Ligue Nationale Contre le Cancer Comité Départemental du Rhône and the Association pour la Recherche sur le Cancer

Carriers of a homozygote *ATM* mutation are characterized by extreme radiosensitivity and increased cancer risk. *ATM* heterozygotes, while having none of the neurological symptoms of the disease, do have increased cancer risk and in particular breast cancer in females. In order to evaluate the role of the *ATM* gene in breast cancer development and radiosensitivity, two approaches have been used. First, expression of the ATM protein has been studied using immunohistochemistry in breast *in situ* and infiltrating duct carcinomas. Positive ATM immunostaining in the inner epithelial cells

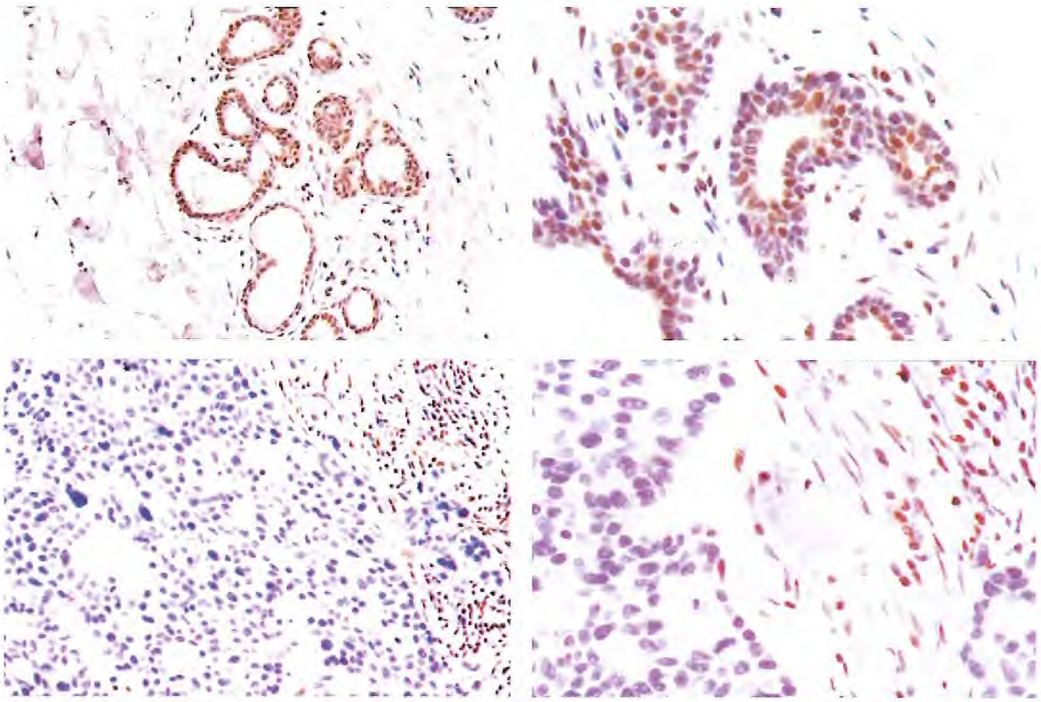

Figure 30. ATM immunostaining in normal breast tissue and breast carcinoma

Top: Normal tissue showing nuclear ATM staining in the inner epithelial cells of breast ducts and no staining in the outer myoepithelial cells. *Bottom*: Invasive ductal carcinoma showing no ATM staining in the tumour area, in contrast to the lymphocytes in the same section. Left-hand panels × 200, right-hand panels × 400

and negative ATM immunoreactivity in the outer myoepithelial cells in normal breast ducts were found (Figure 30). In contrast, in the 17 breast tumours, a significant decrease in ATM immunoreactivity in the tumour epithelial cells was noted. Allelic imbalance in or around the *ATM* gene was found in five out of seven tumours examined. These results suggest that the reduced ATM protein expression may be due, in certain tumours, to deletions within or close to the *ATM* gene. The second approach involved establishing lymphoblastoid cell lines from radiosensitive and non-radiosensitive breast cancer patients. In some of the cell lines, the level of cell survival and p53 induction after radiation exposure were lower than in control cell lines, indicating an alteration in the ATM signalling pathway. Some variation in ATM protein levels was also seen. No mutations were detected in the *ATM* gene in the 10 cell lines established from non-radiosensitive breast cancer patients, whereas *ATM* alterations were detected in four out of 27 radiosensitive breast cancer patients included in this study.

4.1.4

Role of the *ATM* gene in ocular telangiectasias

S. Angèle, M. Vuillaume and J. Hall; in collaboration with M. Mauget-Faÿsse, Lyon, France; with support from the Ligue Nationale Contre le Cancer Comité Départemental du Rhône

A prominent external sign of AT is telangiectasias in the eyeballs and sometimes on the ears and face, which can vary in appearance and sometimes are barely noticeable. Telangiectasias are found as a complication in patients treated by radiotherapy for age-related macular degeneration. These telangiectasias have been found to occur in approximately of 5% of patients and tend to appear at least six months after radiotherapy. In order to investigate whether an alteration in the *ATM* gene is an underlying cause of these telangiectasias, lymphoblastoid cell lines have been established from patients who showed this adverse reaction to radiotherapy. Some of the cell lines show sensitivity to ionizing radiation *in vitro* and altered expression of the ATM protein compared with control cell lines. Mutational analysis of *ATM* in these lines is in progress.

4.2 Genetic determinants of specific cancers

The aim of the programme on genetic susceptibility to cancer is to evaluate the role and importance of inherited conditions that predispose to cancer, by the use of molecular, familial and population-genetic approaches.

Probably less than 5% of cancers occur in individuals who are strongly predisposed to a particular cancer type. If a genetic marker of risk is identified, these individuals (and their relatives) may benefit from screening and early diagnosis. Molecular epidemiological studies may allow the identification of low-penetrance predisposing genes. Such information would be of wider importance for the more common non-familial forms of cancer which may also be associated with genetic predisposition.

During the last 10 years, IARC has contributed to the identification of the genes predisposing to familial medullary thyroid cancer (in the framework of multiple endocrine neoplasia type 2 (MEN 2)), to neurofibromatosis type 2 and to familial breast cancer. Major efforts have been put into the identification of the X-linked lymphoproliferative syndrome (XLP) gene and the mapping of papillary thyroid carcinoma susceptibility genes.

4.2.1
Genetic susceptibility to breast and ovarian cancers

G. Lenoir, O. Sinilnikova, S. Mazoyer, N. Puget and C. Bonnardel; in collaboration with S. de Sanjose, Barcelona, Spain; C. Egan, Boston, MA, USA; C. Lasset, Lyon, France; H. Lynch, Omaha, NE, USA; and the Breast Cancer Linkage Consortium

The overall aim of this project is to study the implication of major susceptibility genes in predisposition to breast and ovarian cancer. With various collaborating centres, we have studied not only high-risk families, but also cases of breast cancer occurring at young age in various parts of the world. Recent work has focused on (1) refining mutation detection strategies for *BRCA1* and *BRCA2* genes, in order to better estimate the contributions of these two genes to breast cancer susceptibility, (2) studying the contribution of *BRCA1* and *BRCA2* germline mutations in early-onset breast cancer, and (3) studying the implication of *BRCA2* in predisposition to ocular melanoma. In parallel, a descriptive study of *BRCA1* and *BRCA2* mutations in developing countries is in progress (Section 1.2.7).

4.2.1.1
Identification of germline BRCA1 *and* BRCA2 *mutations in breast cancer families*

Most previous BRCA1 mutation screening studies conducted on breast cancer families have been aimed at identifying mutations in the coding sequence and splice sites. Mutations in the promoter and untranslated regions, and large rearrangements like the one we previously reported (a 1-kb deletion) (Puget *et al.*, 1997, *Cancer Res.*, **57**, 828–831) are missed by standard mutation detection strategies. In order to look specifically for such germline mutations in the *BRCA1* gene, we have analysed a series of 28 American and 51 French breast cancer families in which no *BRCA1* mutation was identified by classical techniques. No mutations were detected in either the promoter or untranslated regions, and we did not find any deletion of the whole gene. Four families were found to carry distinct deletions [387]. Two of these consisted of internal deletions of 3 kb and 23.8 kb encompassing exon 15 and exons 8 to 13, respectively. These alterations both led to a frameshift in the

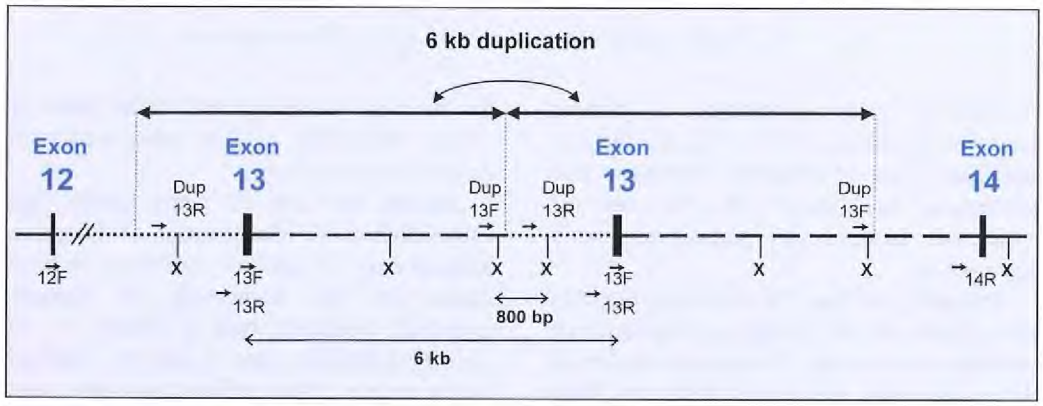

Figure 31. Characterization of the 6-kb germ-line duplication in the *BRCA1* gene in F3173.

Duplication of exon 13, schematically represented, with the location and orientation of primers 12F, 14R, 13F, 13R, Dup13F (GAT TAT TTC CCC CCA GGC TA) and Dup13R (AGA TCA TTA GCA AGG ACC TGT G). The *XbaI* sites (X); introns 12 (*dotted line*) and 13 (*broken line*); and the position and extent of the duplicated region, of the 800-bp *XbaI* fragment generated by the duplication, and of the 6-kb 13F/13R fragment (*two-headed arrows*)are indicated.

mutant mRNA and to premature stop codon-mediated mRNA decay. The other two deletions comprise exons 1 and 2. Based on our previous and present analyses, rearrangements represent 8% (3/37) of all mutations in our set of *BRCA1* American families. We have also identified a new rearrangement: an Alu-mediated 6-kb duplication in the *BRCA1* gene [386] (see Figure 31). This mutation, undetectable by conventional strategies, is likely to be a founder mutation, having been detected in four families with independent geographical origins. Therefore, the search for rearrangements appears mandatory in *BRCA1* mutation screening studies. We plan also to search for germline rearrangements in the *BRCA2* gene in our set of families. Furthermore, in order to better evaluate whether genotype–phenotype correlation exists, we are attempting to better evaluate the molecular consequences of *BRCA1* mutations by studying their impact at the transcriptional and protein levels.

4.2.1.2

BRCA1 *and* BRCA2 *germline mutations in early-onset breast cancer patients*

To study the contributions of germline *BRCA1* and *BRCA2* mutations in breast cancer in the general population, we have analysed a population-based series of early-onset breast cancer patients from the Rhône department of France for mutations in these genes. Women diagnosed with breast cancer before the age 45 years during 1995–97 were identified through a population-based cancer registry and 265 out of 457 (60%) who agreed to participate were interviewed, providing information on personal and familial cancer risk factors. The participation rates were slightly higher in the groups of youngest age. Blood samples have already been donated by 225 patients. For 76 patients diagnosed with breast cancer before 40 years of age, the entire coding sequences and splice junctions of *BRCA1* and *BRCA2* have been analysed. Eleven *BRCA1* and seven *BRCA2* mutations have been identified: ten mutations resulting in generation of a premature stop codon, four missense variants, one in-frame deletion and three intronic variants expected to result in aberrant splicing. This implies that a substantial proportion of breast cancers occurring at young age (≤ 40 years) in the general population is attributable to mutations in the *BRCA1* and *BRCA2* genes (24% (18/76); truncating mutations only 13% (10/76)). 11% (5/46) of patients revealing no family history of breast or ovarian cancer were found to be *BRCA1* or *BRCA2* mutation carriers. This finding supports the need for *BRCA1* and *BRCA2* mutation testing in early-onset breast cancer patients not selected on the basis of a family history of cancer.

Typing for *BRCA1* and *BRCA2* mutations is also in progress among 147 women younger than 45 years consecutively diagnosed with breast cancer in the populations of Tarragona and Girona (Spain), identified through the population-based cancer registries.

4.2.1.3

Ocular melanoma

On the basis, chiefly, of anecdotal reports of cases of ocular melanoma (OM) occurring in families with inherited susceptibility to breast cancer due to *BRCA2* germline mutations, we examined the frequency of *BRCA2* alterations in a series of 62 ocular melanoma cases collected in the Massachusetts Eye and Ear Infirmary, Boston, MA, United States [486]. These cases were selected mainly on the basis of reported family history of breast or ovarian cancer or OM, although the series also included a randomly selected set of cases without family history of cancer. A total of seven germline alterations were found, of which three were likely to be associated with disease. While all three deleterious mutations were found in patients who also had a personal history of breast cancer, only one of the three families

had a family history of breast/ovarian cancer or OM. Although germline *BRCA2* mutations may account for a small proportion of all OM cases, there may be additional loci that contribute to familial aggregation of OM and to the familial association between OM and breast cancer.

4.2.2

The international *BRCA1* and *2* gene carrier cohort study (IBCCS)

D.E. Goldgar, H. Renard, O Yaqoubi and A.J. Sasco; in collaboration with the IBCCS Consortium; with support from the European Union Europe Against Cancer programme

Now that large numbers of mutations in the *BRCA1* and *BRCA2* breast cancer predisposition genes have been identified, there is a need to more precisely determine cancer risks due to mutations in these genes, examine the role of other known risk factors in modifying these risks, and gauge the efficacy of various prevention strategies. To address these questions, we have initiated a multi-centric observational prospective study of identified carriers of *BRCA1* and *BRCA2*. This involves (*a*) development of a computerized registry of mutation carriers worldwide and (*b*) collection of clinical and risk factor follow-up data on at least 2000 carriers followed for a median observation period of 7.5 years. We have established collaborative research agreements with 16 cancer genetics centres in 12 European countries, including three large national centres in the UK, Netherlands and France. At meetings held in Lyon, the questionnaire and protocol were finalized and enrolment into the study began in November 1998. Approximately 600 subjects have now been enrolled, and another 500 mutation carriers identified and contacted. To manage the data collection and transfer efforts, we have set up a database using the ORACLE relational database system.

4.2.3

Mapping of non-*BRCA1* and *2* breast cancer susceptibility loci

D.E. Goldgar, C. Bonnardel, H. Renard and C. Szabo; in collaboration with D.F. Easton, Cambridge, UK; and M.R. Stratton, Sutton, UK; supported by the Association for International Cancer Research

Although *BRCA1* and *BRCA2* are believed to account for the vast majority of families with high incidence of early-onset breast cancer, these genes explain only about half of the excess familial aggregation observed for premenopausal breast cancer. Data from the Breast Cancer Linkage Consortium show that these genes account for only about 40% of families with four or five cases of female site-specific breast cancer. The goal of this project is to identify the chromosomal location of one or more additional breast cancer susceptibility loci and to estimate the frequency and risks due to these genes. An initial series of 135 DNA samples from 17 breast cancer kindreds is being studied at IARC in a total genomic search for linkage of breast cancer to one or more chromosomal regions. A similar set of samples has been studied by collaborators in the UK, and the results will be pooled for analysis. We have genotyped a subset of these families at approximately 500 short tandem repeat markers scattered throughout the genome. Currently three chromosomal regions which show some evidence of linkage in both the UK and IARC family sets are being evaluated further with a denser map of markers in the region and by testing additional families for linkage to these areas. Several previously suggested candidate regions (e.g., chromosome 8p, the *PTEN* locus etc.) have been examined and found not to account for a significant fraction of the families in our set. Based on the results of the initial genomic search and the derived exclusion map, it has become clear that there is more genetic heterogeneity than previously thought, which will require a larger set of families in order to detect any single locus.

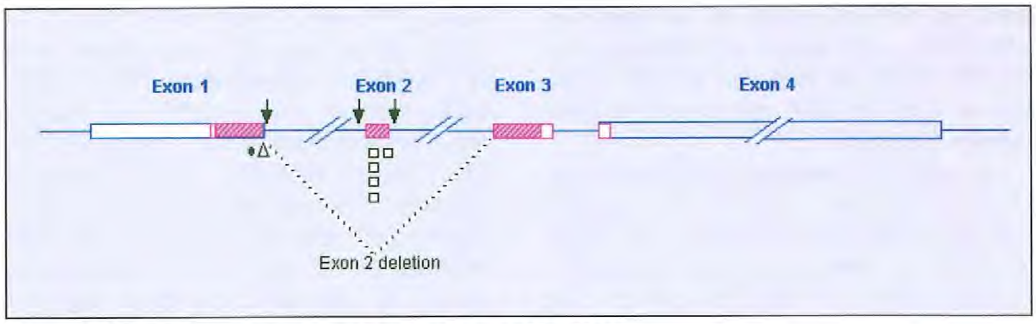

Figure 32. *SH2D1A* gene structure and mutations in XLP patients.

Shaded regions inside the first three of the four exons (boxed) represent the SH2 domain. Two large deletions removing all of the gene and 11 point mutations which inactivate the SH2D1A protein have been identified. ● : missense mutation; Δ : in-frame deletion; □ : nonsense mutations; arrows: splicing mutations.

Accordingly, we are now widening the collaboration and increasing the family set suitable for linkage studies. We have initiated collaborations with, and received DNA samples from, the Fred Hutchinson Cancer Center in Seattle, the NCI-funded Cooperative Family Registry (funded by the US National Cancer Institute; centres in Utah, Toronto, Melbourne, New York and Philadelphia), the M.D. Anderson Cancer Center in Houston, the KconFab project on familial breast cancer in Australia, and the National Oncology Institute in Budapest. This second set of families should provide sufficient power to detect a *BRCA3* locus.

4.2.4

Role of the *SH2D1A* gene in XLP and in other EBV-associated disorders

L. Yin, V. Ferrand, M.F. Lavoué, J. Liang, B.S. Sylla, G. Romeo and Z.-Q. Wang; in collaboration with J. Sumegi, Omaha, NE, USA

X-linked lymphoproliferative disease (XLP) is a rare, inherited immunodeficiency characterized by selective susceptibility to Epstein–Barr virus (EBV). After EBV infection, affected individuals develop fatal or chronic infectious mononucleosis, acquired agammaglobulinaemia (or hypogammaglobulinaemia), aplastic anaemia and malignant lymphoma, alone or in combination. XLP represents a model for the study of other more common lymphoid diseases associated with EBV infection. By haplotype reconstruction in XLP pedigrees and by characterization of a microdeletion (XLP-G) we defined a candidate region for the positional cloning of the *XLP* gene in an interval between *DXS1001* and *DXS8057* in the Xq25 region [55]. The gene *SH2D1A* was identified in this interval by the International Consortium of XLP, which includes IARC [117]. *SH2D1A* consists of four exons encoding a protein of 128 amino acids, containing an SH2 domain, that is likely to have a role in signal transduction. An independent study identified a protein which is identical to SH2D1A and which was subsequently shown to be a negative regulator of signalling lymphocyte activation molecule (SLAM). Another study has identified an additional partner of SH2D1A, the cell surface receptor 2B4 (Tangys *et al.*, 1999, *J. Immunol.*, **162**, 6981–6985), suggesting that SH2D1A may be involved in at least two signal transduction pathways.

In order to elucidate the biological role of *SH2D1A* in the immune system, we have generated an XLP knock-out mouse by targeting a deletion of exon 2 in the murine *SH2D1A* gene. These will be used to define the impact of *SH2D1A* mutations in the development and function of T and B lymphocytes. In addition, the role of EBV

infection will be tested by infecting the mutant mice with murine gammaherpesvirus 68 (MHV-68), an analogue of EBV virus, and looking for XLP phenotypes or other lymphoid diseases.

A systematic mutation study in our series of 19 typical and 8 atypical XLP patients revealed a total of 13 mutations (see Figure 32). All these mutations result in the absence or inactivation of the SH2D1A protein. The identification of *SH2D1A* mutations in two out of eight atypical patients indicates the usefulness of a DNA-based diagnostic approach for XLP [569].

4.2.5

Mapping of gene(s) affecting non-medullary thyroid cancer susceptibility

F. Canzian, R. Corvi, F. Lesueur, M. Martinez-Alfaro, J.D. McKay, S. Pauly, M. Stark, T. Tocco and G. Romeo; in collaboration with D. Bonneau, Poitiers, France; L. Hoffman, Hobart, Australia, and the International Consortium for the Genetic Study of NMTC

Epidemiological studies (Goldgar *et al.*, 1994, *J. Natl Cancer Inst.*, **86**, 1600–1608) have demonstrated the existence of familial clustering of non-medullary thyroid cancer (NMTC), which accounts for ~90% of all thyroid cancers. Its main histological subtypes are papillary thyroid carcinoma (PTC; the most common form) and follicular thyroid carcinoma. Familial NMTC is thought to represent ~5% of all cases of NMTC. Most reports suggest that both genetic and environmental (particularly ionizing radiation) factors are involved in predisposition to NMTC.

We are mapping genes conferring susceptibility to NMTC by linkage analysis in families with multiple cases of NMTC, collected through an international consortium we established in 1995. We have been focusing on the mapping of genes in large pedigrees which show cosegregation with other thyroid pathologies (generally multinodular goitre, MNG). In collaboration with the group of Dr M. Stratton, we mapped the gene *MNG1* to chromosome 14q32 (Bignell *et al.*, 1997, *Am. J. Hum. Genet.*, **61**, 1123–1130) and the gene *TCO* (for tumours with cell oxyphilia) to chromosome 19p13.2 [80]. Other families with oxyphil cell thyroid tumours are compatible with linkage to *TCO*. The largest published NMTC pedigree analysed so far in our laboratory includes eight patients with PTC and eight with MNG (Burgess *et al.*, 1997, *J. Clin. Endocrinol. Metab.*, **82**, 345–348). This family does not show linkage to either *MNG1* or *TCO* [289]. Having completed a genome scan in this family, we are examining regions of possible linkage with additional markers.

We are also using the material from the smaller NMTC families to assess the role of the most obvious candidate genes (*MNG1*, *TCO* and *RET*). Linkage analysis in a subset of 56 pedigrees showed that none of them is a major gene of susceptibility to NMTC as a whole [260]. Subsequently, a larger set of families was used to test 14 other candidate regions.

We have also initiated collection of tumour material from familial and sporadic cases of NMTC. *RET* is frequently activated by chromosomal rearrangements in human sporadic PTC (in 66% of sporadic PTC observed in Ukraine and Belarus 10 years after the Chernobyl accident). We have started studying rearrangements of *RET* in tumour preparations of familial and sporadic NMTCs using both fluorescence in situ hybridization (FISH) and RT-PCR techniques on frozen samples or archival paraffin-embedded tissue sections [115]. This technique might become a useful tool for the study of tumour progression in PTC.

4.2.6

Genetic and family studies of cancers of the head and neck

D.E. Goldgar; in collaboration with R. Eeles and S. Jefferies, Sutton, UK; and W. Foulkes, Montreal, Canada

The goal of this project is to characterize the familial risks of squamous cell carci-

nomas of the head and neck (SCCHN) and to identify potential tumour-suppressor loci that may be involved in the development of these tumours. It is also planned to examine the interaction between genetic/familial factors and the known environmental risk factors (tobacco and alcohol consumption) in producing the disease. A case–control study has been initiated, focusing on cases of multiple primary cancers, one of which is SCCHN, and the other is either also SCCHN or another smoking-associated tumour. Controls are (*a*) age-matched cases of single primary SCCHN and (*b*) age-matched healthy volunteers. All subjects provide questionnaire data on personal alcohol and tobacco usage and other relevant demographic and risk factor data. They are also asked to provide smoking and alcohol data on each of their first-degree relatives and on any cancers which have occurred in their relatives. Examination of epidemiological risk factors in families with two or more cases of related cancers versus families with negative cancer histories will be used to assess potential gene–environment interactions. The two tumours from the cases of multiple primary cancer and a corresponding sample of lymphocyte DNA are to be examined for a series of 100 highly polymorphic microsatellite markers throughout the genome. To date, 86 cases of multiple primary tumours have signed the consent form and completed the study questionnaire, as well as an equal number of single-tumour cases and controls. A subset of the cases have been screened for germline mutations in the *p16* gene; no mutations have yet been identified. Meetings of the collaborators were held in Denver in October 1998 and in Lyon in May 1999 to finalize the planned analyses. We are now developing statistical models to derive the probability that two tumours in a single patient are clonal, given the time interval between them and molecular characteristics (p53, loss of heterozygosity, microsatellite instability, X-inactivation) of each tumour. Data collection is expected to be complete by June 2000.

4.3 Role of oxidative stress in carcinogenesis

Oxidative stress is regarded as a cause of cancer, ageing and other pathophysiological conditions. Various reactive oxygen and nitrogen species such as nitric oxide (NO), superoxide (O_2^-) and hypochlorous acid (HOCl) are produced by mammalian cells and can contribute to oxidative stress by damaging proteins, lipids and nucleic acids. Recent studies have shown that interactions of these reactive species produce new and more potent oxidants (e.g., peroxynitrite from NO and O_2^- and nitryl chloride (NO_2Cl) from HOCl and nitrite). We are studying the role of reactive oxygen and nitrogen species in carcinogenesis from various points of view.

4.3.1

Co-expression of interleukin 8 and inducible nitric oxide synthase in gastric mucosa infected with *cag*A-positive *H. pylori* strains

B. Pignatelli, C.-Q. Li, H. Obshima, C. Malaveille, M. Laval and N. Lyandrat; in collaboration with Dr A. Covacci, Siena, Italy

H. pylori strains possessing the *cagA* gene are thought to be able to induce interleukin 8 (IL-8) expression and to be associated with gastroduodenal diseases. Excess nitric oxide (NO) produced by inducible NO synthase (iNOS) may be involved in inflammatory pathogenesis. We have investigated the relationships between *cag*A and expression of IL-8 and iNOS

messenger RNAs, and the type and degree of inflammation in gastric mucosa. In biopsies from 108 Chinese patients, *H. pylori cag*A and 16S rRNA, as well as human IL-8 and iNOS mRNAs, were analysed using reverse-transcription polymerase chain reaction (RT-PCR). Specimens infected with *cag*A-positive strains had significantly more severe infiltration by mononuclear cells and polymorphonuclear leukocytes, and expressed IL-8 and iNOS mRNA more frequently than those infected with *cag*A-negative strains. iNOS and IL-8 mRNAs were expressed together significantly more frequently in the specimens with moderate or severe inflammation than in those with normal mucosa or mild inflammation. Thus, our results demonstrate that infection with *H. pylori* strains positive for *cag*A induces the expression of IL-8 and iNOS mRNA, suggesting that IL-8 and excess NO play important roles in the pathogenesis of gastroduodenal diseases associated with *H. pylori* infection [262].

DNA extracted from these Chinese biopsies is being analysed for polymorphism of genes encoding myeloperoxidase and other enzymes related to oxidative stress, in order to identify any association of genotype with the severity of gastritis.

Immunodot-blot analyses for 3-nitrotyrosine and oxidized proteins developed in our laboratory are being applied to analyse proteins extracted from the same biopsies to assess oxidative tissue damage mediated by *H. pylori* infection. The genetic status of *H. pylori* (*cag* E and *vir* B11 homologue genes from the pathogenicity island) found in these Chinese biopsies is being analysed to investigate its relationship with oxidative stress.

4.3.2

Animal models of *H. pylori* infection

B. Pignatelli and H. Ohshima; in collaboration with M. Tatematsu, Nagoya, Japan; A. Covacci, Siena, Italy; and B. Bancel and L.-M. Patricot, Lyon, France

It has been reported that *H. pylori* can infect Mongolian gerbils (*Meriones unguiculatus*) and induce gastrointestinal diseases, such as gastritis and ulcers, that mimic the gastric pathology related to human *H. pylori* infection (Hirayama *et al.*, 1996, *J. Gastroenterol.*, **31**, 755–757; Matsumoto *et al.*, 1997, *J. Med. Microbiol.*, **46**, 391–397). Infection with *H. pylori* can induce stomach cancer (Honda *et al.*, 1998; *Cancer Res.*, **58**, 4255–4259; Watanabe *et al.*, 1998, *Gastroenterol.*, **115**, 642–648) in animals and enhance gastric carcinogenesis initiated by stomach carcinogens such as *N*-methyl-*N*-nitrosourea (Sugiyama *et al.*, 1998, *Cancer Res.*, **58**, 2067–2069).

We are studying the role of *H. pylori* infection in gastric carcinogenesis in Mongolian gerbil and mouse models. The relationship between oxidative stress and stomach cancer is being assessed by analysing stomach tissues obtained at different time points after infection with *H. pylori* for biomarkers of oxidative damage and stress. The degree of oxidative damage with various *H. pylori* strains is being correlated with cancer incidence and histopathological features. The effects of other dietary factors such as high salt- or nitrate-containing foods on the oxidative stress induced by *H. pylori* infection are also being examined and we are looking at the effects of *H. pylori* eradication and treatment with chemopreventive agents (e.g. flavonoids), as well as *H. pylori* vaccination, on oxidative damage and stomach pathology.

4.3.3

Effect of eradicating *H. pylori* on oxidative stress

B. Pignatelli, H. Ohshima, M. Laval and N. Lyandrat; in collaboration with B. Bancel, J.C. Souquet, J.L. Gaudin and L.-M. Patricot, Lyon, France; S. Toyokuni, Kyoto, Japan; A.L. Blum and E. Felley-Bosco, Lausanne, Switzerland; and C. Felley, Geneva, Switzerland

The effects of *H. pylori* eradication on oxidative stress have been investigated by comparing stomach pathology and biomarkers of oxidative stress before and after

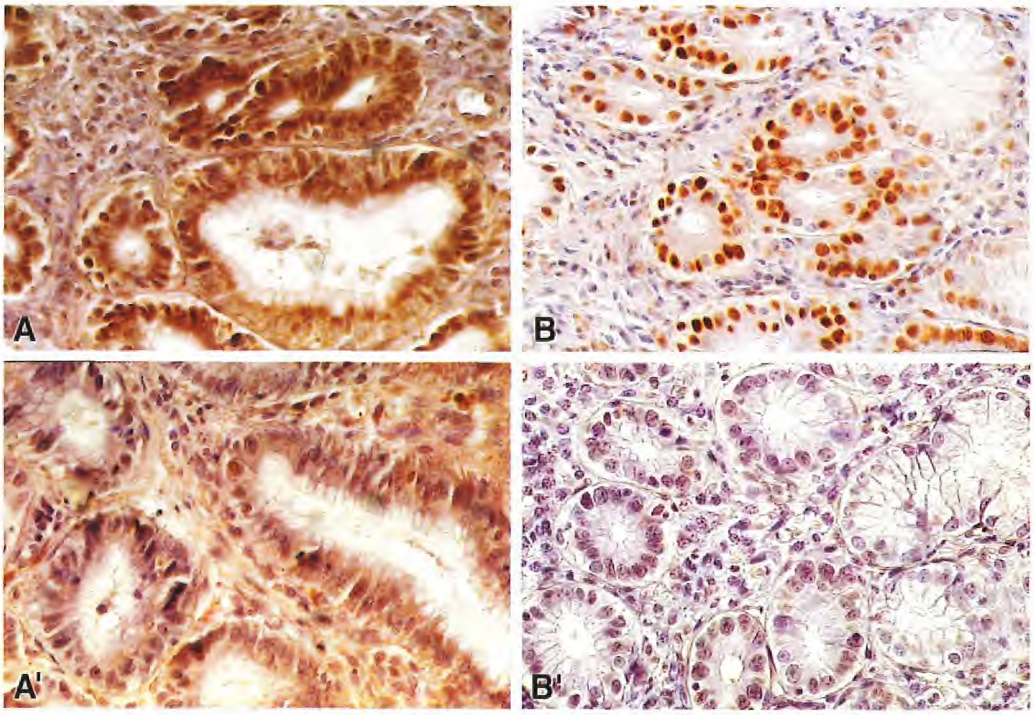

Figure 33. Nitrotyrosine (A, A') and 8-hydroxy-2'-deoxyguanosine (B, B') immunostaining in human gastric mucosa before (A, B) and after (A', B') treatment to eradicate *H. pylori*.

treatment to eradicate the bacteria. Expression of inducible nitric oxide synthase (iNOS) and interleukin-8 (IL-8) and the presence of 8-hydroxydeoxyguanosine (8-OHdG) and 3-nitrotyrosine (NTYR) were analysed immunohistochemically as markers for oxidative/nitrosative DNA and tissue damage. Thirty-four patients infected with *H. pylori* received a tritherapeutic treatment (amoxicillin, clarithromycin and omeprazole). In 26 patients (76%), *H. pylori* was successfully eradicated. This eradication of *H. pylori* resulted in: (*a*) reduction in inflammatory infiltrate, (*b*) a strong reduction in gastritis activity, (*c*) disappearance or decreased expression of iNOS in inflammatory cells of antral biopsies and (*d*) a decrease in levels of NTYR and 8-OHdG in deep foveolar cells of antral gastric biopsies (Figure 33).

We have performed another study in *H. pylori*-infected asymptomatic volunteers, the aims of which were (1) to demonstrate the expression of iNOS, NTYR, manganese-superoxide dismutase (Mn-SOD) and catalase in *H. pylori*-infected individuals by both RT-PCR and immunohistochemistry, (2) to correlate the score of gastritis with IL-8 production and (3) to investigate the effect of eradication of *H. pylori* on the expression of iNOS and IL-8. Biopsies were taken from the corpus and antrum of 10 infected and 12 uninfected volunteers. iNOS was detected in 2/12 in the uninfected group and 8/10 in the infected group. Weak NTYR staining was found in 1/12 in the uninfected and strong staining in 2/10 in the infected group. IL-8 was increased in the infected compared with uninfected, but did not correlate with the gastritis score. We confirmed that iNOS is expressed in inflamed gastric mucosa. Oxidative stress was related to *H. pylori* infection and was reduced after *H. pylori* eradication.

4.3.4

Expression of antioxidant enzymes before and after eradication of *H. pylori* in Venezuelan subjects

B. Pignatelli, H. Ohshima, N. Muñoz and M. Plummer; in collaboration with J. Torrado, San Sebastian, Spain

Production of reactive nitrogen/oxygen species induced by *H. pylori* infection causes oxidative injury which can be prevented by endogenous antioxidant enzymes such as superoxide dismutases (SOD) and catalase. We have studied the effects of *H. pylori* eradication on antioxidant enzyme levels by immunohistochemistry.

A total of 80 subjects aged 35–69 years, from among participants in a chemoprevention trial for precancerous lesions of the stomach in Venezuela (see Section 5.1.2), took part in a study of *H. pylori* eradication. Subjects received a gastroscopy and five biopsies were taken from pre-specified regions of the stomach. They were then randomized to two regimens, regimen A (DeNol 480 mg, amoxicillin 2 g and metronidazole 1 g per day) or B (omeprazole 40 mg and clarithromycin 1.5 g per day) for 14 days. A second gastroscopy was performed 1–2 months after the first one. Presence of *H. pylori* was diagnosed by histological examination. The eradication rates were only 28% by regimen A and 21% by regimen B.

All subjects from whom *H. pylori* was successfully eradicated (8 on regimen A and 6 on regimen B) and a control group of five subjects from each treatment regimen were selected for a study of the antioxidant enzymes Mn-SOD and catalase. These were measured in inflammatory cells (polymorphonuclear and mononuclear cells) and in gastric epithelial cells (foveolar cells, neck cells, and deep glandular cells). Enzyme levels were graded as negative, mild (<10% of cells positive), moderate (10–30% of cells positive) or marked (>50% of cells positive). These grades were given scores 0–3 and the maximum score was used as an overall diagnosis for each subject. Both enzymes were found only in epithelial cells. This finding contrasts with previous experience in French subjects [377]. This discrepancy could be due to a higher degree of oxidative stress in Venezuelan patients than in French patients. It could also result from the type of tissue fixation, as Venezuelan biopsies were fixed in formalin while French samples were fixed in Bouin's solution. There appeared to be a decline in catalase levels for all epithelial cell types after treatment. Mn-SOD was commonly found in neck cells and deep glandular cells and there appeared to be no reduction in levels after treatment. This may be due to the persistence of inflammation and gastritis in the subjects.

4.3.5

H. pylori eradication and antioxidant vitamin supplements reduce gastric juice genotoxicity

C. Malaveille, B. Pignatelli, H. Ohshima and A. Hautefeuille; in collaboration with S. Everett and A. Axon, Leeds, UK

We have previously obtained evidence for a role of intragastrically formed, nitrite-derived, direct mutagens in gastric cancer etiology (Pignatelli *et al.*, 1993, *Eur. J. Cancer*, **29A**, 2031–2039). *H. pylori* may induce gastric carcinogenesis by reducing levels of ascorbate and increasing nitrosation-dependent genotoxicity in gastric juice. We have studied the effect of supplementing dietary antioxidant vitamins in combination with *H. pylori* eradication on these mechanisms in a randomized, double-blind, placebo-controlled trial. Patients undergoing gastroscopy had gastric juice taken for assay of ascorbic acid by HPLC and of nitrosation-dependent genotoxicity, as SOS DNA repair inducibility in bacteria (SOSIP) using the SOS chromotest. *H. pylori*-positive patients were randomized into four groups, receiving bismuth chelate, tetracycline and metronidazole (BTM) or

placebo for two weeks, followed by vitamins C and E or placebo for four weeks. Gastroscopy and sampling were repeated at six weeks. Median SOSIP was higher in controls with normal mucosa than in *H. pylori*-positive patients. SOSIP was correlated with gastric pH ($r = 0.3$, $p = 0.001$) and was higher above pH 4 than below, but did not correlate with ascorbate levels. Patients receiving BTM plus vitamins ($n = 20$) had increased ascorbate levels and decreased SOSIP at six weeks. Those receiving BTM and placebo ($n = 19$) had a non-significant increase in ascorbate but no change in SOSIP. Patients receiving vitamins alone ($n = 21$) had no increase in ascorbate and a non-significant decrease in SOSIP. No changes were seen in the placebo group ($n = 16$). In conclusion, gastric juice genotoxicity is diminished in *H. pylori* infection but increased in hypochlorhydria. This will be relevant for *H. pylori*-infected patients with mucosal atrophy. Eradication therapy plus vitamin C and E supplementation increases gastric ascorbate and may reduce genotoxicity.

4.3.6
Nitric oxide in carcinogenesis

4.3.6.1
Suppression of intestinal polyposis in inducible nitric oxide synthase (iNOS)-deficient $Apc^{Min/+}$ mice

B. Ahn, H. Ohshima, M.P. Cros, M. Laval and N. Lyandrat

Accumulating evidence indicates that overproduction of NO is involved in the pathogenesis of colorectal cancer in both rodents and humans. Min (multiple intestinal neoplasia) mice, which have a germline nonsense mutation at codon 850 of the adenomatous polyposis coli (*Apc*) gene, spontaneously develop multiple adenomas in the small and large intestines at the age of 10–12 weeks. $Apc^{Min/+}$ mice are considered to be an excellent animal model of human familial adenomatous polyposis. In the present study, we utilized $Apc^{Min/+}$ mice to investigate the role of iNOS on intestinal adenoma development. We found that iNOS mRNA and protein were expressed in normal mucosa of small and large intestines of most Min mice (Figure 34). In order to suppress iNOS, we administered the iNOS-selective inhibitor aminoguanidine in drinking water and a diet deficient in L-arginine (a substrate of iNOS). We have also generated iNOS-gene knock-out Min mice ($Apc^{Min/+}iNOS^{-/-}$ or $Apc^{Min/+}iNOS^{-/+}$). The number of adenomas in the small intestine was significantly lower in $Apc^{Min/+}$ mice receiving the iNOS inhibitor or L-arginine-deficient diet as well as in those deficient for the iNOS gene. The tumour incidence and multiplicity in colorectal tissues also significantly decreased in iNOS-gene knock-out Min mice, whereas there was no significant change in mice treated with aminoguanidine or fed the L-arginine-deficient diet. These results suggest that NO produced by iNOS plays an important role as an endogenous factor in the development of intestinal polyposis in Min mice and that an iNOS-selective inhibitor can act as a potential chemopreventive agent for colorectal cancer.

Figure 34. Immunostaining of iNOS in intestinal adenomas of Min mice.

Strong immuno-positive reaction in surface epithelial cells of the adenoma and normal ileal villi but not in dysplastic epithelial cells and crypt cells

4.3.6.2

Immunohistochemical localization of inducible nitric oxide synthase and 3-nitrotyrosine in rat liver tumours

B. Ahn and H. Ohshima; in collaboration with B.S. Han and D.J. Kim, Seoul, Republic of Korea

Human liver cancers have been associated with chronic inflammations such as viral hepatitis B or C. This suggests that prolonged cell damage by chronic inflammation is critical in cancer development. Overproduction of NO and its derivatives (NOx, peroxynitrite) has been implicated as a cause of tissue damage by inflammation, thus contributing to tumour promotion. We have demonstrated by immunohistochemistry the expression of iNOS and 3-nitrotyrosine, a marker of peroxynitrite formation, in preneoplastic and neoplastic rat liver tissues after induction by *N*-nitrosodiethylamine (Figure 35). The preneoplastic lesions were characterized by proliferation of phenotypically altered hepatic foci (PAHF), dysplastic hepatocytes and oval cells. Histologically, the tumours were hepatocellular carcinomas (HCCs) of trabecular, (pseudo)glandular and solid types with or without cholangiocellular involvement. iNOS was located mainly in oval cells, capillary endothelial and muscular cells, epithelia of cholangiomas and glandular HCCs. 3-Nitrotyrosine was observed in the cytoplasms of PAHF and dysplastic hepatocytes in preneoplasias and in the cytoplasm of some living or apoptotic HCC cells, connective tissues, proteinaceous fluids, sinusoidal endothelia of tumourous hepatocytes and cholangiomas in tumours. We therefore suggest that (*a*) chronic tissue damage by chemical carcinogens may act to induce iNOS and peroxynitrite formation; (*b*) oval cells play a key role in development and/or growth of tumour tissues by producing NO via iNOS, which may also cause tissue damage by peroxynitrite; and (*c*) iNOS can be considered as a phenotypic marker in cells of oval cell lineage and neovascularized capillaries in tumour tissues [1].

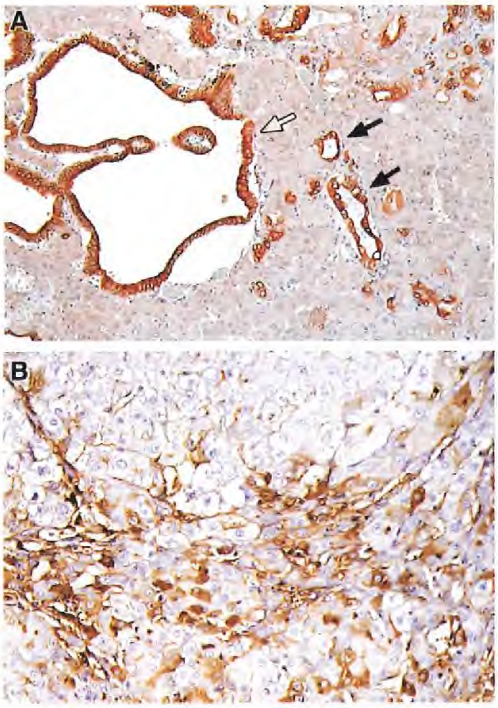

Figure 35. Typical immunohistochemical staining of iNOS and 3-nitrotyrosine

Immunostaining of iNOS in glandular hepatocellular carcinoma (A) and of 3-nitrotyrosine in preneoplastic lesions in both PAHF and dysplastic hepatocytes (B).

We are also conducting a long-term animal experiment to compare *N*-nitrosodiethylamine carcinogenicity in iNOS-deficient mice and in wild-type mice, as well as cell proliferative activity and liver weight changes. The mice were treated twice with the hepatocarcinogen (10 mg/kg) at the ages of 10 days and 31 days old and will be sacrificed at one year.

4.3.6.3

3-Nitrotyrosine and oxidized proteins as markers of oxidative stress in lung cancer patients

B. Pignatelli, C-Q. Li, H. Ohshima, P. Boffetta and V. Gaborieau

Reactive oxygen and nitrogen species formed in tobacco smoke and/or in inflamed

lungs may trigger oxidation or nitration reactions *in vivo* and contribute to carcinogenesis. We have analysed nitrated (NTYR) and oxidized (carbonyls) proteins in plasma as markers of oxidative and nitrosative damage in 94 subjects (lung cancer patients and healthy subjects, active, ex- and non-smokers; see Section 3.7.7), using Western and dot immunoblotting methods. Levels of NTYR-containing proteins were significantly higher in lung cancer patients than in healthy subjects and heavy smoking increased levels of both NTYR and oxidized proteins compared with non-smoking subjects (Figure 36). Western blot analyses showed the presence of two to five NTYR-containing proteins and only one oxidized protein. Our results clearly indicate that tobacco smoking increases oxidative stress and that during cancer development, reactive nitrogen species are also formed.

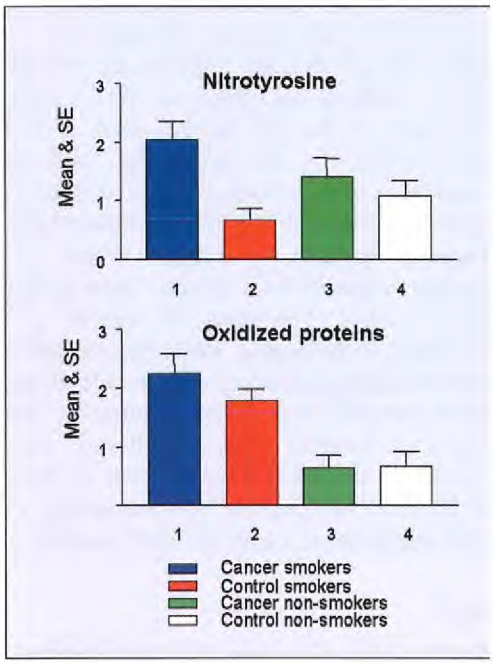

Figure 36. Dot immunoblotting analyses of nitrated (3-nitrotyrosine) and oxidized (carbonyls) proteins in plasma of cancer smokers and non-smokers and control subjects.

4.3.6.4

DNA damage by reactive nitrogen species

H. Ohshima, B. Pignatelli, F. Bianchini, I. Gilibert, M. Masuda and L. Chazotte-Aubert; in collaboration with S. Oikawa and S. Kawanishi, Mie, Japan

Nitroxyl anion (NO^-), the one-electron reduction product of nitric oxide ($NO^\cdot$), can be formed under various physiological conditions. We have used four different assays to study effects of NO^- generated from Angeli's salt on DNA damage. It was found that strong oxidants are generated from NO^-, especially in the presence of H_2O_2 plus Fe(III)-EDTA or Cu(II). NO released from diethylamine-NONOate had no such effect. Distinct effects of hydroxyl radical ($HO^\cdot$) scavengers and patterns of site-specific DNA cleavage caused by Angeli's salt alone or Angeli's salt, H_2O_2 plus metal ion suggest that NO^- acts as a reductant to catalyse formation of $HO^\cdot$ from H_2O_2 plus Fe(III) and formation of Cu(I)-peroxide complexes with a reactivity similar to that of $HO^\cdot$ from H_2O_2 and Cu(II). Angeli's salt and H_2O_2 exerted synergistically cytotoxic effects in MCF-7 cells, determined by lactate dehydrogenase release assay. Thus NO^- may play an important role as a cause of diverse pathophysiological conditions such as inflammation and neurodegenerative diseases, especially when H_2O_2 and transition metallic ions are also present. As NO^- may be formed *in vivo* under a variety of physiological conditions, including formation by NO synthase and from *S*-nitrosothiols and nitrosylhaemoglobin, further studies are in progress to identify NO^--associated specific tissue damage [107, 331].

4.3.6.5

Modification of functions of tumour suppressor p53 protein by nitric oxide

L. Chazotte-Aubert, H. Ohshima and P. Hainaut

Treatment of cultured cells with *S*-nitrosoglutathione results in not only accu-

mulation of p53 protein but also inhibition of its DNA-binding activity (Calmels *et al.*, 1997, *Cancer Res,* **57**, 3365–3369). We are further studying the effects of NO on some functions of the p53 protein such as cell cycle arrest in G1 phase, as well as expression of *p53*-downstream genes such as *p21*, *GADD45* and *Bax*. We have found that tyrosine residues are nitrated in the p53 protein extracted from human breast cancer MCF-7 cells. The level of nitrated p53 increased significantly following treatment with *S*-nitrosoglutathione (Figure 37). It has been reported that tyrosine nitration can occur in several proteins, altering their functions. Our results suggest that nitration of p53 may be important as a mechanism of post-translational regulation of its function.

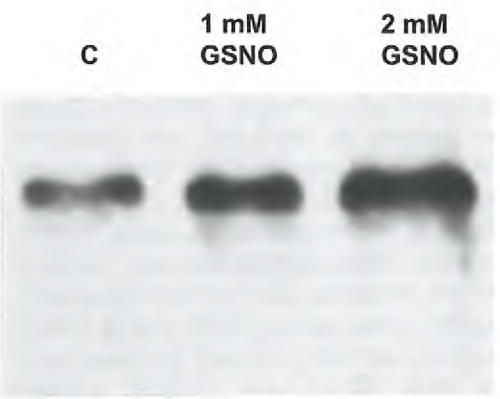

Figure 37. Nitration of p53 with *S*-nitrosoglutathione (GSNO). p53 from MCF-7 cells was immunoprecipitated using a polyclonal antibody against p53 (CM1) and then subjected to Western blot analysis with a monoclonal antibody against 3-nitrotyrosine.

4.3.7

Formation of chlorinated nucleosides by the reaction of nucleosides with hypochlorous acid and human myeloperoxidase

M. Masuda, H. Ohshima, I. Gilibert, B. Pignatelli and M.D. Friesen

Hypochlorous acid (HOCl) is generated from hydrogen peroxide (H_2O_2) and chloride ion (Cl^-) by the haem enzyme myeloperoxidase (MPO), which is secreted by activated neutrophils in inflamed tissues. HOCl is a strong oxidant, which is capable of destroying invading pathogens and malignant cells, but can also damage normal tissues. We have found that various nucleosides react with HOCl to yield chlorinated nucleosides, including the previously unknown 8-chloro-2′-deoxyguanosine, 8-chloro-2′-deoxyadenosine and 5-chloro-2′-deoxycytidine (Figure 38). These chlorinated nucleosides are also formed by human MPO in the presence of H_2O_2 and Cl^-. Tertiary amines such as nicotine dramatically enhance chlorination mediated by HOCl. Genetic polymorphism of MPO has been associated with lung cancer risk, and we propose that chlorination damage mediated by MPO, HOCl and nicotine may play an important role in lung cancer development in smokers. Sensitive and specific methods to measure the chlorinated nucleosides in DNA are under development. The biological significance of these adducts (mutation, incorporation into DNA, repair etc.) is also being investigated.

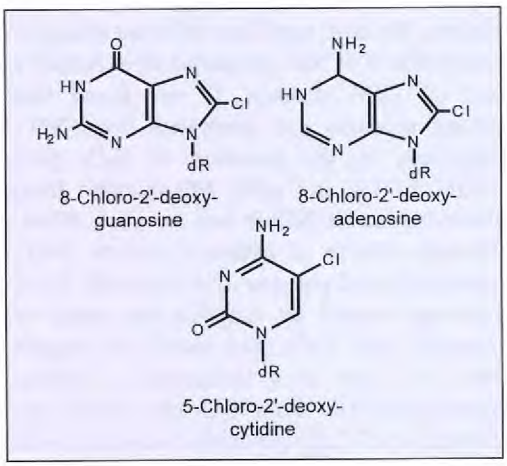

Figure 38. Chlorinated nucleosides isolated from the reaction of nucleosides with hypochlorous acid

Similarly, tyrosine residues in proteins are chlorinated by HOCl to form 3-chlorotyrosine. A polyclonal antibody against 3-chlorotyrosine-containing protein has been raised. This will be used to develop immunoassays for 3-chlorotyrosine as well as to localize chlorination damage in animal and human tissues.

4.3.8
Oxidative DNA damage and diet

F. Bianchini, H. Ohshima, A.-L. van Kappel, E. Riboli and R. Kaaks; in collaboration with S. Elmståhl, Malmö, Sweden; C. Martinez-Garciá, Granada, Spain; and T. Douki and J. Cadet, Grenoble, France

The aim of this project is to investigate relations between markers of oxidative damage and diet, in particular antioxidants. We measured the levels of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodGuo) as a marker of oxidative DNA damage in lymphocytes, and α-tocopherol and several carotenoids in plasma from women with different dietary habits. Women in Granada (Spain), with a typically Mediterranean diet, had significantly higher levels of 8-oxodGuo than women in Malmö (Sweden), with a north European dietary intake pattern (Figure 39). Levels of plasma α-tocopherol and carotenoids were higher in Granada and these values were significantly positively correlated with levels of 8-oxodGuo. Our results do not support the hypothesis that a Mediterranean diet rich in α-tocopherol and carotenoids protects cells against oxidative DNA damage. It is possible, however, that consumption of foods other than fruits and vegetables, including fats, account for the higher levels of 8-oxodGuo in Granada. Measurements are now being made in samples from women in Potsdam (Germany) and (Turin) Italy.

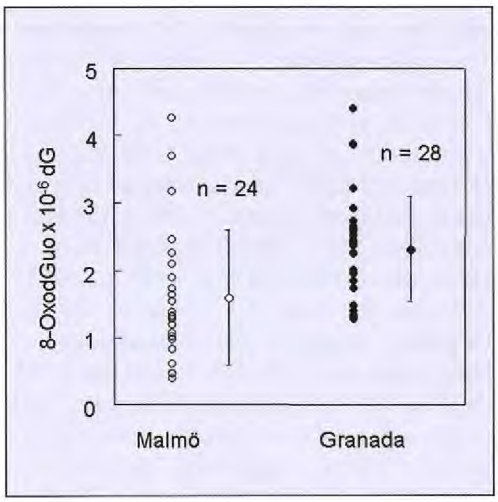

Figure 39. Distribution and mean (± S.D.) of 8-oxodGuo levels in lymphocytes from women in Malmö and Granada (p<0.01 by Wilcoxon's score test)

4.4 Role of cell–cell communication in carcinogenesis

Intercellular communication controls the integrated society of cells in a multicellular organism. Among various forms of such communication, gap junctional intercellular communication (GJIC) is considered to play a pivotal role in the maintenance of tissue homeostasis. GJIC is, in turn, controlled by various factors including cell adhesion molecules. The role of the gap junction proteins (the connexins) and cell adhesion molecules in carcinogenesis is being extensively studied at IARC.

4.4.1
Role of the C-terminal domain of connexin genes in tumour suppression

Y. Omori and H. Yamasaki

We have previously reported that transfection of the gene for connexin 26 (Cx26) into HeLa cells (which express no detectable level of connexins) induces GJIC and suppresses the tumorigenic phenotype of HeLa cells both *in vitro* (proliferation rate, saturation density and anchorage-independent cell

growth) and *in vivo* (tumorigenicity in nude mice). However, transfection of Cx32, Cx40 or Cx43 did not affect these tumorigenic characteristics although all of them induced GJIC in HeLa cells to a similar extent (Mesnil *et al.*, 1995, *Cancer Res.*, **55**, 629–639). The most notable structural difference between connexin proteins is the length of the C-terminal cytoplasmic tail, Cx26 having almost no tail, while Cx43 and Cx32 have long and intermediate ones, respectively. When Cx32 and Cx43 lose their C-terminal tails, they seem to resemble Cx26 in structure. To examine whether Cx32 and Cx43 become tumour-suppressive in HeLa cells when their C-terminal tails are removed, we introduced a stop codon into each of the Cx32 and Cx43 cDNAs to truncate their C-terminal tails and transfected these constructs (ΔCx) into HeLa cells. Both ΔCx cDNAs induced GJIC as efficiently as the wild-type Cx32 and Cx43. Although the truncated connexins did not completely eliminate the tumorigenicity of HeLa cells as Cx26 did, it was clear that deletion of the C-terminal tails gave both Cx32 and Cx43 a capacity for negative growth control, suggesting that the C-terminal tails of these two connexins function as a regulatory region for connexin-mediated growth control in HeLa cells.

4.4.2
Growth-suppression of human hepatocellular carcinoma cells by connexin 26

T. Yano, F.-J. Hernandez-Blasquez, Y. Omori and H. Yamasaki

Our analyses of primary human hepatocarcinomas and chemically-induced rat liver tumours have revealed various anomalies of the gap junctions in most of samples, including no or low expression and aberrant localization of connexin. This suggests that gap junctions are closely involved in tumour suppression in hepatocytes. While both Cx26 and Cx32 are extensively expressed in normal hepatocytes, no Cx26 expression is detectable in the tumorigenic HepG2 cell line, derived from human hepatocarcinoma. Furthermore, Cx32 protein expressed in this cell line is not found at cell–cell contact areas but is retained in the cytoplasm, forming no functional gap junctions. If HepG2 cells could be induced to express the Cx26 gene, the cells might recover certain normal phenotypes such as reduction of growth rate and saturation density, restoration of GJIC, proper localization of Cx32 and absence of tumorigenicity. To examine this possibility, Cx26 cDNA linked to a CMV promoter was introduced into HepG2 cells. Cx26 had a clear effect on cellular structure and cell–cell adherence. The Cx26 proteins were localized at cell–cell contact areas and GJIC was partially restored. Since endogenous Cx32 proteins still remained in the cytoplasm, Cx26 did not appear to promote transport of Cx32 to the membrane. The Cx26 transfectants decreased in saturation density by 25% and Cx26 slightly affected the growth rate. Furthermore, anchorage-independent growth in soft agar was significantly diminished by 50% in Cx26 transfectants. These results suggest that Cx26 plays a pivotal role in growth control of hepatocytes.

4.4.3
Role of GJIC in apoptosis

V. Krutovskikh, C. Piccoli and H. Yamasaki

While the role of GJIC in cell growth regulation has been much studied, its involvement in apoptosis remains unclear. Employing the rat bladder carcinoma BC31 cell line, which displays good coupling capacity due to expression of connexin 43 (Cx43) and a high propensity to apoptosis, we found that during the initial steps of apoptosis, these cells still express Cx43 which continues to be located in areas of cell–cell contact (Figure 40). The apoptotic cells were unable to take up lucifer yellow from the extracellular environment, but

spreading of the dye from individual apoptotic cells into the cytoplasm of surrounding non-apoptotic counterparts suggests that apoptotic cells maintain heterologous GJIC within a cell monolayer. Thus, clusters of dying cells were visible.

Inhibition of intrinsic GJIC in BC31 cells by enforced expression of a dominant-negative mutant of Cx43 neither accelerated the growth rate of these cells nor changed the level of primary apoptosis, but suppressed the formation of clusters of dying cells. As a result, the saturation density of cells increased. A similar effect was observed when intrinsic GJIC in BC31 cells was inhibited by long-term exposure to α-glycyrrhetinic acid.

Overall, these results suggest that GJIC allows the propagation of suicide signals from individual apoptotic cells into contiguous cells in a monolayer. This mechanism may contribute to connexin-mediated suppression of tumour growth.

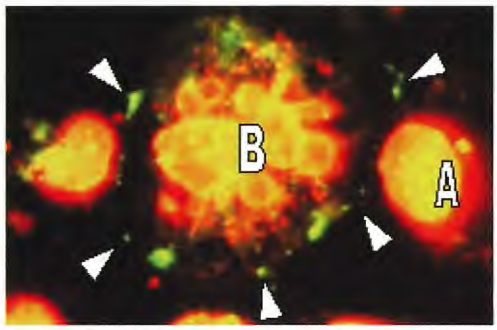

Figure 40. Evidence for implication of GJIC in propagation of cell death.

Expression and subcellular location of Cx43 in monolayer (A) and in apoptotic cells (B). Arrows indicate location of Cx43 in areas of intercellular contact between apoptotic cell (B) and non-apoptotic counterparts (A). Counterstaining with propidium iodide reveals fragmentation of nucleus typical of apoptosis (B).

4.4.4
Connexin-associated proteins

Y. Omori and H. Yamasaki

Transfection of various connexin genes into tumorigenic cells has revealed that connexins suppress cell growth and tumorigenicity in a cell-type-specific manner; thus, Cx26 and Cx43 abolish the tumorigenicity of HeLa cells and rat glioma C6 cells, respectively. The growth-suppressive action of Cx26 in HeLa cells cannot be replaced by expression of other connexin types such as Cx32, Cx40 or Cx43. On the other hand, Cx43 is growth-suppressive in C6 cells. However, any type of connexin is capable of restoring GJIC in both cell lines, suggesting that connexins can control cell growth in a GJIC-independent and connexin-species-specific manner, probably involving signal transduction cascades. To examine this hypothesis, we have started to search for proteins associated with connexin, using a yeast two-hybrid system. We chose the cytoplasmic loop domain of Cx26 as bait because this region is the most different in amino acid sequence between Cx26 and other connexin types. We isolated five independent clones and sequence analysis revealed that all contained part of the same unidentified gene located on human chromosome X. This gene was found to be expressed abundantly in liver, kidney, heart and skeletal muscle as a 1-kb transcribed product. Although we have not yet obtained full-length cDNA, we have confirmed that these protein fragments bind specifically to Cx26 but not to the cytoplasmic loop of Cx32.

4.4.5
Liver-specific transgenic mice carrying a dominant-negative Cx32 mutant gene

M.-L. Zaidan-Dagli, Y. Omori, V. Krutovskikh, N. Martel and H. Yamasaki; in collaboration with T. Ott and K. Willecke, Bonn, Germany

We have previously reported that a mutant form (V139M; valine to methionine at codon 139) of Cx32 inhibits GJIC that is induced in HeLa cells by wild-type Cx32, in

a dominant-negative manner, if these two connexin forms are co-expressed.

To explore the role of Cx32, which is highly expressed together with Cx26 in hepatocytes, in growth control of hepatocytes *in vivo* while avoiding a systemic effect caused by gene disruption, we have generated transgenic mouse lines bearing the Cx32 mutant V139M gene driven by a liver-specific albumin promoter. Two independent lines were obtained, one of which expressed the mutant gene only in the liver, as expected, while the other also showed some expression in kidney, heart, skin and brain. So far no phenotypic difference between these two lines has been seen. The transgenic mice developed normally both before and after birth, and showed no macroscopic difference from the wild type, although GJIC in the liver was reduced by 30–50% in the transgenic mice. Biochemical analysis of general liver function also indicated that all values were within a normal range.

There was no significant increase in spontaneous tumour incidence during a one-year period. Unlike Cx32-deficient mice (Temme *et al.*, 1997, *Curr. Biol.*, 7, 713–716), the BrdU incorporation rate in quiescent hepatocytes of V139M transgenic mice was similar to that of the wild type. However, when 30% of the liver was removed, regeneration was retarded in the transgenic mice, as indicated by the BrdU index. While DNA synthesis in the wild type reached a peak 48 hours after partial hepatectomy, that of the transgenic mice peaked after 72 hours.

To evaluate the susceptibility to chemical hepatocarcinogenesis of the transgenic mice, 15-day-old animals were treated with *N*-nitrosodiethylamine and sacrificed at various intervals. At week 49, tumour multiplicity was significantly higher in transgenic males than in wild-type mice, and tended to be larger. 75% of the transgenic males had hepatocellular adenomas, against only 57% in the wild type, and 42% of the transgenic males developed hepatocellular carcinomas, against only 14% in the wild type.

Since no V139M-specific antibody was available, we could not detect the expression or subcellular localization of the mutant protein separately from the wild type. To examine the behaviour of the mutant protein in mouse liver, the V139M transgenic line was crossed with a Cx32-deficient one. When the V139M protein was expressed in the absence of the wild type in the crossed mouse liver, the mutant was localized not in the cell membrane but at a perinuclear area or in the nucleus although the total signals derived from both wild-type and mutant Cx32 in V139M transgenic mice were detected only at cell–cell contact areas. It therefore appears that the V139M mutant cannot integrate into the cell membrane by itself, but can probably form chimeric connexons with the wild type, that locate properly in the membrane.

Taken together, these results suggest that in our V139M transgenic mice, the mutant Cx32 caused a reduction in GJIC through a dominant-negative mechanism, resulting in retarded liver regeneration and increased susceptibility to chemical hepatocarcinogenesis due to the failure of transmission of an intercellular signal necessary for coordinated cell growth.

4.4.6
Origin of tumour-specific antigenic peptides in mouse lung carcinomas

V. Krutovskikh, G. Reguer and H. Yamasaki; in collaboration with G. Berke, Rehovot, Israel

Two octapeptides (Mut1 FEQNTAQP and Mut2 FEQNTAQA) have been reported to be tumour-associated antigens of two independent lung carcinoma cell lines (Mandelboim *et al.*, 1994, *Nature*, **369**, 67–71). Mutated connexin 37 (Cx37) was proposed to be the origin of both peptides, arising by a Cys54Gln mutation; an additional mutation (Pro59Ala) would give rise to Mut2. A Cys54Gln

conversion would entail three base changes (TGT to CAG) to occur twice in independently derived lung carcinomas, and in the highly conserved extracellular portion of connexins. To examine this unlikely possibility, we amplified tumour DNA from the same lung carcinoma cell lines by PCR and sequenced the coding region encompassing codon 54. We then analysed fragments from digestion of the PCR product by restriction endonuclease MaeIII (specific for GTNAC, which corresponds to the wild-type sequence of codon 54 of Cx37), to look for mutations. Finally, we used mutant-allele-specific PCR to detect the presence of the TGT54CAG mutation. We found only normal Cx37 sequences, including those of codons 54 and 59, in all cell lines. Hence, the peptides Mut1 and 2 cannot be derived from a mutated Cx37 gene as proposed, and their molecular origin remains unclear.

4.4.7

Control of intracellular movement of connexins 43 and 26 by E-cadherin in mouse epidermal cells

F.-J. Hernandez-Blazquez, Y. Omori and H. Yamasaki

We have previously shown that Cx43-mediated GJIC is controlled by E-cadherin in mouse epidermal cells. Thus a cell line lacking E-cadherin (P3/22) was unable to communicate in a high-calcium medium, but GJIC was restored in cells transfected with E-cadherin gene under similar conditions (Jongen *et al.*, 1991, *J. Cell Biol.*, **114**, 545–555). In an E-cadherin-expressing cell line (P3/E1) maintained in a low-calcium medium, Cx43 is present in the cytoplasm and only begins to move to the membrane after a shift to high-calcium medium.

In order to see whether the long cytoplasmic C-tail of Cx43 is important for the control of its localization by E-cadherin, we transfected the Cx26 gene into P3/22 and P3/E1 cells. Cx26 has almost no cytoplasmic C-tail, but its transport to the plasma membrane was similar to that of Cx43. This implies that the presence of a cytoplasmic C-tail is not a prerequisite for E-cadherin-mediated transport of connexins. We also found that E-cadherin is able to move connexin molecules pre-existing in the cytoplasm to the plasma membrane in the absence of *de novo* protein synthesis.

The time-related movement of Cx43 and 26 observed under various conditions suggests that the migration of connexins to the plasma membrane is mediated by the Golgi complex. It appears that before the medium is changed from low to high calcium, the connexin molecules are stored in a pre-Golgi compartment, possibly the endoplasmic reticulum. The microtubules seem to be less important in this process of transport than actins.

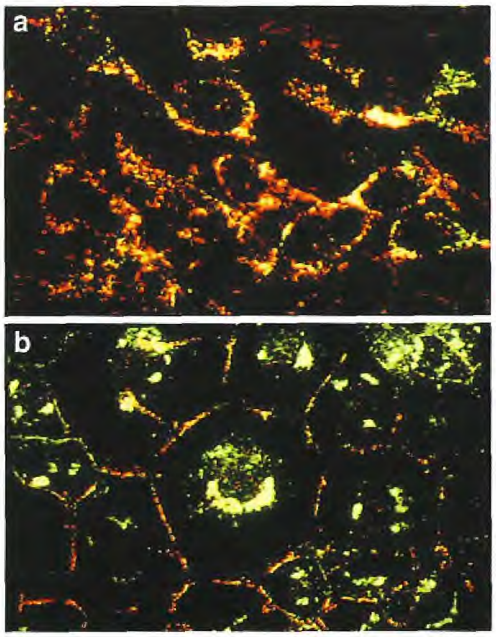

Figure 41. Confocal images of P3/E1 E-cad$^+$ cells (double stain for Cx 43 (green) and Cx 26 (red)) (*a*) in low-calcium medium, showing connexins colocalized in the cytoplasm; (*b*) after 24 hours in high-calcium medium, showing that both Cx 43 and Cx26 have migrated to the membrane and are colocalized at gap junction plaques.

4.4.8
Role of gap junctional intercellular communication in the bystander killing of cancer cells by anticancer gene therapy

M. Mesnil, T. Tanaka and H. Yamasaki

The thymidine kinase of herpes simplex virus (HSV-tk) is able to convert non-toxic nucleoside analogues such as ganciclovir (GCV) into toxic phosphorylated derivatives which prevent the elongation of DNA strands during cell replication. Once the *HSV-tk* gene is introduced into cancer cells, GCV treatment kills not only the cancer cells which express the gene, but also surrounding tumour cells which do not. This phenomenon, called a 'bystander effect', is mediated and enhanced by gap junctions which permit the transfer of phosphorylated GCV molecules from the HSV-tk-expressing cells to the others. From a therapeutic point of view, the bystander effect is important since it may overcome the low efficacy of gene transfer observed in anticancer gene therapy.

We have shown that the infection rate of adenoviral particles carrying the *HSV-tk* gene required to kill a cell population totally can be ten times lower if the infected cells communicate by gap junctions. Increasing endogenous GJIC by treatment with, for example, cyclic AMP, also can double the bystander effect. More recently, we observed that an increased bystander effect can be obtained by means of gene transfer, with a bigenic vector carrying both the *HSV-tk* gene and a connexin (*Cx*) gene. Even expression of a *Cx* gene in only half of the cells induced a bystander effect sufficient for GCV to eliminate almost a whole cell culture. When we mixed HeLa cells expressing either the *HSV-tk* gene or a *Cx* gene in different ratios, we observed that the bystander effect was higher if the HSV-tk and the *Cx* genes were expressed not in the same cell but in separate cells. Although we could not detect any gap junctions between the Cx-expressing cells and the others, dye-transfer was observed between the two cell types, implying that *Cx* gene transfer may be required in order to induce the bystander effect in HSV-tk/GCV anticancer gene therapy. Otherwise, human tumours which are gap-junction proficient would appear to be the best targets for this kind of gene therapy.

The bystander effect induced by another suicide gene, cytosine deaminase (CD), has also been studied. When this gene is expressed, the targeted cells are killed by conversion of 5-fluorocytosine to its toxic derivative 5-fluorouracil. In this case, the bystander effect operates simply by diffusion, not involving gap junctions or cell–cell contacts. When a vector carrying both the CD and uracil phosphoribosyltransferase (UPP) genes was used, the cell-killing effect was 10 times more powerful, due to more efficient production of toxic metabolites of 5-fluorouracil. This killing was independent of the communication capacity of the cells if at least 10% of them were transfected with the vector. However, for lower percentages of cells carrying this vector, the communication capacity did make a difference, since with only 5% CD-UPP cells, the entire cell population could be killed if the cells were communicating through gap junctions.

4.4.9
Identification of transcription factors controlling E-cadherin expression

L. Giroldi and P.-P. Bringuier

The intercellular adhesion molecule E-cadherin is a suppressor of cancer invasion and loss of E-cadherin function during carcinoma progression is associated with decreased patient survival (Giroldi *et al.*, 1994–95, *Inv. Metast.*, **14**, 71–81).

A frequent reason for loss of E-cadherin function in several tumour types is decreased transcription. Our previous study of E-cadherin promoter activity in different cell

backgrounds suggested the existence of a transcriptional repressor acting in cancer cells through binding to specific sequences of the minimal promoter called 'E-boxes' (Giroldi *et al.*, 1997, *Biochem. Biophys. Res. Commun.*, **241**, 453–458). Using the yeast one-hybrid technique, we have been looking for proteins that bind the E-cadherin minimal promoter. We picked up several transcription factors, including AP2 and ERF1 that are known to bind to the E-cadherin minimal promoter. Two of the clones are isoforms of a CAAT box-binding protein (the γ subunit of NFY), one of them not previously identified. One of the clones is a member of the family of the orphan nuclear receptors and it binds E-boxes in the yeast system. One of the clones is unknown. It encodes a putative nuclear protein of about 70kDa with little homology to known proteins. We are currently assessing the biological activity of these proteins.

4.4.10
International Symposium on Cell Adhesion and Communication in Growth Control and Cancer, IARC, Lyon, 19–21 January 1999

H. Yamasaki and C. Déchaux, in collaboration with J.C. Barrett, Research Triangle Park, NC, USA

The role of cell adhesion and communication in growth control has long been studied and some signal transduction mechanisms involved therein have recently been elucidated. Most, if not all, cancer cells show aberrant cell adhesion and/or communication properties. Thus, the mechanisms by which cell–cell interaction controls the cell cycle are important subjects in cell biology and cancer research. The International Agency for Research on Cancer and the US National Institute of Environmental Health Sciences jointly organized an international symposium on 'Cell Adhesion and Communication in Growth Control and Cancer' at IARC, in Lyon on 19–21 January 1999, to allow

Figure 42. Participants at the international symposium on cell adhesion and communication in growth control and cancer, January 1999

scientists actively involved in this field to discuss recent advances. Twenty scientists of international repute presented invited lectures and some 150 participants from 17 countries attended the meeting.

4.5 *Mutator phenotypes and cancer*

It is widely accepted that the accumulation of several genetic alterations, which are necessary for cancer development, is associated with a mutator phenotype. This phenotype, revealed as microsatellite instability, was first described for colon cancer, both human non-polyposis colorectal cancer (HNPCC) and sporadic, and subsequently for many other cancers, including endometrium, stomach and oesophagus.

4.5.1 Mutations of microsatellite sequences in exons of growth-control genes

N. Mironov, W.-B. Zhu, A.-M. Aguelon, L. Jansen and H. Yamasaki

Many genes contain repeated sequences in their coding regions. In most cases, these consist of 3–10 repeats of one nucleotide. We have investigated frameshift mutations in exonic repeats in *ATR, BRCA1* and *BRCA2, PTCH, CTCF, Cx26, NuMa* and *TGFβRII* genes, using human tumour samples from stomach, oesophagus, breast and skin and melanoma, as well as colon cancer and endometrial cancer cell lines, 125 samples in total (Table 4).

We have developed a sensitive method allowing us to distinguish between a wild-type gene and a specific mutation at a simple repeat in this gene, by introduction of a restriction site in a repeat during PCR. Two non-complementary bases were introduced into the primer which covers the simple repeat. The introduced restriction site could distinguish between the wild-type sequence and the mutated sequence (Figure 43).

The method allows detection of a single mutant among 10^3 normal genes. Thus, an alteration in a repeated sequence can be detected unambiguously. The $(A)_8$ repeat of *BRCA2* was found mutated in only two of five colon cell lines with microsatellite instability (MI^+). The *ATR* gene has an $(A)_{10}$ repeat which was altered in two of three MI^+ stomach cancer samples and one of three MI^+ endometrial cell lines. The *TGFβRII* gene (with an $(A)_{10}$ repeat) had the highest frequency of mutations: ten out of thirteen MI^+ samples. At least one sample from each type of cancer except melanomas was positive for *TGFβRII* gene mutations. No mutation was found in repeats in *BRCA1, PTCH, NuMA* and *Cx26* genes in any type of tumour examined. In conclusion, our study indicates that repeats were altered only in MI^+ cells and that the mutation frequencies in the genes studied differ between the genes and between tumour types.

Table 4. Alterations of simple exonic repeats

Tumour tissue	ATR	BRCA2	TGFβRII
HeLa cells	0/1	0/1	0/1
Colon cell lines			
MI^+	0/5	2/5	5/5
MI^-	0/2	0/2	0/2
Endometrial cell lines			
MI^+	1/3	Not done	1/3
MI^-	0/1	Not done	0/1
Stomach			
MI^+	2/3	0/3	3/3
MI^-	0/42	0/38	0/42
Oesophagus			
MI^+	0/2	0/2	3/3
MI^-	0/15	0/15	0/15
Breast (sporadic)	0/19	0/19	1/19
Skin (non-melanoma)	0/17	0/14	3/17
Melanoma	0/20	0/21	0/15
Total			
MI^+	3/13	2/10	10/13
MI^-	0/60	0/55	0/60

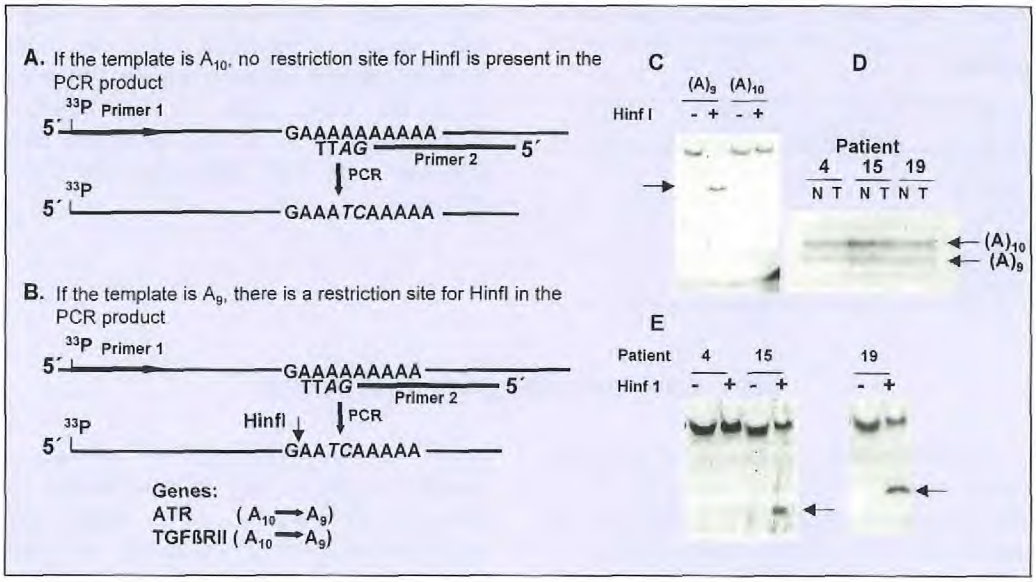

Figure 43. Method to distinguish PCR products synthesized on wild-type and altered repeat templates. **(A)** Scheme illustrating the absence of a *HinfI* restriction site in the PCR product synthesized on DNA containing an $(A)_{10}$ repeat. **(B)** Scheme illustrating the appearance of a *HinfI* restriction site in the PCR product synthesized on DNA containing an $(A)_9$ repeat. These schemes are applicable to both the *ATR* and *TGFβ RII* genes containing an $(A)_{10}$ exonic repeat. **(C)** PCR products containing $(A)_{10}$ or $(A)_9$ repeats of the *TGFβRII* gene were cloned in Bluescript. The PCR product was digested with *HinfI* and separated on an 8% polyacrylamide gel. The undigested and digested parts are indicated by – and +, respectively. **(D)** Conventional PCR was done around an $(A)_{10}$ repeat of the *ATR* gene in gastric cancer samples. **(E)** The same samples as indicated in (D) but processed by a novel method.

4.5.2
Relationship between microsatellite instability and cytosine methylation

W.-B. Zhu, Q.-F. Xiong, H. Yamasaki and N. Mironov

Recent data suggest that there is a correlation between replication error-positive (RER^+) phenotype and aberrant hypermethylation (Ahuja *et al.*, 1997, *Cancer Res.*, **57**, 3370–3374; Lengauer *et al.*, 1997, *Proc. Natl Acad. Sci. USA*, **94**, 2545–2550).

In our previous studies, none of a series of human gastric and human liver tumour samples showed any mutation in the coding sequence of the Cx32 gene, and we only found a point mutation in one rat liver tumour. We concluded that connexin gene mutations rarely occur in human cancers, suggesting that other mechanisms, such as transcriptional inactivation of the gene, may be important. Promoter region methylation is a possibly important alternative mechanism to mutations in the coding region for inactivation of tumour-suppressor genes.

We have investigated the methylation status of one of the two promoter regions of the Cx32 gene in six colorectal cancer cell lines, and found two that expressed Cx32 and had no aberrant methylation at the promoter 1, while the other four cell lines did not express the gene and had hypermethylation of the promoter region, suggesting that aberrant methylation of the promoter region in Cx32 may lead to silencing of the gene (Table 5). We also found a strong association between the methylation status of the Cx32 gene promoter and RER phenotype, with RER^+

Table 5. RER status of cell lines, expression of connexin 32 gene and hypermethylation of its promoter

Colon cell lines	Hyper-methylation	Cx32 expression	RER status
HCT116	+	–	+
HCR15	+	–	+
DLD1	+	–	+
LS180	+	–	+
SW480	–	+	–
SW620	–	+	–

cells having hypermethylation and RER$^-$ cells normal methylation. We are now studying another promoter region, promoter 2 of the Cx32 gene, to see whether methylation status of this promoter also correlates with RER phenotype and Cx32 expression.

4.6 Genomic integrity and cancer

Cancers are the consequence of combined genetic mutations and environmental factors which inappropriately induce activation or inactivation of specific genes leading to neoplastic transformation. Many specific molecules that are involved in DNA damage repair and recombination are important in maintaining genomic stability in response to environmental DNA damage. The goal of our studies is to investigate the function of certain of these molecules in genomic integrity and their relation to cancer and disease susceptibility. To address these questions, we are taking a genetic approach by generating gain-of-function and loss-of-function mutations [546].

4.6.1 Functional analysis of DNA end-binding proteins

4.6.1.1 The function of poly(ADP-ribose) polymerase (PARP) in genomic stability and tumorigenesis

W.-M. Tong, G. Sajithlal, J. Michelon and Z.-Q. Wang; in collaboration with D. Hanahan, San Francisco, CA, USA; S. Jackson, Cambridge, UK; P. Lansdorp, Vancouver, Canada; M. Smulson, Washington, DC, USA; and E.F. Wagner, Vienna, Austria

Poly(ADP-ribose) polymerase (PARP), which catalyses poly-ADP-ribosylation of nuclear proteins following DNA damage, is thought to play a role in maintenance of chromosomal integrity, DNA repair and recombination, cell proliferation and cell death. To elucidate the function of PARP in these processes, mice lacking the gene for this enzyme have been generated and the consequences of lack of PARP are being studied. While PARP$^{-/-}$ cells exhibit normal capacity for repair of DNA damage induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, UV- or γ-irradiation, mutant mice are hypersensitive to high-dose whole-body radiation. In addition, the frequency of spontaneous sister chromatid exchanges (SCE) in PARP$^{-/-}$ cells is increased, and mutant cells contain more micronuclei following DNA damage, demonstrating a role of PARP in maintaining genomic stability. We have also investigated the role of PARP in the maintenance of telomere length, considered to be another 'chromosomal guardian' process. PARP$^{-/-}$ cells exhibit telomere shortening and high levels of chromosomal aberrations (Figure 44), suggesting the importance of PARP in telomere function [123]. The comparative genomic hybridization (CGH) technique revealed high levels of chromosomal aberration with particular chromosomal gains or loss [483].

Despite a high degree of genomic instability, PARP mutant mice do not develop spontaneous tumours. To further

elucidate the role of PARP in tumorigenesis and the importance of genomic instability in tumour development, PARP deficiency was introduced into a mouse strain that is prone to tumours. Transgenic mice ectopically expressing SV40 T antigen under the control of rat insulin promoter (RipTag) were crossed with PARP mutant mice. RipTag transgenic mice develop β-islet tumours with defined progression stages. When the transgene was overexpressed in a PARP mutant background, these mice developed an increased frequency of later-stage β-islet carcinomas compared with controls. These tumours were highly metastatic to various organs, including lymph nodes, liver, intestine and lung. These data demonstrate that the PARP deficiency causes accelerated tumour progression, most likely due to genome instability and telomere dysfunction, and that PARP may serve as a cofactor in suppressing tumorigenesis.

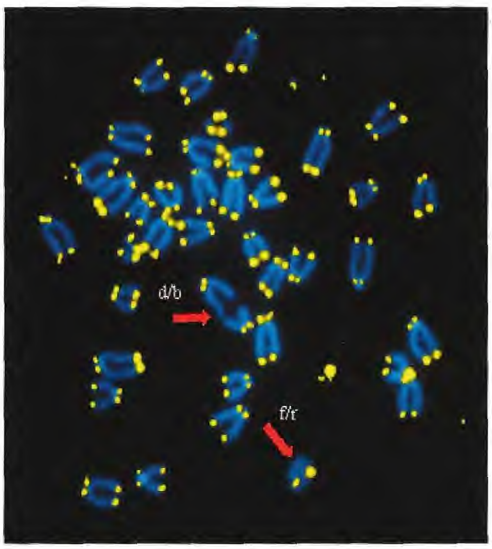

Figure 44. PARP plays an important role in the maintenance of telomere function and genomic integrity. $PARP^{-/-}$ cells exhibit telomere shortening and high levels of chromosomal aberrations.

d/b, dicentric and break; f/r, fragment/ring

4.6.1.2
Functional interaction of PARP and p53 in cellular transformation and tumorigenesis

W.-M. Tong, G. Sajithlal, U. Cortes, J. Michelon and Z.-Q. Wang; in collaboration with P. Lansdorp, Vancouver, Canada; and J. Wesierska-Gadek, Vienna, Austria

PARP and p53 proteins are involved in responses to DNA damage. Inactivation of PARP in mice results in severe genomic instability, yet these mice do not develop spontaneous tumours, suggesting that genomic instability *per se* is not sufficient to cause tumour development. p53 is a major genome guardian molecule, loss of which renders cells susceptible to malignant transformation, probably due to the absence of its function in controlling cell-cycle checkpoints and apoptosis. p53 knock-out mice spontaneously develop various tumour types, such as lymphomas and soft-tissue sarcomas. Although p53 can directly bind to DNA, the function of p53 is believed to be mediated by other DNA break-sensing molecules, such as the protein ATM. PARP binds p53 protein and modifies p53 activity by poly(ADP-ribosyl)ation. We have found that while wild-type p53 protein is absent in PARP-deficient cells, the alternatively spliced form of p53 is constitutively expressed [556], indicating that the regularly spliced p53 is extremely unstable in the absence of PARP. We also observed elevated expression of p73 protein, a p53 homologue, in PARP mutant cells [462]. When PARP deficiency was introduced into a p53 null background, the tumour spectrum of $PARP^{-/-}p53^{-/-}$ mice was wider than in $p53^{-/-}$ controls and included carcinomas of the liver, colon and pancreas (Figure 45). $p53^{+/-}$ mice in a PARP-deficient background also developed breast and brain tumours in addition to lymphomas and sarcomas, reminiscent of the Li–Fraumeni syndrome in humans. The enhanced tumorigenesis seems to be caused by loss of heterozygosity of tumour-suppressor genes

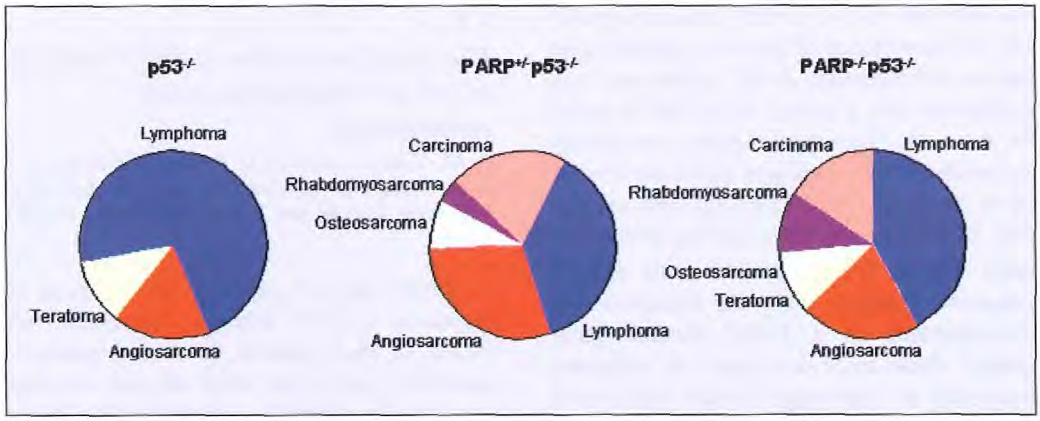

Figure 45. PARP and p53 cooperatively suppress tumour development. Tumour spectrum in PARP- and p53-mutant mice

due to the absence of PARP. While $PARP^{-/-}$ cells exhibited telomere shortening, $p53^{-/-}$ cells showed normal telomere length. Surprisingly, inactivation of p53 in $PARP^{-/-}$ cells or of PARP in $p53^{-/-}$ cells resulted in heterogeneous and elongated telomeres, suggesting a functional interaction between PARP and p53 at telomeres. Indeed, double mutant cells showed severe chromosome aberrations, including end-to-end fusions and aneuploidy. These results indicate that PARP and p53 interact to maintain genome integrity, so that PARP and p53 cooperate in suppressing tumorigenesis.

4.6.1.3

Role of PARP in disease development

Z. Herceg, F. Calevro, W.-M. Tong and Z.-Q. Wang; in collaboration with V. Burkart and H. Kolb, Düsseldorf, Germany; and V. Dawson, T. Dawson and S. Snyder, Baltimore, MD, USA

DNA-damage-induced cell death is proposed to be due to excessive activation of PARP that can deplete NAD^+ and ATP. To elucidate the biological function of PARP in disease development, we have studied the involvement of this molecule in general stress response in diabetes and brain ischaemia models.

Human type 1 diabetes results from selective destruction of insulin-producing pancreatic β-cells during islet inflammation. $PARP^{-/-}$ mice are completely resistant to the development of diabetes induced by streptozotocin [75, 376]. These mice remain normoglycaemic and keep normal levels of total pancreatic insulin and normal islet ultrastructure. Cultured $PARP^{-/-}$ islet cells show resistance to streptozocin-induced lysis and normal intracellular NAD^+ levels [75]. Our results identify NAD^+ depletion caused by massive PARP activation as the dominant metabolic event in islet cell destruction.

We have also examined the hypothesis that PARP mediates neuronal tissue injury after transient focal cerebral ischaemia. After reperfusion and cerebral artery occlusion, ischaemic injury was decreased in $PARP^{-/-}$ and $PARP^{+/-}$ mice compared with $PARP^{+/+}$ littermates (Eliasson *et al.*, 1997, *Nature Med.*, **3**, 1089–1095; [156]). In vitro experiments demonstrate that glutamate/nitric oxide-mediated cell death is probably responsible for the ischaemic damage. These data provide compelling evidence that PARP activation is a primary target in this neurological disease.

We have also investigated a neuronal disease model based on the neurotoxic action of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in inducing parkinsonism in humans and other species. Mice lacking PARP are dramatically protected from the

neurotoxicity of MPTP [270], which potentially activates PARP exclusively in vulnerable dopamine-containing neurons of the substantia nigra. MPTP elicits a novel pattern of poly(ADP-ribosyl)ation of nuclear proteins that completely depends on neuronally derived nitric oxide.

We conclude that nitric oxide, DNA damage and PARP activation play a critical role in DNA damage response and related disorders *in vivo*. This information will be of value in developing strategies involving inhibition of PARP to prevent the manifestation or progression of these diseases in humans. To further elucidate the role of poly(ADP-ribosyl)ation in disease and cellular responses, we are generating mice which lack the enzyme that degrades ADP-ribose polymers, namely poly(ADP-ribose) glycohydrolase (PARG).

4.6.1.4
Generation of mice lacking molecules responsible for DNA repair and transformation

W. Hulla, Z. Herceg, V. Dumon, G. Sajithlal, J. Michelon and Z.-Q. Wang; in collaboration with M. Digweed, Berlin, Germany; and S. Jackson, Cambridge, UK

Transformation/transcription domain-associated protein (TRRAP) is a newly identified member of the ATM/PI3-kinase superfamily. While its role in DNA repair is obscure, TRRAP has recently been shown to act as a cofactor for c-myc and E2F oncoproteins *in vitro*, suggesting a role in neoplastic transformation and cell survival. In order to study the biological function of TRRAP in normal cells and disease development, we inactivated the gene in ES cells and mice using a 'conditional' knock-out technique that will allow us to impose mutations in specific organs at the developmental stage. The targeted ES clones were transfected with a Cre-recombinase-expressing plasmid, which generates various types of recombined alleles of TRRAP. For different purposes, ES clones with a disrupted TRRAP allele or with a 'floxed' allele (an exon flanked by two lox-P sequences) were injected into blastocysts for production of mutant mice. The phenotypes of the mutant mice are being analysed.

The gene for Nijmegen breakage syndrome (NBS; see Section 4.1.1) has been cloned and isolated. Its protein product, nibrin, forms a complex with other molecules, such as Rad50 and Mre11, in response to DNA damage. To investigate the function of this molecule *in vivo* and to establish an animal model, we have generated ES cells in which one allele of nibrin is disrupted by homologous recombination. The targeted ES cells have been used to generate mutant mice. The germline transmission and characterization of mutant animals are in progress.

4.6.2
Role of PARP in apoptosis and necrosis

Z. Herceg, F. Calevro, V. Petrilli and Z.-Q. Wang

Disturbance of the cell death process is associated with many pathological conditions, such as degenerative diseases, autoimmune processes and carcinogenesis. Programmed cell death (apoptosis) accounts for most physiological cell death, whereas necrosis is usually induced by pathological stimuli and causes inflammatory response. Activation of PARP by DNA breaks catalyses poly(ADP-ribosyl)ation, and results in depletion of NAD^+ and ATP, which is thought to induce necrosis. Proteolytic cleavage of PARP by caspases is a hallmark of apoptosis. To investigate whether PARP cleavage plays a role in apoptosis and in the choice by cells to undergo apoptosis or necrosis, we introduced a point mutation into the cleavage site (DEVD) of PARP that renders the protein resistant to caspase cleavage *in vitro* and *in vivo*. After treatment with tumour necrosis factor α, fibroblasts expressing this caspase-resistant PARP exhibited accelerated cell death. This enhanced cell death is attribu-

table to the induction of necrosis and increased apoptosis due to NAD^+ depletion, a mechanism known to kill various cell types, caused by activation of uncleaved PARP after DNA fragmentation. This finding demonstrates that PARP cleavage prevents induction of necrosis during apoptosis and ensures appropriate execution of caspase-mediated programmed cell death [187]. To further elucidate the biological significance of necrosis or altered apoptosis in normal tissue and in disease development, we have generated mice carrying a caspase-resistant PARP, using transgenic and gene-targeting techniques and are characterizing apoptotic response of mutant mice.

4.7 Role of p53 in carcinogenesis

The *p53* tumour-suppressor gene encodes a nuclear phosphoprotein with cancer-inhibiting properties. The development of human cancer often involves inactivation of this suppressor function. *p53* mutations frequently arise somatically, but may also be inherited in families with a predisposition to multiple cancers, as in the Li-Fraumeni syndrome. Point mutations are scattered over more than 250 codons and are common in most forms of human cancer.

Research on *p53* at IARC includes analysis of mutations in inherited and sporadic forms of cancer, in particular cancer of the oesophagus (Section 3.1.1), liver (Sections 3.3.3 and 3.3.7), cervix (Sections 3.4.2 and 3.4.6), brain (Section 3.5), kidney (Section 3.6.4), skin (Sections 3.9.3 and 3.9.4) and lung (Section 3.7.7), as well as studies on p53 protein structure, function and regulation, in relation to cellular response to DNA damage (Section 4.1), to the action of nitric oxide (Section 4.3.6) and to the formation of etheno adducts (Section 6.1.4). A database of *p53* mutations in human cancers is maintained.

4.7.1 Regulation of the p53 protein conformation and activity by redox factors and metal compounds

P. Hainaut, C. Méplan, F. El-Ghissassi, S. North, O. Pluquet, I. Persson, D. Maurici and S. Courtois; in collaboration with M.J. Richard, Grenoble, France; K. Vähäkangas, Oulu, Finland; K. Mann, Anchorage, AK, USA; B. Polla, Paris, France; and T. Frebourg, Rouen, France

The p53 protein is a transcription factor regulating the expression of target genes by binding to DNA through a protein domain which is stabilized by the binding of zinc on conserved cysteine residues. *In vitro*, removal of zinc by chelation prevents DNA-binding, inducing p53 to adopt a conformation similar to that of many p53 mutants. Modulation of the intracellular availability of zinc with cell-permeant metal chelators induces reversible changes in p53 conformation and activity in intact cells [181].

We have shown that cadmium at low concentrations can compete with zinc within the p53 structure. When bound, it induces conversion to a conformation similar to that of mutant p53, leading to functional inactivation of the protein and loss of its ability to act as a negative cell-cycle regulator in cells exposed to γ-radiation. This suggests that modulation of p53 protein function may be one of the molecular mechanisms of cadmium carcinogenicity [295].

We have developed assays *in vitro* (using recombinant p53 protein) and *in vivo* (using intact, cultured cells) to perform metal substitution experiments. Using radioactive zinc, we have shown that incorporation of zinc within the protein is required for proper folding and activation of DNA-binding capacity. In intact cells, renaturation of the protein after chelation of intracellular zinc is dependent upon the presence of zinc in the extracellular medium, suggesting that transport of the metal ions into the cell is required

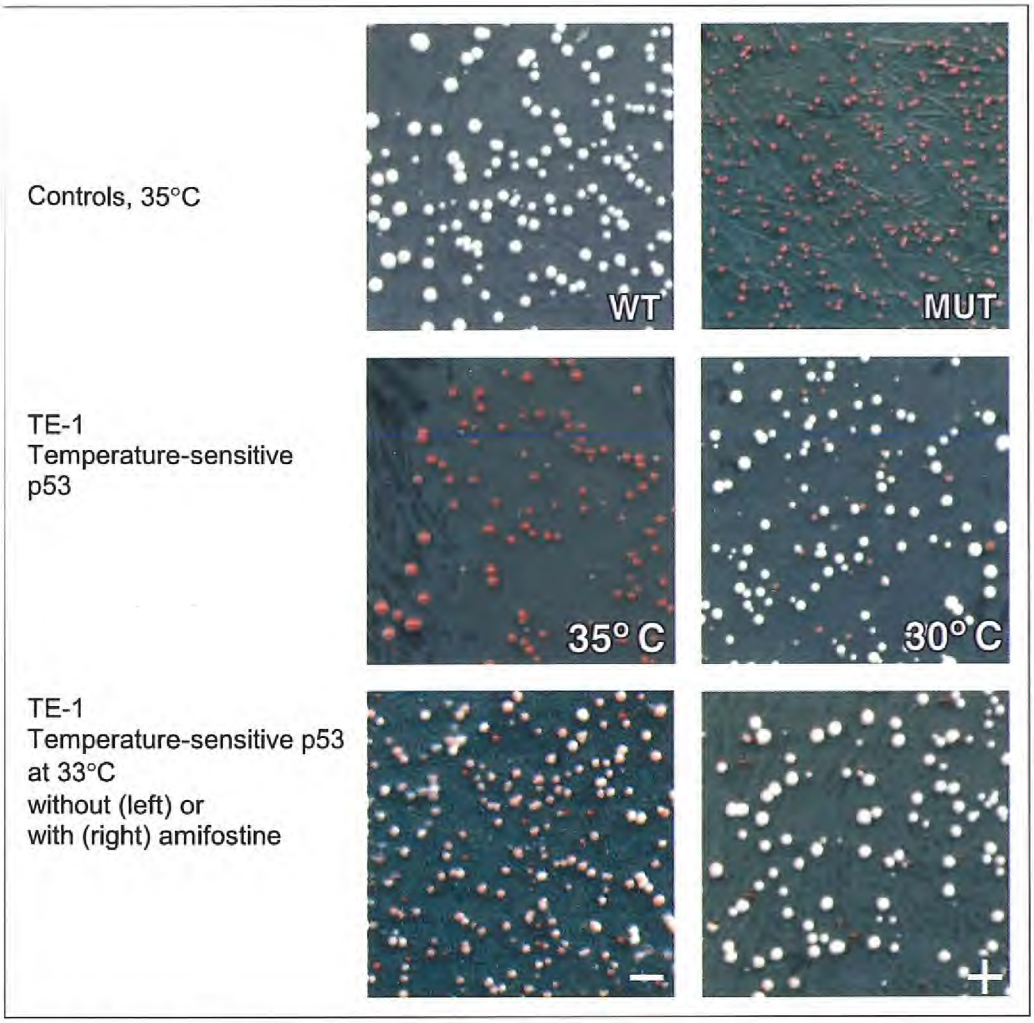

Figure 46. Yeast assay for analysis of p53 protein activity.

A genetically modified yeast strain is used as a reporter system for p53 activity (assay developed by R. Iggo, Lausanne and T. Frebourg, Rouen). When a human p53 gene is inserted into this strain, it grows to form small red colonies if the p53 gene is mutant (MUT) or larger, white colonies if the p53 gene is wild-type (WT) (top line, controls). Using a mutant which is temperature-sensitive for function (TE-1), the yeast grows as red colonies at 35°C and white colonies at 30°C (middle row). Intermediate, pink colonies are obtained at 33°C, showing the temperature-dependent sensitivity of this particular mutant (lower row, left panel). Addition of amifostine to the yeast cultured at 33°C (lower right) (6 mM) induced a shift to white colonies, revealing that this drug enhances p53 function.

to allow proper folding of p53. Moreover, transfection experiments have shown that metallothioneins, a class of intracellular zinc chelators, are efficient modulators of p53 function. We have also obtained preliminary evidence that the redox-repair enzyme Ref-1 may bind to p53. Further studies are in progress to analyse the role of these factors in the metalloregulation of p53. Overall, our data suggest that changes in metal levels may

act as physiological signals that mediate the fine tuning of p53 protein function [56, 296, 297].

We are now examining how such mechanisms affect the response of p53 to benzo[*a*]pyrene, an important component of tobacco smoke that is implicated as a p53 mutagen in lung cancers of smokers. In cultured cells, it induces a delayed p53-dependent cell cycle arrest in G1, preceded by a transient increase in DNA synthesis. As tobacco is one of the main sources of human exposure to cadmium, we are analysing the interactions between these two factors by using cadmium to disrupt p53 function in cultured cells exposed to benzo[*a*]pyrene.

A complementary approach is to examine whether antioxidants play a role as stabilizers of p53 protein activity. In cell-free assays, thiol reduction is required for high-affinity binding of p53 to DNA. Amifostine (ethyol) is a phosphoaminothiol which is used clinically as a radio- and chemo-protector to limit adverse effects of cancer therapy. We have shown that amifostine activates p53 through a pathway which appears to be distinct from the one elicited by DNA-damaging agents. Activation of p53 in normal cells may account for some of the protective properties of amifostine.

In order to set up a screening system to detect compounds that can modulate p53 function, we have taken advantage of a yeast-based functional assay. This is based on the use of a genetically engineered yeast strain containing a reporter gene under the control of a human p53 promoter. In the presence of active p53 protein, these yeasts form normal white colonies (Figure 46). In the presence of inactive (i.e., mutant) p53, the yeasts form smaller, red colonies. We have expressed in these yeasts a mutant p53 with temperature-sensitive conformation. With this mutant, the yeasts adopt a red phenotype at 35°C (inactive p53), a white phenotype at 30°C (active p53) and a pink intermediate phenotype at 33°C. Our screening strategy is based on the addition of defined compounds to the yeast culture medium at 33°C and scoring the restoration of the white phenotype. Amifostine restores the function of the mutant at 33°C; further experiments using other compounds are in progress. Such compounds have potential interest in preventive, protective or therapeutic approaches.

In the course of studies on the regulation of p53 protein, we have identified a new variant form of the protein, generated by internal initiation of in-frame translation at an ATG located at codon 40 (p53Δ40). This variant lacks the 40 N-terminal amino acids containing the transactivation domain but retains intact DNA-binding and oligomerization domains. When co-expressed with normal p53, this variant forms hetero-oligomers with the normal protein and modulates its transcriptional activity. In experiments with genotoxic chemicals, p53Δ40 was specifically induced after exposure of cells to cisplatin but not to other chemicals tested. Thus, this variant may play a role in the regulation of p53 in response to some forms of genotoxic stress.

4.7.2
IARC database of p53 mutations in cancer

P. Hainaut, R. Montesano and T. Hernandez; in collaboration with M. Hollstein, Heidelberg, Germany; C.C. Harris, Bethesda, MD, USA; P. Rodriguez-Tome and A. Robinson, Hinxton, UK

Since the first identification of tumour-specific mutations in human cancers in 1989, more than 10 000 p53 mutations have been reported. These data represent a unique source of information about cancer-causing mutations in the human setting. Over the past two years, we have undertaken a reconstruction of the database to adapt to the rapidly growing amount of data and to the needs of a larger community of users. We have developed a new, relational database format using Access™ and a system for data mining

and analysis using FileMaker Pro 4.0. The database is accessible through the Internet at http://www.iarc.fr/p53/homepage.htm [190, 191], and is updated twice a year. In parallel, a database of germline p53 mutations, initially developed by P. Kleihues and H. Ohgaki, is also maintained.

The content of the database has been cleaned and checked, enriched with clinical information and information on individual risk factors (whenever possible) and a standard classification of pathologies has been adopted (based on the International Classification of Diseases for Oncology, ICD-O). We have also developed research projects using the database, in two different directions. One is an analysis of relationships between mutations and environmental exposures, and the second is a search for correlations between mutations and the clinical parameters of the tumours. This second aspect is based on integration of the mutation data with available knowledge on p53 protein structure and function. In a meta-analysis of all mutations in lung cancer that have been reported, we confirmed that smokers were characterized by a unique mutation profile, with specific mutations at codons known as sites of adduction of benzo[*a*]pyrene metabolites in experimental studies [188]. Several common mutations in various tumour types are associated with shorter overall survival after therapy. Further studies are in progress to collect good quality clinical data in order to strengthen these correlations.

PART 5. PREVENTION AND EARLY DETECTION OF CANCER

5.1 Studies of primary prevention of cancer

Primary prevention of cancer covers all interventions aimed at preventing initiation of carcinogenesis, by either removing exposure to a carcinogenic agent or inducing mechanisms to counteract the effect of such exposure, for example by vaccination or by administration of a protective chemical substance (chemoprevention). In general, prevention of exposure to a carcinogen will always be beneficial, but it is still important to evaluate the extent of the benefit. In contrast, administration of a foreign substance, or of a natural substance in unnatural quantities, may well lead to undesirable side-effects that can negate any cancer-preventive benefit. It is therefore particularly important that such interventions are subjected to very careful scrutiny at all stages of their planning and implementation.

The first intervention study aimed at assessing the use of vaccines in cancer prevention was initiated 13 years ago in The Gambia, to evaluate the effectiveness of hepatitis B vaccination in the prevention of liver cancer. Similar intervention studies to assess the effectiveness of HPV vaccines, now under development, in the prevention and treatment of cervical neoplasia, are being planned.

Chemoprevention trials to evaluate the effect of antioxidant vitamins in prevention or regression of precancerous lesions of the stomach and of the oral cavity are in progress in Venezuela and India.

5.1.1
Gambia Hepatitis Intervention Study

D.M. Parkin, R. Montesano, E. Bah, G. Kirk and O. Lesi; in collaboration with H.C. Whittle and M. Mendy, Fajara, The Gambia; A.J. Hall, London, UK; and C.P. Wild, Leeds, UK

The Gambia Hepatitis Intervention Study (GHIS) is conducted by the International Agency for Research on Cancer in collaboration with the Government of the Republic of The Gambia and the United Kingdom Medical Research Council (MRC) laboratories in The Gambia. In its first phase, hepatitis B vaccine was introduced over a five-year period (1986–90) into the expanded programme of immunization (EPI) of The Gambia, so that about one half of the children born in these years (60 000 individuals) received the vaccine, while an equal number did not. The final effectiveness of vaccination will be judged by following these two cohorts over an extended period (35 or more years). In Phase II of the study, the short-term effectiveness of vaccination in preventing infection and chronic carriage with hepatitis B virus (HBV) was assessed by surveys in 1996–97. The vaccine proved to have 95% efficiency in protecting against chronic HBV infection up to the age of nine years.

Phase III began in 1998. The long-term objective is to assess the impact of HBV vaccination on the incidence of hepatocellular carcinoma. A cancer registry is maintained in The Gambia, which records all new cases of cancer and of hepatic cirrhosis diagnosed in the population. Cases occurring in age groups compatible with the study cohorts (born 1986–91) are linked with the study database, to determine their vaccination status. Technical support is provided to the medical services (pathology and radiology) concerned with diagnosis of liver disease, to optimize case-finding and management.

The data collection methods used by the registry have been reviewed and strengthened, to improve completeness of registration. The success of the evaluation will depend upon the linkage between the incident cases of

Figure 47. Participants at meeting on liver cancer, the Gambia, March 1998

liver cancer and chronic liver diseases (cirrhosis) identified in the age groups potentially enrolled into the vaccination and control cohorts, and the GHIS database. This is done by means of personal identifiers, site of vaccination scar, and foot and palm prints. Studies of these linkage procedures were undertaken with cases of childhood cancer (and chronic liver disease) recorded by the registry and a sample of 200 children attending hospitals and clinics in different parts of the country. At the same time, further work was begun to remove duplicate records from the GHIS database and to clarify inconsistent data.

In March 1998, a conference on hepatitis B immunization and prevention of hepatocellular carcinoma in sub-saharan Africa was held in The Gambia, in association with WHO. It was attended by experts on hepatitis B virus, cancer research and public health from all continents (Figure 47). The meeting reviewed the first 10 years of the GHIS and the status of vaccine development and immunization projects worldwide, and prepared a series of recommendations to ensure that hepatitis B vaccine be incorporated into immunization programmes in all countries of sub-saharan Africa.

Alongside the main study, several ancillary studies are in progress, utilizing the GHIS infrastructure. A case–control study is investigating the role of other risk factors in liver cancer: exposure to aflatoxins and their interaction with HBV; hepatitis C virus and HBV variants; this study is supported by a contract from the United States National Cancer Institute. Another study is assessing the prevalence of the 249^{ser} p53 mutation, indicative of past exposure to aflatoxin B_1 in sera of individuals from The Gambia (see Section 3.3.7). Associated with this project is an evaluation of the accuracy of estimating alpha-fetoprotein in dried spot blood on filter paper for diagnosis of primary liver cancer. Studies of mutant hepatitis viruses are in progress in collaboration with the MRC and the School of Veterinary Medicine, London, UK. Genomic changes in the virus may permit it to escape neutralization by the immune response to the current vaccine type; this possibility has obvious public health implications.

5.1.2

Pilot intervention studies to reduce aflatoxin exposure in Guinea, Africa

M. Castegnaro and L. Garren; in collaboration with C.P. Wild, Leeds, UK; and A. Sylla, Kindia, Guinea

A study to determine the source of contaminated food and the most critical stage for

contamination (pre- or post-harvest) is being carried out in four villages representative of Lower Guinea. In each village, 15 families have been selected for food collection. In each family, two adults will also be selected for blood collection for analysis of aflatoxin–albumin adducts. Food has been sampled at three seasons: just after harvest, after about four months of storage, and after about eight months of storage. The samples are stored at –20°C until analysis. Analysis of the food samples for aflatoxin content has been performed at IARC, using two methods: high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC). The TLC method is being set up at a laboratory in Guinea and, in the meantime, some of the samples from the second sampling series have been analysed by HPLC at IARC for quality control. Comparison of these data revealed some discrepancies, the reasons for which are being investigated. One may be linked to grinding and homogenization of the samples, as demonstrated by duplicate analysis at IARC by both methods. A second problem is a substance interfering with aflatoxin G_1 on HPLC. This behaves as an aflatoxin on immunoaffinity columns and could not be separated from aflatoxin G1 by changing the HPLC conditions.

5.1.3 Chemoprevention trial on precancerous lesions of the stomach in Venezuela

N. Muñoz, M. Plummer and C. Lavé; in collaboration with O. Andrade, E. Cano, D. Castro, G. Lopez, W. Oliver, V. Sanchez and J. Vivas, San Cristobal, Venezuela; E. Buiatti, Bologna, Italy; J.C. Bravo, Cali, Colombia; R. Salkeld, Basle, Switzerland; and J. Torrado, San Sebastian

Gastric carcinogenesis is believed to be a multi-stage process in which the occurrence of stomach cancer is preceded by a series of precancerous stages: chronic gastritis, atrophy, intestinal metaplasia and dysplasia. The aim of this double-blind, placebo-controlled intervention trial is to determine whether antioxidant vitamins can block progression through these stages. It is taking place in the state of Tachira, Venezuela, in a population at high risk of stomach cancer, and takes advantage of the infrastructure created by the local gastric cancer control program, in particular the presence of highly skilled endoscopists.

The original design of the trial included a treatment phase for *Helicobacter pylori* infection (94% of subjects were *H. pylori*-positive at baseline). However, after pilot studies showed low eradication rates, the anti-*H. pylori* treatment phase was deleted from the protocol. (See also Section 4.3.4 for a study of changes in antioxidant enzyme expression in one of the pilot studies.) Low eradication rates were also observed in a similar intervention study carried out in Costa Rica [481].

Subjects were randomized to treatment with antioxidant vitamins (vitamin C (750 mg/day), vitamin E (600 mg/day) and β-carotene (18 mg/day)) or to placebo. Treatment was distributed every 1–2 months for three years. At recruitment, a dietary questionnaire was completed, five biopsies were taken from prespecified areas of the stomach, and blood and urine specimens were collected from each patient.

The trial commenced in May 1992. The target for recruitment of 2200 subjects was achieved in February 1995. By June 1999, 1263 subjects had completed treatment with gastroscopy, 217 had completed treatment but without having the final gastroscopy and 720 had withdrawn from the trial. Since the results of various randomized trials have suggested a harmful effect of β-carotene in individuals at high risk of stomach cancer, all smokers and ex-smokers were transferred to the placebo group in March 1996. An interim analysis on the first 220 subjects to complete the trial showed no difference between the treatment and control groups.

The relationship between Lewis antigens and severity of lesions at baseline was investigated in subjects with intestinal metaplasia. Severity of intestinal metaplasia correlated strongly with anomalous Lewis a antigen expression. A weak relationship was observed between Lewis antigen secretor status and severity of intestinal metaplasia, with non-secretors having more advanced lesions, but the association was not statistically significant. Secretor status was not related to *H. pylori* status or gastric damage.

The primary endpoint of the trial is the change in histological diagnosis between the beginning and the end of treatment. Any underlying change in the gastric epithelium may be obscured by measurement error in this histological diagnosis, and this will reduce the power of the study to show an effect of the antioxidant treatment. There are various sources of measurement error: intra-observer variation; biopsy error, caused by the fact that multi-focal lesions may be missed when biopsies are taken, or that the biopsy quality may not be sufficient to make a diagnosis; inter-observer variation between the three pathologists who made the diagnoses; and changes in diagnostic criteria over the course of the study. In order to minimize measurement error, a validation study is being conducted, consisting of a histological review by a single pathologist. A revised diagnosis of all gastric biopsies taken at baseline and at completion of the trial is made for all subjects who complete the trial. Use of the revised diagnosis in the final analysis should remove inter-observer variation and changes in diagnostic criteria as sources of measurement error. As of August 1999, 393 subjects had been reviewed. The review will be completed by early 2000.

5.1.4
HPV vaccines for cervical neoplasia

N. Muñoz, R. Herrero and M. Plummer; in collaboration with C. Bratti and A.C. Rodriguez, San José, Costa Rica; P. Coursaget, Tours, France; L. Gissmann, Munich, Germany; K. Jansen, J. Boslego and E. Barr, West Point, PA, USA; and J. Schiller, M. Schiffman and A. Hildesheim, Bethesda, MD, USA

Several groups are currently involved in the development of prophylactic vaccines against HPV infection. The immunogens of choice appear to be the virus-like particles (VLPs), which have been produced for HPV 16, 6, 11, 18, 31, 33, 35, 39 and 45 by various groups [513]. Most of these VLPs appear to be strongly immunogenic in animal models, but have not been tested in humans [120].

A small number of HPV types (16, 18, 31, 45, 59) are responsible for more than 80% of invasive cancer cases, and the ideal vaccine is likely to include a combination of VLPs of these types. Alternatively, the initial studies may reveal that VLPs from one type protect against infection with other types.

We are collaborating with four groups developing HPV vaccines, at Tours University, France [513], the United States National Cancer Institute (NCI), the German Cancer Research Centre, Heidelberg, and MediGene, and Merck Research Laboratories (MRL) in the United States. MRL has developed an HPV VLP vaccine that is being tested in phase I–II clinical trials.

Plans are being made for two institutes in Cuba and Brazil to produce the HPV 16 and 18 VLP vaccines developed by Dr Coursaget, according to good manufacturing practice (GMP). A protocol for phase I–III trials using this vaccine has been prepared.

Dr Gissmann (Heidelberg) has developed a chimeric HPV 16 vaccine (HPV 16 VLP/E7) that has both prophylactic and therapeutic effects. Phase I–II trials are to be conducted Germany in 2000 and we are collaborating in plans for a phase III trial in Madras, India, in 2000.

Drs Lowy and Schiller, at NCI, have developed an HPV 16 VLP-based vaccine. Phase I–II trials to assess the safety and immunogenicity of this vaccine have been carried out in collaboration with the Center

for Immunization Research at Johns Hopkins University. Plans are being developed to start phase II and III trials in Costa Rica in 2000.

A meeting was held in July 1999 with investigators from MRL to discuss possibilities for collaboration. It was concluded that collaboration might involve:

- MRL providing assistance in testing specimens from IARC studies for HPV markers;
- Information sharing: IARC and MRL will share data on the natural history of HPV infection and cervical neoplasia and on phase I and II trials, with the aim of accelerating the design and implementation of phase III trials.
- Joint implementation of phase III trials

5.1.5 Chemoprevention of oral cancer

R. Sankaranarayanan and D.M. Parkin; in collaboration with B. Mathew, K. Ramadas, G. Thomas, B. Kuruvilla, T. Somanathan, E. Abraham and P.R. Sudhakaran, Trivandrum; India; and J. Nair and H. Bartsch, Heidelberg, Germany

Retinoid supplementation is reportedly associated with regression of oral leukoplakias and decreased risk of second primary cancers in treated head and neck cancer patients. To assess the efficacy of retinoids in reducing the incidence of oral cancer in high-risk subjects, non-smoking subjects with non-homogeneous oral precancerous lesions (ulcerated leukoplakia, erythroplakia, verrucous leukoplakia and nodular leukoplakia) not suitable for excision, identified among a population in southern India, are being recruited and randomized to receive either vitamin A (200 000 IU per week for five years) or no supplementation. Around 183 subjects (94 in the intervention and 89 in the control group) with oral precancers have been recruited since 1997, and are followed up every three months to look for progression of existing lesions and new lesions. Two subjects in the intervention group and none in the control group have developed oral cancer. However, compliance of participants with long-term vitamin supplementation and follow-up has proved unsatisfactory.

Occurrence of multiple primaries in treated head and neck cancers is an important determinant of prognosis; preventing these events can increase long-term survival. Subjects with treated primary cancers of the lip, tongue, oral cavity, oropharynx, hypopharynx and larynx and with at least a six-month disease-free period after treatment are being recruited in a hospital-based randomized controlled trial in Trivandrum, India, to evaluate the role of long-term vitamin A supplementation (200 000 IU per week for five years) in preventing second primary cancers. Around 70 subjects with treated head and neck cancers have been randomized since 1998, and are being followed up every three months in special clinics.

5.2 Evaluation of cancer-preventive agents

H. Vainio, A.B. Miller, P. Nettesheim, M. Rautalahti. The following members of other units have contributed to the programme: R. Baan, V. Krutovskikh, C. Malaveille, H. Ohshima, B. Pignatelli, R. Sankaranarayanan, P. Toniolo, A.L. Van Kappel-Dufour and J. Wilbourn

IARC launched a new programme and book series, the *IARC Handbooks of Cancer Prevention*, in 1997. The aim of the programme is to evaluate scientific information on agents and interventions that may reduce the incidence of or mortality from cancer. The *Handbooks* contain the findings derived from critical reviews and evaluations of evidence for cancer prevention by international working groups of experts. Recommendations for actions for cancer prevention are given when the evidence is judged adequate;

the *Handbooks* also indicate when additional research is needed.

The *Handbooks* are intended to assist national and international authorities in devising programmes of health promotion and cancer prevention. The first four volumes in the series related to agents potentially of value for chemoprevention. However, agents that may be of relevance to the public health aspects of cancer prevention will be evaluated in the future.

5.2.1 Vitamin A

Preformed vitamin A compounds (largely all-*trans*-retinol and retinyl esters) play a critical role in nutrition. Vitamin A and retinyl esters appear to inhibit development of certain preneoplastic lesions, probably through the actions of the retinoid receptors. A number of observational studies and randomized clinical trials have been carried out within a broad range of intakes which have little or no effect on the levels of retinol in the circulation. The intervention studies have been carried out with vitamin A doses ranging approximately from 50 to 250% of normal daily dietary intakes of vitamin A. The period of supplementation has not extended beyond five years, and the duration of follow-up has been limited. Animal experimental studies have also been performed to evaluate the hypothesis that vitamin A deficiency might increase cancer risk.

A working group of 20 scientists from 11 countries met in Lyon on 13–19 May 1998 to review the evidence on the cancer-preventive activity of preformed vitamin A (retinol and retinyl esters). The working group found evidence suggesting *lack of cancer-preventive activity* of preformed vitamin A in humans for cancers of the upper aerodigestive tract, lung, breast (among postmenopausal women), colorectal, bladder, prostate, and stomach. There is *inadequate* evidence with respect to cancer-preventive activity for all other sites. An important limitation to the use of preformed vitamin A in humans is its toxicity, in particular the apparent sensitivity of the developing embryo to teratogenesis at levels of supplemental retinyl palmitate as low as 25 000 IU per day, and possibly even lower. In experimental animals there is *limited* evidence that retinyl esters have cancer-preventive activity. The working group noted that the potential chemopreventive effects of high doses of preformed vitamin A seen in rat mammary cancer models are encouraging, but these effects are typically seen at doses that are toxic or teratogenic in humans. Therefore, the working group concluded that there is little evidence that, within the wide range of doses bordered by deficiency and toxicity, modulating preformed vitamin A intake will have any substantial cancer-preventive effect in humans. The results of the meeting have been published as Volume 3 of the *IARC Handbooks of Cancer Prevention*.

5.2.2 Retinoids

The retinoids are a class of compounds structurally related to vitamin A. In the last 30 years, more than 2500 retinoids have been synthesized and biologically tested, with the objective of identifying those with an enhanced therapeutic ratio. The majority have been studied for their cancer-preventive activity in experimental models, and some in clinical trials in humans, largely of patients at risk of second primary tumours. No observational studies in humans have been carried out, as these agents are not present naturally except for some as metabolites of retinol. In experimental systems, retinoids have been associated with inhibition of cell growth, induction of differentiation, induction of programmed cell death (apoptosis) and inhibition of angiogenesis. Some of the retinoids are of value for treating a variety of dermatological disorders.

On 24–30 March, 1999, a working group of 22 scientists from nine countries met in

Lyon to consider the evidence on the cancer-preventive activity of nine retinoids judged to have sufficient human and/or animal data to permit evaluation, namely, all-*trans*-retinoic acid, 13-*cis*-retinoic acid, 9-*cis*-retinoic acid, all-*trans*-*N*-(4-hydroxyphenyl)-retinamide, etretinate, acitretin, all-*trans*-*N*-ethylretinamide, targretin and LGD 1550. The working group concluded that only for 13-*cis*-retinoic acid was there *limited evidence* of cancer-preventive activity in humans and experimental animals. Therefore, 13-*cis*-retinoic acid probably has cancer-preventive activity in humans. However, the agent has a relatively low therapeutic ratio of efficacy to toxicity, and it is an established human teratogen. For all the other eight agents considered, the human evidence was judged to be *inadequate*. Only for all-*trans*-*N*-(4-hydroxyphenyl)retinamide was there *sufficient evidence* of cancer-preventive activity in experimental animals, for 9-*cis*-retinoic acid there was *limited evidence* in experimental animals, and for all-*trans*-*N*-ethylretinamide, there was evidence of *lack of cancer-preventive activity* in experimental animals. For the remainder, the evidence in experimental animals was considered *inadequate*. For nearly all these agents, even if they are eventually shown to be effective for cancer prevention in humans, toxicity is likely to be a limiting factor for their use. The results of these evaluations were published in Volume 4 of the *IARC Handbooks of Cancer Prevention*.

5.3 Safe handling of carcinogens and destruction of carcinogenic wastes

Several cytostatic drugs have been classified by IARC as human carcinogens or probable/possible human carcinogens. Hospital staff or family members handling excreta from patients treated with antineoplastic drugs or equipment contaminated by such excreta, such as urinals and chamber pots, may be more heavily exposed than trained hospital nurses or pharmacists. In addition, handling of these drugs, in pure form or in solution, generates residual amounts of cytotoxic solutions, which should not be discarded into the domestic sewage system without prior inactivation. This section presents two approaches to protect personnel and the environment from risks due to these drugs.

5.3.1

Degradation of cytostatic drugs

M. Castegnaro; in collaboration with M. de Méo, Marseille, France; S. Hansel, Montpellier, France; and M.H. Sportouch, Béziers, France

A report on the use of a solution of 5% sodium hypochlorite to degrade 32 cytostatic drugs has been prepared for the French Ministry of Environment and several articles have been published (Hansel *et al.*, 1997, *Int. Arch. Occup. Environ. Health*, **69**, 109-114; Castegnaro *et al.*, 1997, *Int. Arch. Occup. Environ. Health*, **70**, 378–384) or are in preparation. The usefulness of this method for decontamination of urine from treated patients is now being tested. Preliminary results indicate that sodium hypochlorite can be a powerful tool to degrade antineoplastic agents and their metabolites in urine into non-mutagenic residues.

5.3.2

Safe handling of genotoxic substances, training courses and dissemination of information

M. Castegnaro; in collaboration with M. Falcy, Paris, France

A document describing good practices for handling genotoxic substances and methods of decontamination of chemical carcinogens has been prepared in collabora-

tion with the Société Française de Toxicologie Génétique, for publication in French by the Institut National de la Santé et de la Recherche Médicale [96, 122, 276, 301] and in English by the International Programme on Chemical Safety (WHO) [95, 121, 302].

IARC participated in the preparation of several sections, and in the review, of the WHO document *Safe Management of Wastes from Health-Care Activities: a WHO Guide for Developing Countries*. A training session on safe handling of cytostatic drugs in health care was held at IARC on 20–21 April 1998, in collaboration with the Institut National de Recherche et de la Sécurité (INRS) (see Section 7.3.2). INRS has taken over the organization of these courses, in collaboration with IARC. Several presentations to companies and courses at universities on the safe handling of cytostatic drugs and of genotoxic compounds have been held. Advice has been given to companies on setting up a room for safe handling of drugs.

5.4 *Studies of screening for cancer*

Screening is a means of achieving early detection of certain cancers and precancerous lesions in non-symptomatic people, so as to allow treatment before the disease becomes incurable. The efficacy of screening for a particular cancer is established if it results in a significant reduction in mortality from the disease without incurring disproportionate costs. A screening procedure should be considered for implementation as a public health policy for entire populations or high-risk groups only after it has been thoroughly evaluated for effectiveness and costs in experimental settings.

5.4.1 Screening for cancer of the breast in the Philippines

D.M. Parkin and P. Pisani; in collaboration with D.B. Esteban, C.A. Ngelangel and A.V. Laudico, Manila, The Philippines; with support from the US Army Medical Research Development Command

A randomized controlled trial of screening for breast cancer by physical examination performed by trained nurses was established in 1995 in the Manila area of the Philippines. 202 health centres serving the area were randomized to the intervention and control arms. Files of the eligible resident population were obtained from two sources and computerized. The numbers of distinct records (women) identified are 219 000 and 188 000 in the intervention and control groups respectively.

By the end of 1997, the first round of examinations was completed; 154 000 women had been interviewed and offered physical examination; 90.1% accepted. Of these, 3492 (2.3%) were identified as having a referable abnormality by the examiner. Compliance with follow-up of the women screened positive (clinic attendance and diagnostic procedures) is poor, with only 32% receiving a definitive diagnosis after assessment. By June 1998, 33 malignant breast cancers had been identified by screening.

This rate of compliance with referral of women detected positive at physical examination is far too low for the intervention to have any impact on the risk of dying from breast cancer in the intervention group. The intervention was therefore discontinued after completion of the first screening round and follow-up of the target population was undertaken. Follow-up is the responsibility of the two population-based cancer registries serving the Manila area. For breast cancer cases, a special case-finding mechanism has been established and information on size and extent at diagnosis of incident cancers is recorded. This information will be used to

evaluate the effectiveness of the prevalent screen (incidence and mortality rates in the two groups), as well as identifying the risk factors for breast and other female cancers in this population. No analytical study has ever been conducted to explain the relatively high incidence of breast cancer in this population. The information collected by interview at the time of the intervention will allow us to quantify the excess incidence attributable to known risk factors.

5.4.2
Early detection of cervix cancer in developing countries

R. Sankaranarayanan, D.M. Parkin, R. Herrero and N. Muñoz; in collaboration with R. Anand, Madras, India; R. Chakrabarthy, P. Basu, R. Chatterjee and M. Siddiqi, Calcutta, India; K. Dinshaw, S.G. Malwi, S. Shastri and D. Saranath, Bombay, India; L. Fernandez, Havana, Cuba; B.M. Nene, P.S. Dale, K. Jayant, A.M. Budukh and P.S. Chauhan, Barshi, India; R. Rajkumar and J. Cherian, Ambillikai, India; J. Sellors, Hamilton, Canada; G. Shyamalakumary, Ernakulam, India; J. Thomas and A. Omgbodun, Ibadan, Nigeria; V. Tsu, A. Bishop, J. Sherries, Seattle, WA, USA; and R. Wesley, N. Sreedevi Amma, N. Dhakad, T. Somanathan and M.K. Nair, Trivandrum, India; with support from the Bill and Melinda Gates Foundation

Cervical cancer continues to be the most common cancer and an important cause of death among women in their most productive period of life in many developing countries, but programmes of screening by cytology (Pap smear) in these areas have proved impracticable or unsuccessful. Other potential approaches to control of the disease include health education to improve awareness, screening based on visual examination of the cervix and testing for HPV.

The role of health education in achieving greater awareness among the population, to encourage interaction with health services leading to early detection and appropriate treatment, is being evaluated in a non-randomized controlled trial, initiated in 1994, in Barshi, central India, with the help of the local cancer registry. Messages on cervical cancer risk factors, symptoms, signs and the facilities for early diagnosis and treatment are spread among the intervention population by person to person and group education programmes. The first round of intervention covering the entire group of target women has been completed and the second round commenced in 1999. This study has so far accrued 680 000 (389 000 in the intervention and 291 000 in the control group) women-years during 1995–98. An interim analysis of results for this period indicated that more than 60% of women with cervical cancer in the intervention group were detected in stages I and II as opposed to 26% in similar stages in the control group. Though the compliance with treatment was similar in both groups (two thirds of patients completing treatment), the four-year cumulative fatality from cervical cancer was 23% in the intervention group compared with 40% in the control group. The relative risk of death from cervical cancer in the intervention group was 0.62 by the end of the fourth year of follow-up. A cluster randomized controlled trial to further address the role of educational intervention in a rural population Ambillikai, southern India, was initiated in 1999.

Two cross-sectional studies to evaluate the comparative efficacy of visual inspection with acetic acid (VIA) without magnification and of cytology in India have been completed [422, 423]. The results indicated that VIA, compared with cytology, had similar or higher sensitivity to detect moderate dysplasia or more advanced lesions, as

Figure 48. Women participating in the study of early detection of cervix cancer in India

Table 6. Performance characteristics of the screening tests

Performance criteria	Trivandrum		Ernakulam	
	VIA	Cytology	VIA	Cytology
Detection rate per 1000 women (CIN II +)	15.7	15.0	53.6	34.7
Specificity	92.2%	92.7%	68.0%	89.5%
Positive predictive value	17.0%	17.2%	14.8%	25.4%

indicated by the comparison of detection rates of lesions by these approaches, with histopathology and/or colposcopy used to establish a final diagnosis among those positive for one or both screening tests and in a sample of subjects negative for both; the specificity of VIA was lower than that of cervical cytology in one of the studies (Table 6). A study in Ibadan, Nigeria, is evaluating the comparative performance of VIA and cytology in the African setting.

Another study in Trivandrum, India, is assessing the role of Lugol's iodine as a parallel test in improving the performance, particularly the specificity, of VIA. A recently initiated study in Calcutta, India, is evaluating the use of the Aviscope, a magnifying device, to improve the specificity of VIA and the feasibility of using this device as a mini-colposcope. Both studies also address the effectiveness of HPV testing in detecting lesions and the feasibility and effectiveness of colposcopy and treatment of precancers in field conditions. They also provide a framework for training, particularly in colposcopy and treatment of cervical intraepithelial neoplasia (CIN) by cryotherapy and loop electrosurgical excision procedure (LEEP). An intensive course on these topics was conducted in Barshi, India and a simple manual to train nurses and doctors in colposcopy is being prepared in collaboration with the Department of Family Medicine, McMaster University, Canada.

Two cluster randomized intervention trials to assess the cost-effectiveness of VIA, cytology and HPV testing in reducing incidence of and mortality from cervical cancer were initiated in 1999. A total of 180 000 women aged 30–69 years in two rural districts of central and southern India will be subjected to one of the above interventions and followed up for several years.

Very limited expertise on diagnosis and management of cervical precancers exists in many high-risk countries. Training facilities will be organized in selected locations in Asia, Africa and South America to train master trainers from low-resource countries in early detection and prevention of cervical neoplasia. These training centres will be linked to active early detection programmes.

5.4.3
Oral cancer screening in developing countries

R. Sankaranarayanan, D.M. Parkin and P. Pisani; in collaboration with L. Fernandez Garrotte, J. Lence Anta and R. Camacho, Havana, Cuba; B. Mathew, K. Ramadas, I. Ahmed, M. Pandey, T. Somanathan, E. Abraham, G. Thomas, B. Kuruvilla, P. Sebestian, N. Sreedevi Amma and M.K. Nair, Trivandrum, India; and R. Rajkumar and J. Cherian, Ambillikai, India; with support from the Association for International Cancer Research

Oral cancer is a suitable disease for screening and visual examination of the mouth is a feasible and suitable screening test. However, it is not known whether organized screening with oral visual inspection can reduce the incidence of and mortality from this cancer cost-effectively. A community-based cluster randomized trial in Trivandrum district, India, to address this issue, was initiated in 1996, with the help of the local cancer registry. In the first round of screening, completed by May 1998, 114 000

subjects (59 000 intervention and 55 000 control group) aged 35 years and above were recruited. Of the 3585 subjects in the intervention group referred for follow-up examination, 52% were examined by doctors, who diagnosed 36 subjects with oral cancers and 1328 with oral precancers. Of the 63 oral cancers recorded by the cancer registry, 47 were in the intervention group and 16 in the control group, yielding incidence rates of 56.1/100 000 person years and 20.3 in the intervention and the control groups, respectively [416]. The programme sensitivity for detection of oral cancer was 76.6% and the specificity 94.0%; the positive predictive value was 1.0% for oral cancer. In the intervention group 72.3% of the cases were in stages I–II as opposed to 12.5% in the control group. The three-year case fatality rates were 14.9% (7/47) in the intervention group and 56.3% (9/16) in the control group. Around 13 000 subjects included in the first round had been re-examined by May 1999. The second round was initiated in July 1998.

A case–control study to evaluate the Cuban oral cancer screening programme has been completed and further descriptive evaluation is continuing. The role of health education and mouth self-examination is being examined in the rural population of Ambillikai, southern India.

PART 6. METHODS FOR CANCER RESEARCH

6.1 Methods for measuring and monitoring exposure to particular carcinogens

Epidemiological studies have in the past often relied on very imprecise information about exposure to potentially carcinogenic agents, leading to misclassification and a consequent weakening of the resolving power of the study. An understanding of the molecular and cellular aspects of carcinogenesis now permits the development of biomarkers of exposure which improve the precision of exposure measurement. This improved precision is particularly critical where the relative risk associated with an exposure is small. Modern analytical techniques are being applied to this problem, for use both in IARC projects and more generally by cancer researchers worldwide.

6.1.1
Mass spectrometric methods for measuring genetic susceptibility and carcinogen exposure

6.1.1.1
A new, accurate method for genotyping by mass spectrometric analysis of short DNA fragments

M. Friesen, P. Jackson, M. Lleonart and B. Chapot; in collaboration with J.D. Groopman, S.J. Laken, K.W. Kinzler and B. Vogelstein, Baltimore, MD, USA

A method called short oligonucleotide mass analysis (SOMA) has been developed to produce small DNA fragments from PCR products for analysis of defined DNA variations by mass spectrometry [253]. The genomic region to be analysed is amplified by PCR with primers containing a sequence for the type II restriction endonuclease *Bpm* I. *Bpm* I digestion of the PCR products yields polymorphic fragments as small as seven bases, which are then analysed by liquid chromatography linked to electrospray ionization mass spectrometry (Figure 49). This approach was validated using seven different variants within the *APC* tumour-suppressor gene, and yielded a perfect correlation with results obtained by DNA sequencing. Both the sense and anti-sense strands are analysed independently, and several variations can be analysed simultaneously following multiplex PCR. These results provide the basis for a generally applicable and highly accurate method to directly determine the mass of variant DNA sequences. When applied in conjunction with a suitable internal standard, the approach has potential for accurately measuring small amounts of mutated DNA in the presence of a large wild-type background.

6.1.1.2
Measuring human exposure to the food-borne carcinogen PhIP

M. Friesen and J. Michelon; in collaboration with H.A.J. Schut, Toledo, OH, USA; and P.T. Strickland, Baltimore, MD, USA

An extremely sensitive and specific technique has been developed to quantitatively measure recent human exposure to 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), a heterocyclic aromatic amine formed during high-temperature cooking of meat, that causes colon, prostate and breast cancer in rats. This method, which is based on gas chromatography/mass spectrometric measurement of PhIP and PhIP metabolites in human urine, has been validated by comparison with data obtained using an HPLC fluorescence technique. The method has also been used to measure the decrease in urinary unmetabo-

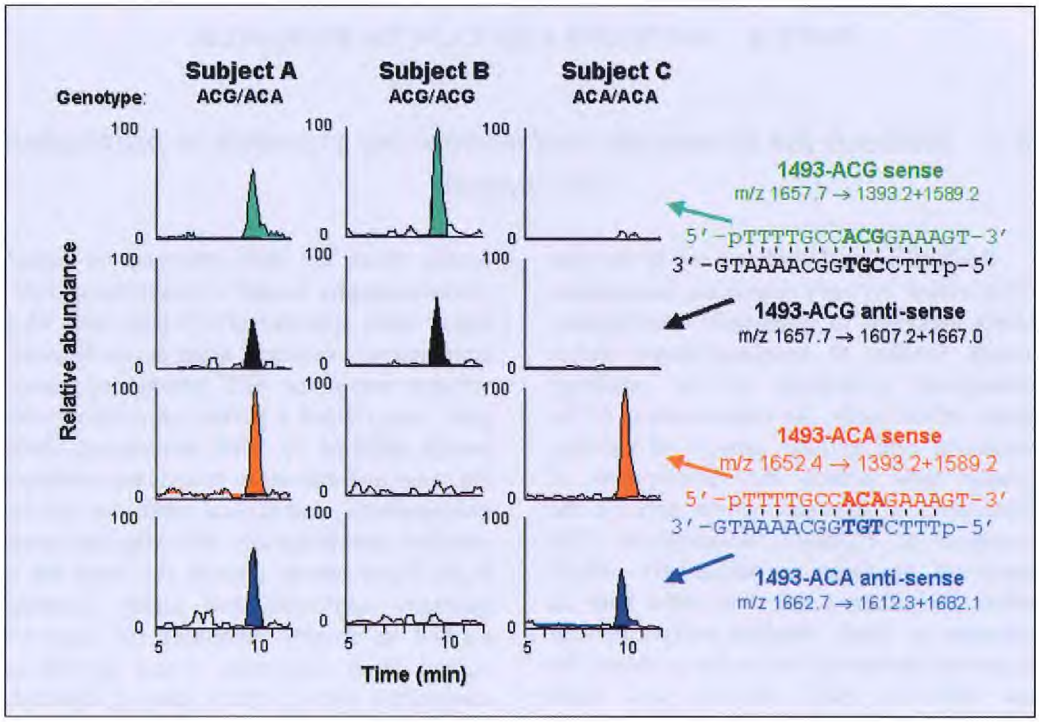

Figure 49. SOMA analysis of a variant sequence in the human APC gene at codon 1493, for subjects with three possible genotypes. The mass/charge ratios (m/z) specific for each oligonucleotide are indicated.

lized PhIP in female F344 rats given both PhIP and the chemopreventive agent indole-3-carbinol in the diet (Schut *et al.*, 1997, *Mutat. Res.*, **376**, 185–194).

6.1.1.3

Measuring human exposure to tobacco smoke

M. Friesen, P. Boffetta, S. Lea and S. Atawodi; in collaboration with W. Ahrens, Bremen, Germany; I. Brueske-Hohlfeld, Oberschleissheim, Germany; V. Constantinescu, Bucharest, Romania; C. Fortes, Rome, Italy; A. Mukeria, Moscow, Russian Federation; and F. Nyberg, Stockholm, Sweden

Haemoglobin (Hb) adducts of 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB), a metabolite of two tobacco-specific nitrosamines [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and *N*′-nitrosonornicotine], have been measured as biomarkers of exposure to tobacco smoke [4], as part of a study on genetic alterations and susceptibility to lung cancer among nonsmokers. In red blood cells collected in six collaborating centres, HPB–Hb adducts were measured by Ficoll gradient, release of HPB by alkaline hydrolysis from Hb, clean-up by solid-phase extraction and analysis of an electron-capturing derivative by gas chromatography/electron capture mass spectrometry. Before analysis of samples from study subjects, the reproducibility of this approach was validated with blood from donors. The subjects consisted of 18 smokers and 52 never-smokers. HPB–Hb adduct levels were significantly higher ($p = 0.02$) in smokers (26 ± 13 fmol HPB/g Hb) than in never-smokers (20 ± 8 fmol HPB/g Hb). These results suggest that the level of HPB–Hb adducts, measured by a method modified to facilitate use in multicentre studies, can be a useful biomarker of exposure to tobacco smoke.

6.1.2

Postlabelling methodology study

M. Castegnaro; in collaboration with D.H. Phillips, Sutton, UK; and 36 scientists from 12 countries

Further analysis of the results from the collaborative ^{32}P-postlabelling study has demonstrated how reductions in inter-laboratory variability can be achieved by appropriate use of standards, and that DNA adduct levels determined by mass spectrometry and by ^{32}P-postlabelling are generally in good agreement [375].

6.1.3

Analysis of fumonisins and of sphingolipids as their potential biomarkers

M. Castegnaro and L. Garren; in collaboration with M. Dutton, Durban, South Africa; and A. Pfohl-Leszkowicz and E. Pinelli, Toulouse, France

The development and validation of biomarkers of exposure to fumonisins for use in epidemiological studies requires analytical validation of the methods and also demonstration that the biomarkers truly reflect exposure at the individual level. The aim of this project is to develop and apply analytical methods based on the establishment of a qualitative and/or quantitative relationship between either plasma or urine toxin levels or impaired sphingolipid (sphinganine/sphingosine) ratio, and the dietary intake of the mycotoxins. The correlation between the incidence of bound fumonisin in tissues and the results from the analytical method is also being examined.

A method for analysis of sphinganine and sphingosine in human and animal urine and tissues (Castegnaro *et al.*, 1996, *Natural Toxins*, **4**, 284–290) has been modified for application to human sera [92] and tested. A method for analysis of fumonisins in human serum has been established.

Preliminary analysis of samples collected in the Tugela valley of South Africa, where exposure to fumonisins is known to occur, has shown that in 1998 the population was exposed to only low levels of fumonisins. In the blood of the exposed persons, no alteration in sphingolipid biosynthesis was detected.

The mechanism of action of fumonisin B_1 (FB_1) has been investigated. FB_1 was shown to increase protein kinase C (PKC) translocation and to stimulate mitogen-activated protein kinase (MAPK). The effect of FB_1 on the arachidonic acid cascade in a human epithelial cell line and the signal transduction pathway regulating phospholipase A_2 (PLA_2) activation have been investigated. We observed that FB_1 stimulated PLA_2 activity and increased arachidonic acid release by a mechanism independent of PKC activation, but strongly dependent on the MAPK pathway. In addition, FB_1 increased cAMP production and protein kinase A activation. These events represent a pathway of down-regulation of the arachidonic acid cascade. The increase in cAMP was correlated with prostaglandin production by cyclooxygenase [380].

6.1.4

Biological monitoring of exposure to carcinogens that form DNA etheno adducts

A. Barbin, G. Brun, V. Dumon and Z.-Q. Wang; in collaboration with H. Barstch, J. Nair and M. Hollstein, Heidelberg, Germany; F.-L. Chung, Valhalla, NY, USA; A. Devaux, Vaulx-en-Velin, France; J. Laval, Villejuif, France; G.P. Margison and R. Elder, Manchester, UK; B. Tudek, Warsaw, Poland; and E.W. Vogel and M. Nivard, Leiden, The Netherlands

6.1.4.1

Formation and repair of etheno adducts in rodents

We have previously measured the formation of background levels of $1,N^6$-ethenoadenine (εA) and $3,N^4$-ethenocytosine (εC) in DNA from the liver, lung, kidney and lymphocytes from unexposed Sprague–

Dawley rats and the accumulation of εA and εC in liver and of εC in lung and kidney DNA from rats exposed to vinyl chloride. This study has now been completed by the analysis of other tissues from these animals, using the immunoaffinity/^{32}P-postlabelling method [9]. Background levels of εA and εC were measured in the brain, spleen, testes and heart. The endogenous formation of ethenobases, which has thus been observed in all the tissues examined, probably originates from lipid peroxidation products such as *trans*-4-hydroxy-2-nonenal (HNE). In animals exposed to vinyl chloride, levels of etheno adducts were increased significantly in the testes and spleen. There was no correlation between absolute levels of ethenobases in DNA and organ susceptibility to vinyl chloride-induced carcinogenesis. However, the accumulation of εA in hepatic DNA may partly determine the mutation spectra in the *ras* and *p53* genes in hepatic tumours induced by vinyl chloride in rats [7, 53].

It has been shown that, *in vitro*, εA is repaired by the mammalian 3-methyladenine DNA glycosylase (ANPG) enzyme, whereas a different DNA glycosylase is involved in the removal of εC from DNA. To test whether ANPG plays an important role in the repair of εA (but not εC) *in vivo*, levels of εA and εC are being compared in wild-type C57BL/6J mice and in mice deficient in ANPG. In liver and brain DNA from two-year-old animals, no difference in etheno adduct levels was observed between the two strains. In six-week-old mice treated with vinyl carbamate (a proximate metabolite of urethane), levels of εA in liver and lung DNA six hours after treatment were significantly higher in treated animals than in untreated controls, and ANPG$^{-/-}$ mice exhibited twice as much εA as the wild-type strain. The levels of εA decreased with time in both strains, but at 72 h were still higher than the control values in the knock-out mice, whereas, in wild-type mice, they were similar to the background levels. These results show that ANPG can excise εA *in vivo* and suggest the existence of a back-up repair system for this DNA lesion.

6.1.4.2

Effects of DNA repair deficiency on genotoxic effects of lipid peroxidation products in cell cultures

The effects of repair deficiencies on DNA damage induced by HNE and its oxidation product 2,3-epoxy-4-hydroxy-nonanal (EH) are being investigated in cell cultures (established and primary embryonic fibroblasts) derived from wild-type mice and from knock-out mice deficient in the repair proteins MSH2 and PARP. Etheno adducts are measured by immunoaffinity/^{32}P-post-labelling, and DNA strand breaks and alkali-sensitive sites by the Comet assay. Treatment conditions were established to ensure >70% survival. Dose–response relationships were obtained for ethenobases and for strand breaks, which increased at HNE or EH concentrations of up to 0.1 mM. The levels and persistence of these lesions will be compared with other biological end-points (cytotoxicity) in different cell lines (heterozygous and homozygous deletion mutants as well as double mutants).

6.1.4.3

Analysis of etheno adducts at the DNA sequence level

A procedure is being established to study the formation and repair of etheno adducts and other DNA lesions in the *p53* gene at the DNA sequence level. It is based on ligation-mediated PCR and the use of DNA glycosylases to cut the glycosidic bond of adducted bases. Initial experiments were performed on a plasmid carrying part of the human *p53* gene. After treatment with HNE, this plasmid was examined for sensitivity to

cleavage by several repair enzymes. It was observed that HNE produces DNA lesions which can be cleaved by the AlkA and Fpg proteins but not by the ANPG protein.

6.1.4.4

Carcinogenesis in PARP-deficient mice

A one-year carcinogenesis experiment has been initiated to determine whether $PARP^{-/-}$ mice are more or less sensitive than wild-type animals to the tumorigenic effects of etheno-adduct-forming chemicals. Twelve-day-old mice (40 wild-type and 40 $PARP^{-/-}$) were given a single intraperitoneal injection of urethane (6 mmol/kg bw). Tumours will be scored and kept for further histological and molecular analyses.

6.1.5

Development of a new method to analyse 3-nitrotyrosine

H. Ohshima, I. Celan, L. Chazotte-Aubert, B. Pignatelli and H.F. Mower

3-Nitrotyrosine (NTYR) has been measured immunohistochemically in human tissues as a marker of nitrosative stress caused by reactive nitrogen species (e.g., peroxynitrite, nitrogen oxides). A new simple method to analyse NTYR in plasma and tissue proteins has been developed using HPLC with an electrochemical detector, which is both sensitive and selective for NTYR [330].

6.2 Epidemiological methods

6.2.1

Development and evaluation of analytical methods for genetic epidemiology

D.E. Goldgar; with support from the US National Institutes of Health

This project explores important analytical, statistical and design issues in cancer genetic epidemiology. Specifically, we are involved in the following set of studies: (*a*) to investigate the optimal strategies for mapping and identifying low-penetrance genes for common cancers, with the focus on a comparison between linkage and association-based strategies; (*b*) implementation of a likelihood-based approach to combined linkage and association testing on general pedigree structures [175]; (*c*) examination of the power of existing data-sets for detecting the presence of modifier genes in high-risk breast cancer studies; (*d*) mathematical models for determining the age of specific recurrent mutations based on multilocus haplotype data in mutation carriers [322]. Some of these projects rely largely on computer-simulation of data under appropriate genetic models in order to evaluate different sampling and gene-detection strategies. Recently, we have extended our analysis of family history to consider the relative efficiencies of different family history criteria in selecting families for genetic testing.

6.2.2

Projections of future cancer incidence and mortality rates using age–period–cohort models

P. Brennan, I. Bray and P. Boffetta

Past trends in tobacco consumption in central and eastern Europe have resulted in some of the highest lung cancer mortality rates worldwide being observed in this region. We have adopted a Bayesian age–period–cohort model to project future trends for lung cancer for some central and eastern European countries. Our 10- to 20-year projections indicate that lung cancer mortality will peak among men in the Czech Republic,

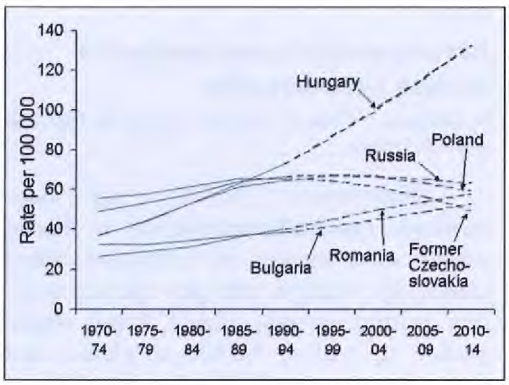

Figure 50. Trends (1970–94) and projections (1995–2014) in male lung cancer mortality in central and eastern Europe

Poland, the Russian Federation and Slovakia, and may even decline, whereas rates in Romania and Bulgaria will continue to increase (Figure 50). Dramatic increases are projected for Hungarian men, where the already high mortality rate of 73.1/100 000 in 1990–94 is expected to increase to 100.6/100 000 by 2004, with even further increases by 2014. Rates are projected to increase moderately among women in the Czech Republic, Poland, Romania and Slovakia and should remain stable in Russia and Bulgaria. In Hungary the high mortality rate of 14.3/100 000 is projected to increase to 25.3/100 000 by 2004, and increase even further by 2014. These increases, especially those in Hungary, are due to large cohort effects among the population born in the period 1940–50. Similar work is being conducted for other tobacco- and alcohol-related cancers in central and eastern Europe, and also for lymphoproliferative disorders using incidence data from a series of cancer registries worldwide.

PART 7. PUBLICATIONS, EDUCATION AND TRAINING

7.1 Publications

The aim of the IARC publications programme is to ensure rapid and wide dissemination of information from Agency projects to other cancer researchers and public health decision-makers worldwide. Improvements in computer technology have permitted simplification and acceleration of the processes of document transfer from authors to the Publications Service, editing and page layout, and transfer to printers.

The IARCPress complements the promotion and distribution activities of Oxford University Press and the World Health Organization Distribution and Sales Service, with the aim of improving the visibility and availability of the Agency's publications. Since its launch in early 1996, it has attracted large numbers of customers by active promotion through mailings and displays at scientific meetings and sold increasing numbers of books (an 18% increase from 1996 to 1997, 23% increase from 1997 to 1998 and an expected 75% increase from 1998 to 1999; Figure 51), especially on account of its rapid service.

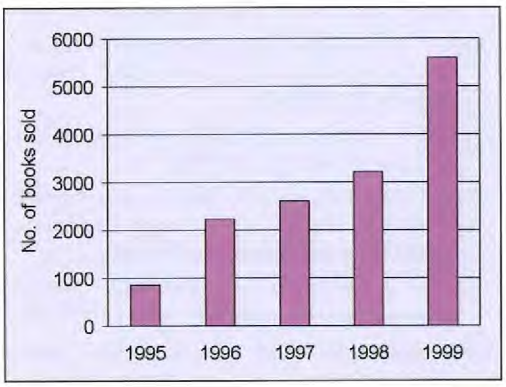

Figure 51. Book sales from IARCPress since its inauguration in 1995 (number for 1999 estimated)

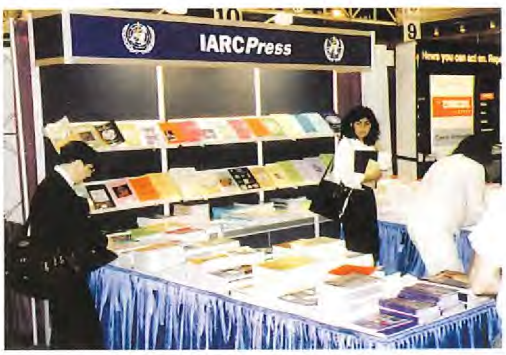

Figure 52. An IARCPress display, at the annual meeting of the American Association for Cancer Research in Philadelphia, April 1999

7.1.1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

This programme is described in detail in Section 2.1.1. New volumes published during the period under review are the following:

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 71, *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 72, *Hormonal Contraception and Post-Menopausal Hormonal Therapy*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 73, *Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents, and Some Other Substances*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 74, *Surgical Implants and Other Foreign Bodies*

7.1.2 IARC Scientific Publications

The Advisory Committee on Publications, chaired by Dr P. Boffetta, continues to

review proposals for new publications, with particular emphasis on the relevance of the work to the Agency's programme and on the procedures in place for each volume to ensure high scientific quality.

The following new publications appeared during the period under review:

Quantitative Estimation and Prediction of Human Cancer Risks (IARC Scientific Publications No. 131)

International Incidence of Childhood Cancer, Volume 2 (IARC Scientific Publications No. 144)

Cancer Survival in Developing Countries (IARC Scientific Publications No. 145)

Results of Short- and Medium-term Tests for Carcinogens, and Data on Genetic and Related Effects in Carcinogenic Hazard Evaluations (IARC Scientific Publications No. 146)

Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis (IARC Scientific Publications No. 147)

Metabolic Polymorphisms and Susceptibility to Cancer (IARC Scientific Publications No. 148)

Epidemiology of Childhood Cancer (IARC Scientific Publications No. 149)

Exocyclic DNA Adducts in Mutagenesis and Carcinogenesis (IARC Scientific Publications No. 150)

Survival of Cancer Patients in Europe: the Eurocare-2 Study (IARC Scientific Publications No. 151)

7.1.3 IARC Technical and Internal Reports

The IARC Technical Reports are specialized publications with a limited market. IARC Internal Reports are documents prepared within the framework of specific projects for use in-house and by collaborators in the project. The following reports were published during the period under review:

Mortalité par cancer des immigrés en France 1979–1985 (IARC Technical Report No. 26)

The Risk of Cancer in Thre Generations of Young Israelis: a Study of Migrants and their Descendants (IARC Technical Report No. 27)

Survey of Cancer Registries in the European Union (IARC Technical Report No. 28)

Cancer Risk from Occupational Exposure to Wood Dust (IARC Technical Report No. 30)

Histological Groups for Comparative Studies (IARC Technical Report No. 31)

Automated Data Collection in Cancer Registration (IARC Technical Report No. 32)

European Multi-centre Case–Control Study of Lung Cancer in Non-Smokers (IARC Technical Report No. 33)

Cancer in Thailand, Volume 2 (IARC Technical Report No. 34)

Cancer Registration Techniques in the Newly Independent States of the Former Soviet Union (IARC Technical Report No. 35)

Cancer Incidence and Mortality in Spain: Patterns and Trends (IARC Technical Report No. 36)

Report of an Ad-Hoc IARC Monographs Advisory Group on Physical Agents (IARC Internal Reports No. 98/002)

CanReg3 Manual, English version (IARC Internal Reports No. 98/003)

Report of an Ad-Hoc IARC Monographs Advisory Group on Priorities for Future Evaluations (IARC Internal Reports No. 98/004)

Manuel d'utilisation de CanReg3, Version française (IARC Internal Reports No. 99/001)

IARC Multicentre Study of Cancer Risk Among Workers of Four European Mercury Mines and Mills (IARC Internal Reports No. 99/002)

International Classification of Diseases for Oncology. Third edition. Field trial version (IARC Internal Reports No. 99/003)

International Case–Control Study of Cancers of the Brain and Salivary Gland and of Leukemia (IARC Internal Reports No. 99/004)

7.1.4 IARC Handbooks of Cancer Prevention

The aim of the IARC Handbooks of Cancer Prevention is to evaluate scientific information on agents and interventions that

may reduce the incidence of or mortality from cancer. The programme is fully described in Section 5.2. The following volumes were published during the period under review:

IARC Handbooks of Cancer Prevention, Volume 2, *Carotenoids*

IARC Handbooks of Cancer Prevention, Volume 3, *Vitamin A*

IARC Handbooks of Cancer Prevention, Volume 4, *Retinoids*

7.1.5

Histopathological Typing of Human Tumours

The first edition of the 'blue book' series on histopathological typing of human tumours was published by WHO (Geneva), and the second edition, now close to completion, was published by Springer-Verlag (Heidelberg). The Agency has initiated a third edition, of which the layout and content will be similar to those of the sucessful *Pathology and Genetics of Tumours of the Nervous System*. This will be a joint series with the WHO Cluster of Noncommunicable Diseases (Dr J. Chen) and the Cluster of Evidence and Information for Policy (Dr J. Frank).

The editorial and consensus metings for the first two volumes, on tumours of the nervous system and tumours of the digestive tract, were held in 1999, and both books are expected to be published in early 2000.

7.1.6

Directory of On-going Research in Cancer Prevention

E. Demaret, R. Sankaranarayanan and H. Vainio; in collaboration with N. Becker and J. Wahrendorf, Heidelberg, Germany

The *Directory of On-going Research in Cancer Prevention* is issued on the Internet (http://www.dep-iarc.fr/prevent.htm/) and will also be made available on CD-ROM. It is produced jointly with the German Cancer Research Centre, Heidelberg, and is a unique source of information on current work in defined areas of human cancer prevention, for scientists, clinicians, public health professionals and policy makers [417, 420]. For the purpose of inclusion in the Directory, cancer prevention studies are defined as interventions aiming to reduce incidence of or mortality from cancer or to modulate intermediate end-points thought to be (not necessarily validated) surrogates for cancer incidence and/or mortality. Projects carried out in 23 countries contributed to the 104 abstracts included in the current version of the Directory; 57 biological materials banks are also listed, as well as addresses of population-based cancer registries.

7.1.7

Directory of Agents being Tested for Carcinogenicity

The aims of this project are to survey chemicals and other agents being tested for carcinogenicity in experimental animals worldwide under circumstances in which publication of the results can reasonably be expected, and to make this information freely and widely available. For each chemical or agent under test, the laboratory, principal investigator, species, strain, route of administration, dosage levels and the stage of the bioassay are recorded; references are provided to published results. Extensive bioassays of new pharmaceutical and agricultural agents carried out by commercial firms to support registration of these agents for sale are often not published and therefore are not available to the Directory.

Because of the large cost involved in undertaking such long-term bioassays the numbers of chemicals being tested is continually diminishing. The Directory is therefore also interested in following shorter-term tests being undertaken using strains of genetically modified animals.

The Directory is published electronically, through the Internet. It is updated several times yearly to reflect the progress of studies, publication of completed studies and initiation of new bioassays as new information is received.

7.1.8
Electronic publication

The dissemination of international cancer statistics has hitherto been through the IARC Scientific Publications series, IARC Technical Reports and articles in peer-reviewed journals. However, it has become evident that data are increasingly required not only by epidemiologists, but also by a wider public, using more accessible media, which allow easy updating. This led to the launch in 1997 of the electronic publication series 'CancerBase', with the aim of providing statistical data on cancer incidence, mortality and prevalence together with easily used software to manipulate the data. CancerBase 3, GLOBOCAN 1, contains incidence and mortality data from 24 major cancers for all the countries and areas in the world in 1990. Published in late 1998, it sold over 500 copies in the first nine months of 1999. CancerBase 4 is an update and enhancement of EUCAN90 that provides the most up-to-date statistics on cancer incidence, mortality, prevalence and survival in the 15 countries of the European Union (see Section 1.1.2.2).

A second way to disseminate information to a large audience is through the World Wide Web (Internet). The IARC home page has been redesigned, to present a more uniform look and feel that allows easier navigation and access to information on IARC programmes, personnel and publications. The site is fully searchable with a Boolean search engine. A personnel directory is available with clickable e-mail links. Additional back-end databases are planned to work in conjunction with IARC's online bookstore. The catalogue of publications is available in Portable Document Format (PDF).

A number of scientific databases are available via the IARC home page. Simplified versions of GLOBOCAN and EUCAN (see above) with limited statistics and options are available through the *CANCERMondial* web page (http://www-dep.iarc.fr), which also provides access to the huge World Health Organization cancer mortality database.

The database of mutations in the p53 protein is described in Section 4.7.2 (http://www.iarc.fr/p53/homepage.htm). The IARC Monographs database, which became operational in December 1997, is maintained on a dedicated server (http://193.51.164.11), and allows searchable access to the complete listing of Monographs evaluations in English and French and searching of the narrative summaries of the Monographs evaluations in English, as well as other information including the preamble to the IARC Monographs and the Directory of Agents Being Tested for Carcinogenicity (see Section 7.1.6).

7.2 Cancer research fellowships programme

7.2.1
IARC research training fellowships

R. Montesano and E. El Akroud

The aim of this programme is to provide young postdoctoral scientists from any country in the world with training in aspects of cancer research ranging from biostatistics and epidemiology to mechanisms of chemical and viral carcinogenesis, so that they can return to their own country to implement and develop programmes in cancer research or cancer control. The majority (64%) of the 482 fellowships awarded since 1966 have

come from western Europe, Japan, North America, Israel, Australia and New Zealand while 18% came from eastern Europe and 18% from other countries of Africa, Asia and South America (Figure 53). Host laboratories have been mainly located in western Europe (51%) and North America (47%). The programme is one of the few to provide training in epidemiology, and the 102 fellowships awarded so far in this discipline have contributed substantially to the development of cancer epidemiology in a number of countries. A review of the fellowships programme over the last 30 years has been published [305].

The Fellowships Selection Committee met twice in Lyon during 1998/99 to review applications; the members of the Committee were:

Dr A.-L. Børresen-Dale (1998)
Department of Genetics
Institute for Cancer Research
The Norwegian Radium Hospital
Oslo, Norway

Dr N. Breslow (1998, 1999) (*Chairman*)
Department of Biostatistics
University of Washington
Seattle, WA, USA

Dr J. Cairns (1998) (*Vice Chairman*)
Clinical Trial Service Unit
Radcliffe Infirmary
Oxford, UK

Dr B. Mansourian (1998) (*WHO representative*)
Office of Research Policy and Strategy Coordination
World Health Organization
Geneva, Switzerland

Dr K. Nilsson (1999) (*UICC representative*)
Department of Genetics and Pathology
Uppsala University Hospital
Uppsala, Sweden

Fellows from:		Fellows to:
France	53	34
IARC, Lyons	–	58
Japan	42	3
Italy	34	2
USA	29	232
Russian Federation	27	–
Israel	25	–
United Kingdom	25	97
P.R. China	25	1
India	21	–
Australia	16	3
Other countries	185	79
Total:	482	509[a]

Figure 53. IARC fellows 1966–99: countries of origin and host countries

[a] Twenty-seven fellows had two host countries

Dr N. Odartchenko (1998) (*UICC representative*)
Swiss Institute for Experimental Cancer Research
Epalinges s/ Lausanne, Switzerland

Dr M.A. Pierotti (1998, 1999)
Divisione di Oncologia Sperimentale A
Istituto Nazionale per lo Studio e la Cura dei Tumori
Milan, Italy

Dr J. Pouysségur (1998, 1999)
Centre de Biochimie – CNRS UMR 6543
Faculté des Sciences
Nice, France

Dr H.M. Rabes (1998, 1999)
Institute of Pathology
Ludwigs Maximilians University München
Munich, Germany

Dr H. Tsuda (1998, 1999)
Experimental Pathology and Chemotherapy Division
National Cancer Center Research Institute
Tokyo, Japan

Dr J. M. Vasiliev (1998, 1999)
Russian Cancer Research Center
Moscow, Russian Federation

Dr R. Weiss (1999)
Windeyer Institute of Medical Sciences
University College London
London, UK

The Agency representatives were Dr R. Montesano, Dr P. Boffetta (1998) and Dr D. Goldgar (1999), who has taken over responsibility for the programme from Dr Montesano.

In 1998, among a total of 94 candidates, 48 were declared eligible and 10 received awards; in 1999, among a total of 60 candidates, 38 were declared eligible and 11 fellowships were finally awarded. The distribution of fellowships awarded by discipline is given in Table 7, and the list of fellows in Table 8.

The Italian Association for Cancer Research has continued its generous support of the Fellowships Programme, providing a total of US$90 000 over the two-year period.

7.2.2 IARC postdoctoral fellowship programme

Z.-Q. Wang and E. El Akroud

In 1998, a Special Training Award Selection Committee composed of senior IARC scientists was set up to select candidates for postdoctoral fellowships tenable at IARC in order to increase the number and quality of postdoctoral fellows at IARC. The members were: Dr E. Cardis (1998, 1999), Dr D. Goldgar (1998, 1999), Dr E. Riboli (1998, 1999), Dr Z.-Q. Wang (1998, 1999) (Chairman) and Dr H. Yamasaki (1998, 1999). This programme also now evaluates applications for the Visiting Scientist Award intended for established research scientists who wish to spend up to one year at the IARC.

The Special Training Award Selection Committee met for the first time in June 1998 to review a total of 35 applications received, 16 of which had been transferred from the Research Training Fellowships

Table 7. Distribution of research training fellowships awarded by discipline

Scientific discipline	No. of fellowships		
	1998	1999	1966–99
Epidemiology and biostatistics	1	1	102
Cell biology, cell differentiation and cell genetics	6	4	114
Chemical carcinogenesis	–	3	67
Viral carcinogenesis	–	1	59
Biochemistry and molecular biology	2	1	86
Others	1	1	54
Total	10	11	482

Selection Committee. Eighteen applications were judged eligible and four of the five recommended were awarded, one each in the fields of epidemiology, molecular pathology, molecular genetics and biochemistry.

The Committee met again at the end of March 1999 to review a total of 51 applications received. Thirty-seven eligible applications were evaluated and three out of the six recommended were awarded, two in epidemiology and one in molecular pathology.

7.2.3
Visiting Scientist Awards

In 1998, this Award was given to Professor C.B. Ijsselmuiden (Department of Community Health, University of Pretoria, South Africa), who spent six months in the Unit of Descriptive Epidemiology, and in 1999 to Professor A. Metspalu (Institute of Molecular and Cell Biology, University of Tartu, Estonia), who will spend one year in the Unit of Genetic Cancer Susceptibility.

Table 8. Fellowships awarded in 1998 and 1999

Name	Institute of origin	Host institute
1998		
AVNI, D.	Department of Biochemistry The Hebrew University – Hadassah Medical School Jerusalem, Israel	Dana Farber Cancer Center Boston, MA, USA
CALIN, G.A.	Medical Genetics Department The Victor Babes Institute Bucharest, Romania	Department of Experimental and Diagnostic Medicine University of Ferrara Ferrara, Italy
CHIRIVI, R.G.S.	Laboratory of Biology & Treatment of Metastasis Mario Negri Institute for Pharmacological Research Bergamo, Italy	Department of Immunology & Vascular Biology The Scripps Research Institute La Jolla, CA, USA
GUARDAVACCARO, D.	Institute of Neurobiology National Research Council Rome, Italy	Department of Pathology New York University Medical Center New York, NY, USA
KLEIN, L.	Department of Cellular Immunology German Cancer Research Centre Heidelberg, Germany	INSERM U.373 Institut Necker Paris, France
LLOYD, D.R.	Institute of Cancer Research Haddow Laboratories Sutton, Surrey, UK	Department of Biological Sciences Stanford University Stanford, CA, USA
MORRIS, C.M.	Centre de Recherches en Biologie Macromoléculaire, CNRS Montpellier, France	Department of Molecular Biology The Scripps Research Institute La Jolla, CA, USA
SAGE, J.	INSERM U.470, Centre de Biochimie Université de Nice-Sophia Antipolis Nice, France	MIT Center for Cancer Research Howard Hughes Medical Institute Cambridge, MA, USA
SEPEHR, A.	National Research Institute of Tuberculosis and Lung Diseases Tehran, Iran	Units of Descriptive Epidemiology and Mechanisms of Carcinogenesis IARC Lyon, France

SHIMADA, K.	Department of Applied Biological Chemistry Laboratory of Molecular Biology Tohoku University Sendai, Japan	Chromatin Research Unit Swiss Institute for Experimental Cancer Research Epalinges/Lausanne, Switzerland
1999		
BROWNING, H.L.	University of Colorado MCD Biology Boulder, CO, USA	Imperial Cancer Research Fund Cell Cycle Laboratory London, UK
CIEMERYCH, M.A.	Institute of Zoology University of Warsaw Department of Embryology Warsaw, Poland	Dana-Farber Cancer Institute Harvard Medical School Department of Cancer Biology Boston, MA, USA
DANTZER, F.	Unité de Cancérogenèse et Mutagenèse Moléculaire et Structurale UPR 9003/CNRS, ESBS Illkirch, France	Institute of Medical Microbiology Department of Molecular Biology The National Hospital Oslo, Norway
FAYADAT, L.A.C.	INSERM U.38 Faculty of Medicine Marseillle, France	Stanford University Department of Biological Sciences Stanford, CA, USA
HORVATHOVA, E.	Cancer Research Institute of Slovak Academy of Sciences Department of Mutagenesis and Carcinogenesis Bratislava, Slovakia	Rowett Research Institute DNA Instability Group Aberdeen, Scotland, UK
LOUIS, S.N.	Austin & Repatriation Medical Centre Clinical Pharmacology & Therapeutics Unit Department of Medicine Heidelberg, Vic., Australia	Institut Cochin de Génétique Moléculaire Laboratoire d'Immuno-Pharmacologie Moléculaire UPR 0415 CNRS Paris, France
MYCIELSKA, M.E.	Jagiellonian University The Jan Zurzycki Institute of Molecular Biology Krakow, Poland	Imperial College of Science, Technology and Medicine Departments of Biology and Physiology London, UK
SAARIKOSKI, S.T.	Finnish Institute of Occupational Health Department of Industrial Hygiene and Toxicology Helsinki, Finland	UCLA Medical Center Center for the Health Sciences Department of Pathology and Laboratory Medicine Los Angeles, CA, USA
SANGWA LUGOMA, G.	Kinshasa University Faculty of Medicine Kinshasa, D.R. Congo	McGill University Department of Epidemiology & Biostatistics Montreal, Quebec, Canada
SHAO, J.-Y.	Cancer Center Sun Yat-Sen University of Medical Sciences Department of Pathology Guangzhou, PR China	Microbiology and Tumor Biology Research Centre Karolinska Institute Stockholm, Sweden
TUMANOV, A.	Engelhardt Institute of Molecular Biology Russian Academy of Sciences Moscow, Russian Federation	Frederick Cancer Research & Development Center Basic Research Program Cancer & Developmental Biology Laboratory Frederick, MD, USA

7.3 *Training courses*

In 1998–99, IARC organized 12 courses, some in collaboration with other institutions. Courses are held in English unless otherwise indicated.

7.3.1

Course for cancer registrars in sub-Saharan Africa, 16–25 March 1998, Johannesburg, South Africa

This course was designed for clerks in cancer registries. Twenty-nine participants attended, from Botswana, Lesotho, Malawi, Namibia, Nigeria, South Africa, Swaziland, Tanzania, The Gambia, Uganda, Zimbabwe. It was organized in liaison with Dr Freddy Sitas, of the South African Institute for Medical Research and received financial support from the US National Cancer Institute (Dr F. Welsch). Ms S. Whelan from IARC coordinated the course.

7.3.2

Safe handling of cytostatic drugs for health workers, 20–21 April 1998, Lyon, France

Thirty participants from France attended this course, which was organized, as on previous occasions, in collaboration with the French Institut National de la Recherche et de la Sécurité (INRS). The course provided advanced training for nurses and public health workers followed by practical sessions at the Hôpital Edouard Herriot (Lyon). The course directors were Dr M. Castegnaro from IARC and Dr M. Falcy from INRS.

7.3.3

Nordic Institute for Advanced Training in Occupational Health (NIVA)/IARC molecular epidemiology course, 19–24 April 1998, Naantali, Finland

The first part of the course focused on biomarkers of various types, their scientific basis and their use in practice (molecular dosimetry, individual susceptibility, DNA repair and mutations in cancer-related genes), and the last two days were devoted to epidemiological issues. Some 18 countries were represented among the 36 participants at the course, many from countries of eastern central Europe. The course received financial assistance from the US Environmental Protection Agency (EPA). The course leaders were Dr P. Boffetta from IARC and Dr K. Husgafvel-Pursiainen of the Finnish Institute of Occupational Health.

7.3.4

Summer school on cancer registration and applications in epidemiology, 11–29 May 1998, Lyon, France

This third summer school was attended by 21 participants from Bahrain, Bolivia, Bulgaria, Ethiopia, Guatemala, India, Iran, Korea (Republic of), Nigeria, Pakistan, Palestinian National Authority, Russia, Spain, Sri Lanka, Tanzania, The Gambia and Yemen (Republic of). Most of the participants were IARC collaborators from cancer registries wishing to receive further training in cancer registration, cancer registry data management using CANREG software and cancer epidemiology. The course consisted of three weeks' training in Lyon followed by a few days in different European cancer registries to gain practical experience.

7.3.5

Course for cancer registrars in the Pacific area, 20–29 July 1998, Noumea, New Caledonia

This course was held in collaboration with the South Pacific Commission, Dr R. Hughes and the WHO/WPRO Non-communicable Diseases Unit. Twelve participants from

the Cook Islands, Marianas Islands, Federated States of Micronesia, French Polynesia, Guam, New Caledonia, Palau, Papua and New Guinea, Samoa, Solomon Islands, Tonga and Vanuatu attended. Dr P. Pisani from IARC was the course director. The course focused on the routine activities of data abstraction, coding and quality checking.

7.3.6

ENCR/IARC course on geographical analysis methods for cancer registries, 29 September–2 October 1998, Lyon, France

The European Network of Cancer Registries, in collaboration with IARC, focused its annual course for cancer registry staff and researchers involved in data analysis on geographical methods (cancer clusters, mapping). The 30 participants came from Finland, France, Germany, Italy, Poland, Portugal, Slovenia, Spain, Sweden, the Netherlands, UK and Yugoslavia.

7.3.7

Third Gaslini–IARC course in cancer genetics, 24–29 September 1998, Sestri Levante, Italy

This third course was attended by 41 students from 14 European countries. The format of the course is based on morning lectures and afternoon workshops. A novel aspect this year was an emphasis on clinical as well as basic aspects of cancer genetics.

7.3.8

Course on infections that increase the risk of cancer, 13–18 December 1998, Veyrier-du-Lac, France

This course, attended by 36 participants, reviewed the latest results relating infection with viruses, bacteria and parasites to human cancer. Agents covered included hepatitis B and C viruses, human papillomavirus, human herpes type 8 virus, HIV, *Helicobacter pylori* and Epstein–Barr viruses. Emerging hypotheses on the role of other infectious agents and new strategies on prevention were also presented. The course director was Dr N. Muñoz.

7.3.9

Summer school on cancer registration and applications in epidemiology, 3–28 May 1999, Lyon, France

The 1999 summer school followed the same pattern as the 1998 one (Section 7.3.4) and welcomed 19 participants from Algeria, Armenia, Chile, China, Congo, Honduras, India, Kenya, Malaysia, Mexico, Panama, Romania, Rwanda, Saudi Arabia, Oman, Swaziland, Trinidad and Tobago, Tunisia and the United Arab Emirates. All of them are working in cancer registries and were here to improve their knowledge of data management and statistics methods. Dr R. Sankaranarayanan was the course director.

7.3.10

Curso sobre prevencion y control del cancer, 27 September–7 October 1999, San José, Costa Rica (in Spanish)

This course had many new features. It was entirely devoted to cancer control and prevention, with the aim of providing medical staff and public health decision-makers with not only a better scientific understanding of the problem but also practical advice on national programmes for prevention and control, particularly anti-tobacco campaigns. The course also had a strong practical component, with site visits to the main cancer control activities in Costa Rica. National cancer programmes were presented by the participants and critically reviewed by the faculty and participants. The course director was Dr N. Muñoz. The course was organized in collaboration with Dr S. Robles from PAHO and Dr M. Ronderos, Director

Figure 54. Participants at the cancer epidemiology course in San José, Costa Rica

General of Health Promotion and Prevention of Colombia. Nearly 50 participants came from 12 countries of Central and South America (Figure 54).

7.3.11

Fourth Gaslini–IARC course in cancer genetics, 29 September–3 October 1999, Sestri Levante, Italy

This fourth cancer genetics course attracted 70 students from 19 European and seven other countries. The success of the course is due to the high scientific standard of the morning lectures and afternoon workshops. The addition this year of evening research seminars, by N. Hastie, W. Reik and J. Burn, was greatly appreciated.

7.3.12

Course on cancer epidemiology—principles and methods, 15–26 November 1999, Khon Kaen, Thailand

This course was devoted to the practical applications of the principles and methods of cancer epidemiology. Particular emphasis was given to the public health dimension of the cancer problem in the region. Some 48 participants attended, from Bangladesh, China, the Gambia, India, Indonesia, Laos, Malaysia, Nepal, Philippines, Thailand and Viet Nam.

7.3.13

IARC Technical Transfer Awards

Two promising participants at the cancer epidemiology course held in Abidjan in 1998 were selected to receive further training at IARC. Dr Ghislain Sangwa Lugoma from the Faculty of Medicine, University Clinics of Kinshasa, Democratic Republic of Congo, worked with the Unit of Field and Intervention Studies and Dr N'Famoussa Diane from the Centre National d'Anatomie Pathologique, University of Conakry, Guinea worked with the Unit of Epidemiology for Cancer Prevention. The third awardee, Dr Hector Posso, of the Division of Epidemiology, Instituto Nacional de Cancer, Santafé

de Bogotá, Colombia. was selected during the course on cancer control and prevention in Costa Rica.

7.3.14

IARC textbook on cancer epidemiology

The textbook *Cancer Epidemiology: Principles and Methods* is now available in English and Spanish and the French edition is close to publication. It has been used with great success in IARC courses and the English edition is the best-seller of the IARC publications programme in 1999, with 1175 copies sold by IARCPress in 10 months.

PART 8. SCIENTIFIC SUPPORT ACTIVITIES

8.1 Computing support service

M. Smans, P. Damiecki and B. Kajo

Since the installation of a greatly enhanced configuration at the end of the last biennium, use of the new facilities has steadily grown. This is true for the scientific storage server as well as for more general use of file servers in the office automation area. Much effort has been expended on helping users to replace obsolete equipment and to make good use of network resources.

The improvement of the LAN capacity has permitted the onset of workgroup type networking, several units having studied the possible advantages of dedicated servers in their area. Technical expertise is provided to facilitate the installation of such servers as well as user training, when necessary, to manage part or all of these new resources. This trend is likely to continue and further improvements of the LAN capacity will be made to allow this to happen.

Communication has become a major application of computer systems. E-mail is now so widely and intensively used that improvements to this facility are being planned, in order to enhance its total capacity and to install modern features. Dedicated web servers are now running in various units, adding to the existing and increasing traffic on the official IARC site. The speed of our link was increased from 64 to 128 kbps, and a second link has been installed on a test basis.

8.2 Library and information services

H. Miido, M. Coudert and L. Ossetian

The IARC library works closely with the Computing Support Service to identify and implement technological advances which improve and simplify user access to library applications. The library home pages, accessible through intranet, allow library users to select library services from a single menu. Each service has a standard format, and is easy to use, thus eliminating the need for library users to learn complicated database formats and languages. Interfaces have been built to search library databases, such as the library catalogue, or to interact with commercial software such as FileMakerPro, Reference Manager and Current Contents.

Library services available through the intranet include the ability to search books through Boolean logic combinations of a number of fields, e.g., author, title, year, keyword, series etc.; browse the latest Library Bulletin and order reprints of staff publications; browse the journal holdings; search Medline through the US National Library of Medicine web browser; search Current Contents; order reprints of articles not in the IARC library; search journals online; and e-mail to the library any requests or comments. Enhancements under development include the ability to search World Health Organization documents and annual reports held by the library and access Reference Manager databases.

Although accessing library services has evolved over time, the basic tasks of the

library remain the same: ordering, processing and maintaining books; subscribing to journals; maintaining in-house databases; and processing interlibrary loans. These tasks, formerly performed on the VAX computer, have been transferred to the library Windows NT server. Medline records previously accessed through CD-ROMs, are now searchable through the Internet. The identification of on-line journals has become an important feature of the Library home pages, and the library staff spend increasing amounts of time searching the Internet for information.

Accessing library services through the network has undoubtedly become easier for the library user. However, this has required increasing computer-literacy on the part of the library staff. Educating library users and disseminating information continue to play an important role in the library activities. Library staff present papers at meetings, take part in discussion groups concerning the future of libraries and publish results of unique systems and procedures developed at IARC.

8.3 Common laboratory services

8.3.1 Animal house

Z.-Q. Wang, C. Witt, D. Galendo and M.-P. Cros

The animal house provides technical support for the various tumorigenesis studies of IARC. This animal facility is free of specific pathogens and now maintains about 50 strains of mice. Breeding stock and experimental animals are maintained and some strains of animals are bought from commercial suppliers for specific experiments.

The technical staff of the animal house perform and assist in a variety of procedures for research projects, such as chemical carcinogenesis, tumour implantation, hepatectomy, vasectomy and administration of chemical substances by various routes, e.g. intravenous, intraperitoneal and subcutaneous, as well as painting and gavage. All manipulations are carried out according to the specific IARC guidelines for manipulation of animals.

Transgenic and knock-out mice have become powerful tools for the study of tumour biology, since genetically modified animals provide a unique system to study interactions of specific environmental insults and genetic information in mammals. In addition, these mutant mice are also indispensable models for studying the functions of newly-identified genes that control cancer susceptibility. The animal house has already hosted 35 strains of transgenic and knock-out mice that were either imported through scientific collaborations or generated by the Unit of Gene–Environment Interactions.

During this biennium, the instrumentation and facilities in the animal house have been upgraded to comply with the European Union's guidelines. The animal house is continuing to keep full experimental records of all studies performed in the facility, in accordance with good laboratory practice.

The animals are used by all of the laboratory-based research units and programmes of IARC.

8.3.2 Histopathology laboratory

H. Ohgaki, M. Laval and N. Lyandrat

The histology laboratory processes all histological materials from experimental animals in the Agency, as well as biopsy material sent by Agency researchers carrying out field work abroad.

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE THIRTY-NINTH SESSION OF THE IARC GOVERNING COUNCIL

7–8 May 1998

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Annex 2

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Annex 3

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Assistant (Documents)	Ms M.-H. CHARRIER
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Unit of Environmental Cancer Epidemiology

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Visiting scientists	Dr I. BRAY, IARC Postdoctoral Fellowship (15.10.98–14.10.99) Dr J. KORTE, IARC Postdoctoral Fellowship (from 11.12.99) Dr N. MALATS, Special Training Award (until 28.2.98) Dr F. NYBERG, Special Training Award (19.10.98–18.10.99) Dr A. PITARD, Special Training Award (from 4.10.99) Dr E. RAPITI, Special Training Award (until 28.2.98) Dr D. SALI, Special Training Award (until 4.11.98, half-time) Dr E. WARD, sabbatical (3.8.98–27.8.99)
Assistants (statistics)	Mr D. COLIN Mr G. FERRO
Data clerk	Ms V. GABORIEAU
Equipment operator	Ms M. GARRONI (part-time)
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Secretary	Ms M. GEESINK

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Medical consultant	Dr R. SARACCI
Scientists	Dr R. KAAKS
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Laboratory technicians	Mr D. ACHAINTRE Ms B. VOZAR
Coordination Aid	Ms J. DEHEDIN (from 17.8.98)
Clerks	Ms C. BIESSY (from 8.3.99) Ms S. DAVID (from 26.4.99) Mr M. MIGINIAC (until 4.5.98) Mr J. VIGNAT (from 2.11.98)
Assistants (Statistics)	Ms C. CASAGRANDE Mr B. HEMON
Students	Dr V. CHAJÈS (until 31.1.98) Ms M. ELAHI (until 30.11.98 and from 1.3.99) Ms K. HULTÉN (9.2.98–31.1.99) Ms T. NORAT (until 31.1.98)
Secretary	Ms S. SOMERVILLE

Unit of Field and Intervention Studies

Chief	Dr N. MUÑOZ
Scientist	Dr R. HERRERO
Visiting scientists	Dr S. KLUG, Special Training Award (30.3.98–24.4.98 and 1.3–31.7.99) Dr E. LAZCANO, Special Training Award (from 16.6.99)

	Dr R. ORTIZ, Special Training Award (from 16.10.99) Dr G. SANGWA LUGOMA, IARC Technical Transfer Award (6.1.98–3.4.98)
Statistician	Mr M. PLUMMER
Assistant (Courses)	Ms M. DAVIS
Assistants (Statistics)	Ms A. ARSLAN Ms C. LAVE
Laboratory technician	Mr F. ODEFREY (from 1.9.98)
Student	Ms J.S. SMITH, grant from 3M Pharmaceuticals and Chateaubriand fellowship
Secretary	Ms H. LORENZEN

Unit of Descriptive Epidemiology

Chief	Dr D.M. PARKIN
Scientists	Dr E. KRAMAROVA Dr P. PISANI Dr R. SANKARANARAYANAN Dr A. VIZCAINO (until 30.11.99)
Visiting scientists	Dr F. BRAY, Special Training Award (1.3–30.5.98 and from 1.10.98) Dr E. CHIRPAZ (2.11.98–1.5.99) Dr H. GARCIA-GIANNOLI, Special Training Award (part-time) (1.8.98–30.6.99) Professor C. IJSSELMUIDEN, IARC Visiting Scientist Award (7.1.98–6.1.99) Dr P. PINHEIRO, Special Training Award (28.8–30.11.99) Dr J. SMITH (5.10.98–4.2.99) Dr D. YZÈBE (4.5–30.10.98)
Assistant (Statistics)	Ms M.T. VALDIVIESO GONZALES
Equipment operator	Ms K. PITAKSARINGKARN (from 1.7.98)
Technical officers	Ms A. BAUTISTA (Manila) (from 1.2.98) Ms S. WHELAN Ms R. WINKELMANN (until 7.9.99)
Informatics officer	Mr J. FERLAY
Assistants (Statistics)	Mr A. COOKE Mr E. MASUYER
Technical assistants	Ms E. DEMARET Mr E. LUCAS (from 19.11.99)

Students	Ms S. DHAL, Special Training Award (1.4–7.8.98) Ms M. HASHIBE, Special Training Award (1.7–30.9.98) Mr N. MITTON, Special Training Award (1.3–30.6.98) Ms E. SANTANA, Special Training Award (half-time) (from 1.4.99) Mr B. TOHOUNDJONA, Special Training Award (1.4.98–31.3.99)
Secretaries	Ms E. BAYLE Ms O. BOUVY Ms B. GEOFFRE
Clerks	Ms I. EMERY Ms F. PETIT (half-time) (until 30.3.98)

Gambia Hepatitis Intervention Study

Coordinator	Mr E. BAH
Research assistant	Ms M. MENDY
Visiting scientists	Dr G. KIRK (until 15.5.99) Dr O. LESI (from 24.8.99)

Unit of Genetic Epidemiology

Chief (also Responsible Officer, Fellowships, from 1.7.99)	Dr D. GOLDGAR
Scientist	Dr C. SZABO (15.7– 30.11.98 and 7.1.99–6.12.99)
Visiting scientists	Dr M. BADZIOCH, Special Training Award (until 10.7.99) Dr P. PATMASIRIWAT, WHO fellowship (1.2–10.6.99) Dr P. RUIZ FLORES (12.5–12.8.99) Dr S. SAXENA, UICC fellowship (20.7–15.11.98) Dr F. VOGL, Special Training Award (from 1.9.99) Dr X.-C. ZHI, Special Training Award (25.6–24.11.98)
Student	Mr A. SIBERT (until 6.10.98)
Laboratory technician	Ms C. AUDOYNAUD-COUR (until 27.2.98, from 30.3.98 until 14.5.99 and from 15.9.99)
Assistant (Statistics)	Ms H. RENARD
Technical assistant	Ms C. BONNARDEL
Secretary	Ms Y. GRANJARD (half-time)
Clerk (Statistics)	Mr O. YAQOUBI (from 4.1.99 until 3.12.99)

Unit of Endogenous Cancer Risk Factors

Chief	Dr H. OHSHIMA
Scientists	Dr F. BIANCHINI-KAAKS Dr C. MALAVEILLE Dr B. PIGNATELLI
Visiting scientists	Dr B. AHN, Korean Science and Engineering Foundation Fellowship (until 19.10.98) Dr G. BELLEC, Fellowship from Institut Danone (30.3–18.9.98) Dr C.-Q. LI, IARC Research Training Fellowship and Special Training Award Dr M. MASUDA, Sabbatical leave from the Kyoto Prefectural University of Medicine (from 1.9.98) Professor M. MOWER, sabbatical leave from the University of Hawaii (15.1–1.7.98 and 2.6–30.7.99)
Laboratory research assistant	Ms I. GILIBERT
Laboratory technician	Ms A. HAUTEFEUILLE
Students	Mr S. AURIOL, Special Training Award (until 27.3.98) Ms I. CELAN, Special Training Award (27.4–24.7.98; 9.11.98–28.2.99; 1.4–31.7.99) Ms L. CHAZOTTE-AUBERT, Special Training Award Mr B. DUROUX, Special Training Award (5.1–31.7.98) Ms A. ELLUL-TILLOY, Special Training Award (until 31.10.98)
Secretary	Ms P. COLLARD

Unit of Gene–Environment Interactions

Chief	Dr Z.-Q. WANG
Scientists	Dr A. BARBIN Dr M. CASTEGNARO Dr M. FRIESEN (on sabbatical leave until 9.9.98) Dr Z. HERCEG
Visiting scientists	Dr F. CALEVRO, Special Training Award (1.2–1.11.99) Dr V. DUMON, European Commission, Special Training Award (from 9.3.98) Dr W. HULLA, Special Training Award (until 31.8.98 and 1.2–31.7.99) Dr P. JACKSON, Association for International Cancer Research, Special Training Award (tenable at the Johns Hopkins University, Baltimore, MD, USA, until 30.9.98) Dr M. LLEONART, National Institute of Environmental Health Sciences/Johns Hopkins University, Special Training Award (from 9.11.98) Dr G.B. SAJITHLAL, Swiss Government, Special Training Award (from 18.5.99) Dr W.-M. TONG, Association for International Cancer Research, Special Training Award

Laboratory research assistants	Ms G. BRUN Ms L. GARREN
Laboratory technicians	Ms B. CHAPOT Ms J. MICHELON
Students	Ms O. BRUNAUD (4.5–14.8.98) Mr B. CHAFFARD (1.4–31.7.99) Mr U. CORTES (from 20.7.99) Mr C. MARTIRE (1.4–22.7.98) Ms V. PETRILLI (from 1.9.99) Ms A. RADDA (7.12.98–28.2.99)
Secretaries	Ms A.M. MAILLOL Ms Z. SCHNEIDER (half-time) (until 30.11.99)

Animal House

Veterinary adviser	Dr C. WITT
Laboratory research assistant	Ms D. GALENDO
Laboratory technicians	Mr J. CARDIA-LIMA Ms M.-P. CROS Mr R. DRAY Mr J. GARCIA

Unit of Mechanisms of Carcinogenesis

Chief (also Responsible Officer, Fellowships, until 30.6.99)	Dr R. MONTESANO (until 30.10.99)
Scientists	Dr P. HAINAUT Dr J. HALL Dr H. NAKAZAWA (until 30.9.98)
Visiting scientists	Dr C. BARNAS (until 2.11.98) Dr S. BOIVIN-ANGELE, Special Training Award Dr K. CASTREN, IARC Research Fellowship (until 2.11.98) Dr K. MANN, sabbatical leave (from 1.10.99) Dr D. MAURICI, Special Training Award (from 17.1.98 Dr S. NORTH-CHASSANDE, Fellowship from the Ligue Nationale Contre le Cancer and Special Training Award Dr D. PEIXOTO-GUIMARAES (from 4.6.98) Dr I. PERSSON, Fellowship from INSERM/MFR and Special Training Award (from 8.5.98) Dr S. PORNTOSAPON, Special Training Award (30.9.98–29.3.99) Dr A. SEPEHR (from 12.2.99) Dr P. TANIÈRE, Detachment from the Edouard-Herriot Hospital and UMR 5641, CNRS
Laboratory research assistants	Ms G. MARTEL-PLANCHE Ms A.-M. RANDON Ms M. VUILLAUME

Students	Ms S. COURTOIS (from 14.9.98) Ms T. HERNANDEZ-BOUSSARD, Special Training Award (until 29.1.99) Ms M. KALLASSY, Special Training Award (until 31.3.98) Ms C. MÉPLAN, Fellowships from the Ligue Nationale Contre le Cancer and Volvic and Special Training Award Mr. O. PLUQUET (until 30.6.98 and from 18.1.99) Ms S. SEEMANN (from 1.9.99)
Assistant (Fellowships)	Ms E. EL-AKROUD
Secretary	Ms M.WRISEZ

Unit of Genetic Cancer Susceptibility

Chief	Dr G. ROMEO
Scientists	Dr F. CANZIAN Dr B. SYLLA Dr L. YIN
Visiting scientists	Dr R. CORVI, Special Training Award Dr M.R. DE MIGLIO, fellowship from the Associazione Italiana per la Ricerca sur Cancro (until 20.10.98) Dr E. GORMALLY, Special Training Award (from 12.7.99) Dr M. STARK, fellowship from DAAD and Special Training Award (until 30.11.98)
Students	Mr D. COX, Special Training Award (from 24.9.98) Mr S. DEUTSCH, Special Training Award (24.9.98–30.10.99) Ms V. FERRAND, Special Training Award (from 20.4.98) Mr F. HEITZMANN (until 1.5.98) Mr F. HUMBERT, Special Training Award (until 30.9.98) Ms K. ILC, Special Training Award (until 4.1.99) Ms C. JOST, Special Training Award (from 15.2.99) Mr C. LAFAYE, Special Training Award (14.7.99) Ms F. LESUEUR, Special Training Award Ms J. LIANG, Special Training Award (from 1.11.98) Dr M. MARTINEZ-ALFARO, fellowship from Société Française d'Exportation des Ressources Educatives and Special Training Award (from 7.10.98) Mr J. McKAY, fellowship from Royal Hobart Hospital and Special Training Award (from 15.2.99)
Laboratory research assistant	Ms M. F. LAVOUE
Laboratory technicians	Mr C. LAFAYE (15.7.98–24.12.99) Ms S. PAULY Ms T. TOCCO
Secretary	Ms A. TROCHARD

Unit of Viral and Hereditary Factors in Carcinogenesis

Head	Dr G. LENOIR (joint appointment with the Université de Lyon)
Visiting scientists	Dr S. MAZOYER, Special Training Award and INSERM Scientist (until 30.4.98) Dr O. SEROVA-SINILNIKOVA, Postdoctoral Fellow and Scientist from Hospices Civils de Lyon Dr I. WANG-SONG, IARC Consultant Fellowship (until 15.12.98) Dr R. WILMOTTE, Postdoctoral Fellow, Special Training Award (until 20.10.99)
Students	Ms E. BIOT, Hospices Civils de Lyon (until 2.5.98) Ms S. CHOPIN, Special Training Award (from 2.3.98) Ms S. GINOLHAC, Hospices Civils de Lyon (until 30.4.98) Ms S. PICOT, Hospices Civils de Lyon (until 13.5.98) Ms N. PUGET, Fellow from the Comité Départemental de Haute Savoie, Ligue Nationale contre le Cancer and Special Training Award (until 31.9.99)

Unit of Molecular Pathology

Chief	Dr H. OHGAKI
Visiting scientists	Dr S. COLELLA, IARC Research Training Fellowship and Special Training Award (from 2.11.98) Dr H. FUJISAWA, grant from Kanazawa University and Special Training Award (until 30.6.99) Dr M. FUKUDA (until 24.9.98) Dr H. HUANG, Special Training Award Dr M.B. MAHLER ARAUJO (15.9.98–15.12 98) Dr J. MASUOKA, IARC postdoctoral fellowship (from 1.10.99) Dr M. NAKAMURA, Nara Medical University grant (from 1.9.98) Dr A. PERAUD, grant from Gertrud-Reemstra-Stiftung (until 28.2.98) Dr A. SANKILA, grant from the Academy of Finland (from 18.1.98) Dr T. WATANABE, grant from Nihon University, Japan (from 27.9.99) Dr F. YANG, Special Training Award (1.12.98–30.11.99)
Laboratory research assistant	Mr J.-C. BEREZIAT (until 30.6.99)
Students	Ms Y. DAIKH (15.7.98–18.8.99) Ms G. REGUER (10.5–12.10.99) Mr R. REIS (from 5.1.98)
Secretary	Ms A. RIVOIRE

Histopathology Laboratory

Laboratory research assistant	Ms M. LAVAL
Laboratory technician	Ms N. LYANDRAT

Unit of Multistage Carcinogenesis

Chief	Dr H. YAMASAKI
Scientists	Dr V. KRUTOVSKIKH Dr M. MESNIL (until 31.12.99) Dr N. MIRONOV Dr Y. OMORI (until 31.12.99)
Visiting scientists	Dr P.-P. BRINGUIER, on secondment from Université Claude Bernard, Lyon Dr L. GIROLDI, Special Training Award Dr F.-J. HERNANDEZ-BLASQUEZ, FAPESP Fellowship Dr L. JANSEN, IARC Research Training Fellow (until 26.6.98) Dr K. KAWASAKI, Special Training Award (until 2.9.99) Ms J. LONCAREK, Special Training Award (from 2.6.99) Dr T. SUZUKI, Fellowship from Japanese Ministry of Technology (until 31.7.98) Dr T. TANAKA, Japanese Fellowship (until 31.8.99) Dr Q.-F. XIONG, Special Training Award (from 10.3.99) Dr K. YAMAKAGE, Special Training Award (until 30.4.98) Dr T. YANO, Japanese Fellowship Dr M.-L. ZAIDAN-DAGLI, FAPESP Fellowship Dr W.-B. ZHU, Special Training Award (until 30.4.98)
Laboratory research assistants	Ms A.-M. AGUELON-PEGOURIES Ms N. MARTEL Ms C. PICCOLI
Student	Ms G. REGUER, Special Training Award (until 9.5.99)
Secretary	Ms C. DECHAUX
Laboratory aides	Ms M. ESSERTEL Ms N. FARINA Ms M. MARANHAO Ms G. TCHOUA (from 1.6.98) (half-time) Ms S. VEYRE (until 30.4.98)

Unit of Carcinogen Identification and Evaluation

Chief	Dr J. RICE
Scientists	Dr R. BAAN (from 1.10.98) Dr M. BLETTNER (until 5.3.99) Dr Y. GROSSE (from 2.6.98) Dr D. McGREGOR Mr J. WILBOURN
Technical Officers	Ms C. GENEVOIS (9.3.98–12.3.99) Ms C. PARTENSKY

Technical Assistants	Ms D. MIETTON Ms J. MITCHELL
Secretary	Ms S. REYNAUD
Clerks	Ms S. EGRAZ Ms M. LEZERE

Unit of Chemoprevention

Chief	Dr H. VAINIO
Scientist (Acting Chief)	Dr A. MILLER (1.9.98–31.8.99)
Visiting scientist	Dr P. NETTESHEIM (1.4–30.9.99)
Technical assistant	Ms A. MENEGHEL
Secretary	Ms J. THEVENOUX

Unit of Radiation and Cancer

Chief	Dr E. CARDIS
Scientists	Dr A. KESMINIENE (from 24.8.98) Dr M. MARTUZZI (until 12.6.98)
Visiting scientist	Dr D. RICHARDSON (from 27.9.99)
Clerks (Statistics)	Ms E. AMOROS Ms A. MONNET (from 1.9.99)
Students	Ms M. KILKENNY, Special Training Award Ms V. TENET, Special Training Award (from 26.5.99) Ms I. THIERRY-CHEF, Special Training Award
Secretaries	Ms B. ANDRIEUX (half-time) Ms O. DRUTEL (half-time)

Unit of Epidemiology for Cancer Prevention

Chief	Dr A.J. SASCO (from INSERM, on special assignment to IARC)
Visiting scientists	Dr R. AH-SONG, Special Training Award (until 31.12.98) Dr L. LAFOREST, Special Training Award (from 13.12.99) Dr G. LE MAB, Special Training Award (8.2.99–31.8.99) Dr B. RACHET, Special Training Award (until 30.6.99)
Students	Ms F. CARRIOT, Public health intern (from 1.11.99) Ms C. COURIS, Special Training Award and fellowship from the Ligue Nationale contre le Cancer (25.5.98–31.8.99) Ms D. D'HARCOURT, Special Training Award (from 1.4.98) Mr C. DUSSART, Ecole Nationale de Santé des Armées (until 1.9.98)

	Ms I. GENDRE, Special Training Award (until 31.12.98) Ms A. JUGE, Université Claude Bernard Lyon I (2.2–4.9.98) Ms M. MARSOT, Special Training Award Ms A. VAN ROSMALEN, University of Maastricht (1.3–31.8.99)
Secretary	Ms M. RENAUD
Clerk	Ms V. BENHAIM-LUZON

Editorial and Publications Service

Technical officer	Ms C. GOLDGAR (until 14.3.98)
Assistant, publications	Mr C. MARKWOOD (from 1.5.98 until 17.8.99)
Assistant (IARC Press)	Ms S. COTTERELL
Secretaries	Ms M. MAINAUD Ms E. PEREZ (half-time)
Laboratory research assistant (Photography)	Mr G. MOLLON
Trainees	Mr J. CROIBIER Ms S. MOULIN (12.5.98–11.5.99) Ms S. LEE (from 1.12.99)

Library

Librarian	Ms H. MIIDO
Technical assistant (search analyst)	Ms M. COUDERT
Assistant (Library)	Ms L. OSSETIAN

Division of Administration and Finance

Director	Mr M.P. JOHNSON (until 31.10.99)
Administrative assistant	Ms D. MARCOU

Translation

Translator	Dr N. GAUDIN
Secretary	Ms A.-C. MORET

Personnel

Personnel officer	Ms A. ESCOFFIER
Clerk	Ms C. MOGENET
Social adviser	Ms M.A. VIOT-COSTER

Budget and Finance

Finance officer	Mr A. MITRA

Administrative assistants	Mr C. AUGROS Ms W. FEVRE-HLAHOLUK
Assistant (Accounting)	Ms M. HERIN
Assistant (Payments)	Ms F. ROMAGNAN
Clerk (Cashier)	Mr D. HORNEZ
Clerk (Accounts)	Ms D. LOMBARDO
Clerks (Finance)	Ms F. FLORENTIN (half-time) Ms A. SEGURET (half-time)
Special trainee award	Mr E. ZEGWARD (from 9.11.98)

Computing Services Group

Head/Computer systems manager	Mr M. SMANS
Computer analyst/System manager	Mr P. DAMIECKI
Computer operator	Ms B. KAJO (half-time)
Trainee	Mr P. VAN DER HAGEN (29.6.98–15.8.99)

Administrative Services

Administrative services officer	Mr G. GUILLERMINET
Administrative assistant	Ms R. ALLOIN
Clerk	Ms M. MARSAL-LEPETIT
Switchboard operator	Ms R. KIBRISLIYAN
Driver	Mr J.-F. DURAND-GRATIAN
Usher (Messenger)	Mr M. JAVIN
Maintenance technicians	Mr M. BARBIEUX Mr M. BAZIN Mr J.-P. BONNEFOND Mr G. THOLLY
Assistant (Registry)	Ms M. GREENLAND
Clerk (Registry)	Ms L. VIGIER
Assistant (Supplies)	Ms J. POPOFF
Clerks (Supplies)	Ms M. ONGARO Mr L. RIPERT (1.12.98–3.9.99)
Trainee	Mr F. ROUSSET (from 9.11.98)
Equipment operator (Reproduction)	Mr D. GRAIZELY (until 17.6.99)

Annex 4

SHORT-TERM VISITING SCIENTISTS AND TRAINEES

Visitors

Dr B. Ahn, Unit of Endogenous Cancer Risk Factors (21 December 1998–5 February 1999)
Dr C.T.T. Anh, Unit of Descriptive Epidemiology (5–20 August 1999)
Dr P. Amati, Unit of Genetic Cancer Susceptibility (23 February–6 March 1998)
Dr M. Badiali, Unit of Genetic Cancer Susceptibility (28 September–20 November 1998)
Mr E. Bah, Unit of Descriptive Epidemiology (14–19 June 1999)
Dr E. Bakhanova, Unit of Radiation and Cancer (11–22 October 1999)
Dr B. Bancel, Unit of Endogenous Cancer Risk Factors (from 19 October 1999) (part-time)
Ms L.T. Banda, Unit of Descriptive Epidemiology (19 September–2 October 1999)
Dr A. Bergström, Unit of Descriptive Epidemiology (8–15 February 1998)
Dr G. Berke, Unit of Multistage Carcinogenesis, ICRETT fellowship (15 March–10 April 1999)
Dr Y. Bhurgri, Unit of Descriptive Epidemiology (10 January–14 February 1999)
Dr D. Bonneau, Unit of Genetic Cancer Susceptibility (23–27 February 1998)
Mr E. Chokunonga, Unit of Descriptive Epidemiology (14–27 September 1998)
Dr A. Cook, Unit of Radiation and Cancer (4–22 November 1999)
Dr J. Deddens, Unit of Radiation and Cancer and Unit of Environmental Cancer Epidemiology (7–11 December 1998; 15–24 March 1999)
Dr E. De Stefani, Unit of Environmental Cancer Epidemiology (10–16 September 1999)
Mr J. Doughty, Unit of Radiation and Cancer (14–18 November 1999)
Professor K.A. Echimane, Unit of Descriptive Epidemiology (2–11 June 1999)
Dr U. Egeli, Unit of Genetic Epidemiology and Unit of Viral and Hereditary Factors in Carcinogenesis (15 June–15 August 1998)
Dr S.Y. Eser, Unit of Descriptive Epidemiology, ENCR Fellowship (23 May–5 June 1999)
Dr L. Fernandez, Unit of Field and Intervention Studies (3–7 May 1999)
Dr T. Fletcher, Unit of Environmental Cancer Epidemiology (2–27 November 1999 and 13–21 December 1999)
Dr C.K. Gajalakshmi, Unit of Environmental Cancer Epidemiology (23–29 July 1998)
Dr M. García-Gómez, Unit of Environmental Cancer Epidemiology (30 August–10 September 1999)
Dr M. Goldman, Unit of Field and Intervention Studies (8 June–18 July 1998)
Dr D. Gupta, Unit of Environmental Cancer Epidemiology, UICC/ICRETT Fellowship (22 May–20 June 1998)
Dr H.R. Harach, Unit of Genetic Cancer Susceptibility (23–28 June 1998)
Dr S. Illychov, Unit of Radiation and Cancer (11–22 October 1999)
Dr J. Iscovich, Unit of Environmental Cancer Epidemiology (5–16 January 1998)
Dr S. Jamieson, Unit of Multistage Carcinogenesis, NOVARTIS Foundation fellowship (1 October–18 December 1998)
Professor V. Janout, Unit of Environmental Cancer Epidemiology (7–17 September 1998)
Dr K. Jong, Unit of Radiation and Cancer (26 April–15 May 1999)
Dr K. Kjaerheim, Unit of Environmental Cancer Epidemiology (21–28 September 1998, 20–25 November 1999)
Dr S.-J. Klug, Unit of Carcinogen Identification and Evaluation (3 August–11 September 1998)
Dr A. Konogorov, Unit of Radiation and Cancer (2–11 March 1998)
Dr V. Krjuchkov, Unit of Radiation and Cancer (11–22 October 1999)
Dr B. Kuruvila, Unit of Descriptive Epidemiology (27 September–27 October 1998)

Dr I. Malakhova, Unit of Radiation and Cancer (2–11 March 1998)
Dr J. Manjer, Unit of Nutrition and Cancer (26 October–16 December 1998)
Dr N. Martin, Unit of Descriptive Epidemiology (23–28 September 1999)
Dr B. Mathew, Unit of Descriptive Epidemiology (22–28 October 1998)
Dr E. Matos, Unit of Field and Intervention Studies (22–26 February 1999)
Dr P. Medhipour, Unit of Genetic Epidemiology (13–27 January 1998)
Dr K. Meguenni, Unit of Descriptive Epidemiology (30 January–28 February 1999)
Dr H. Møller, Unit of Environmental Cancer Epidemiology (10–28 May 1999)
Dr C. Murta, Unit of Field and Intervention Studies (20 June–31 August 1999)
Ms S. Nambooze, Unit of Descriptive Epidemiology (14 September–9 October 1998)
Dr R. Ortiz, Unit of Field and Intervention Studies (11–31 January 1999)
Dr M.A. Pajel-Calilung, Unit of Descriptive Epidemiology (25–30 October 1998)
Dr T. Partanen, Unit of Environmental Cancer Epidemiology (17 October–16 November 1999)
Dr F. Pellegrini, Unit of Nutrition and Cancer, "Mario Negri" fellowship (from 11 October 1999)
Dr M. Peluso, Unit of Endogenous Cancer Risk Factors (22–26 June 1998)
Dr N.M. Quoc, Unit of Descriptive Epidemiology (18–31 January 1999)
Dr R. Rajkumar, Unit of Descriptive Epidemiology (21 June–11 July 1999)
Dr J.W. Sellors, Unit of Descriptive Epidemiology (5 September–5 October 1998)
Dr J. Siemiatycki, Unit of Environmental Cancer Epidemiology (25 February–6 March 1998)
Dr L. Simonato, Unit of Environmental Cancer Epidemiology (several short-term visits)
Ms S. Sriamporn, Unit of Descriptive Epidemiology (25 June–13 July 1998, 19–30 March 1999, 16–28 September 1999)
Dr P. Stattin, Unit of Nutrition and Cancer (22 March–1 April 1999)
Dr N. Stavridou, Unit of Endogenous Cancer Risk Factors (15–19 March 1999)
Dr B.W. Stewart, Director's Office (29 November–10 December 1999)
Professor T. Suzuki, Unit of Endogenous Cancer Risk Factors (14–29 September 1998)
Mr S. Tsolis, Unit of Endogenous Cancer Risk Factors (15–19 March 1999)
Dr T. Tynes, Unit of Environmental Cancer Epidemiology, UICC/ICRETT Fellowship (12 January–27 February 1998)
Dr V. Vatanasapt, Unit of Descriptive Epidemiology (23–28 September 1999)
Dr H. Wabinga, Unit of Descriptive Epidemiology (12–18 June 1999)
Dr G. Wessels, Unit of Descriptive Epidemiology (8–12 June 1998)
Dr P. Wessman, Unit of Radiation and Cancer (2–12 November 1999)
Dr S. Wiangnon, Unit of Descriptive Epidemiology (23–28 September 1999)
Dr A. Woodward, Unit of Radiation and Cancer (26 April–7 May 1999)
Mr G. Wright, Unit of Carcinogen Identification and Evaluation (17–25 August 1999)
Ms P. Yuenyao, Unit of Descriptive Epidemiology (23–28 September 1999)

Trainees

Mr L. Alazay, Unit of Genetic Cancer Susceptibility (16 September–30 November 1999)
Mr D. Antos, Unit of Endogenous Cancer Risk Factors (1 September–15 September 1999)
Ms M.-C. Barioz, Unit of Multistage Carcinogenesis (9–16 September 1999)
Ms J. Bellon, Unit of Multistage Carcinogenesis (20 April–26 June 1998)
Ms J. Birraux, Unit of Gene-Environment Interactions (19 April–25 June 1999)
Ms A. Boisgontier, Unit of Mechanisms of Carcinogenesis (15 April–30 June 1998)
Ms B. Bonnevay, Unit of Epidemiology for Cancer Prevention (17 May–4 June 1999)
Ms D. Bourouba, Unit of Viral and Hereditary Factors in Carcinogenesis (14 September–12 October 1998)
Mr J. Butler, Unit of Environmental Cancer Epidemiology, Special Training Award (6 April–29 May 1998)
Ms M.-A. Cazalis, Unit of Mechanisms of Carcinogenesis (29 March–14 May 1999)

Ms S. Chaduiron, Unit of Multistage Carcinogenesis (19 April–25 June 1999)
Mr A. Cheng, Unit of Endogenous Cancer Risk Factors (26 October–4 December 1998)
Ms M. Cohen, Unit of Epidemiology for Cancer Prevention (25 May–23 August 1999)
Ms E. Courtois, Unit of Multistage Carcinogenesis (5–15 April 1999)
Mr O. Dauwalder, Unit of Epidemiology for Cancer Prevention (1–5 February 1999)
Mr B. Duroux, Unit of Gene–Environment Interactions, Animal House (3–31 August 1998)
Mr M. El Aouadi, Unit of Gene–Environment Interactions, Animal House (2 July–7 August 1998 and 26 July–23 August 1999)
Mr B. Fichot, Unit of Multistage Carcinogenesis (20 April–26 June 1998)
Ms M. Fournier, Unit of Epidemiology for Cancer Prevention (14 April–13 May 1998)
Ms N. Fournier, Unit of Viral and Hereditary Factors in Carcinogenesis (3 April–30 June 1999)
Mr S. Gabilly, Unit of Multistage Carcinogenesis (19 April–30 July 1999)
Mr F. Grapeloux, Unit of Genetic Cancer Susceptibility (30 March–7 May 1998)
Mr Y. Guy, Unit of Viral and Hereditary Factors in Carcinogenesis (8 July–8 September 1999)
Ms R. Habib, Unit of Radiation and Cancer (22 November–17 December 1999)
Ms M. Juban, Unit of Mechanisms of Carcinogenesis (1 June–10 July 1998)
Ms D. Kaczmarczyk, Unit of Epidemiology for Cancer Prevention (2–20 March 1998)
Ms L. Khellas, Unit of Epidemiology for Cancer Prevention (2–20 November 1998)
Ms M. Ku, Unit of Descriptive Epidemiology, Special Training Award (4 June–15 August 1998)
Ms M. Leelakriangsak, Unit of Mechanisms of Carcinogenesis, ICRETT fellowship (28 April–30 June 1998)
Mr T. Louat, Unit of Viral and Hereditary Factors in Carcinogenesis (1 February–30 July 1999)
Ms C. Maddock, Unit of Epidemiology for Cancer Prevention (15–19 March 1999)
Mr G. Maire, Unit of Mechanisms of Carcinogenesis (14 June–6 August 1999)
Mr L. Maritan, Unit of Gene–Environment Interactions (20 April–26 June 1998)
Mr C. Martire, Unit of Gene–Environment Interactions, Animal House, Special Training Award (23 July–28 August 1998)
Ms C. Medina, Unit of Gene–Environment Interactions (6 January–31 March 1998) (part-time)
Dr E. Menet, Unit of Genetic Cancer Susceptibility (17–21 May 1999)
Dr N'Famousa Diane, Technical Transfer Award, Unit of Epidemiology for Cancer Prevention (13–January–3 April 1998)
Ms M. Palmer, Unit of Environmental Cancer Epidemiology, Special Training Award (2 June–31 July 1998)
Ms S. Parikh, Unit of Environmental Cancer Epidemiology, Special Training Award (18 October–26 November 1999)
Ms G. Parnaud, Unit of Endogenous Cancer Risk Factors, Fellowship from the Ligue Nationale contre le Cancer du Gers (11 January–5 February 1999)
Ms A. Radda, Unit of Gene–Environment Interactions, Animal House, Special Training Award (5 July–4 September 1999)
Ms N. Raymond, Unit of Genetic Cancer Susceptibility (17–21 May 1999)
Mr L. Richiardi, Unit of Environmental Cancer Epidemiology (12–16 April 1999)
Ms S. Ritou, Unit of Endogenous Cancer Risk Factors (26 January–27 February 1998)
Mr G. Rodrigo, Unit of Mechanisms of Carcinogenesis (6 April–3 May 1999)
Ms S. Salonen, Unit of Descriptive Epidemiology (12–18 July 1999)
Mr J. Schaeffer, Unit of Multistage Carcinogenesis (19 April–25 June 1999)
Ms V.W. Setiawan, Unit of Descriptive Epidemiology, Special Training Award (1 July–24 September 1999)
Ms C.-J. Tsai, Unit of Descriptive Epidemiology, Special Training Award (1 July–23 September 1999)
Ms C. Verney, Unit of Mechanisms of Carcinogenesis (29 March–14 May 1999)
Ms A.C. Wong Te Fong, Unit of Mechanisms of Carcinogenesis (30 March–7 May 1998)

Annex 5

RESEARCH AGREEMENTS BETWEEN IARC AND VARIOUS INSTITUTIONS

1 January 1998–31 December 1999

Cancer registries

DEB/73/16	International Association of Cancer Registries (Provision of a secretariat and other supporting services)
DEP/87/01	Hanoi Cancer Institute, Hanoi, Viet Nam (Cancer Registry of Hanoi)
DEP/87/02	National Institute of Public Health, Bamako, Mali (Cancer Registry of Mali)
DEP/89/10	Department of Pathology, National University of Trujillo, Trujillo, Peru (Cancer Registry of Trujillo)
DEP/91/04	National Centre of Anatomo-Pathology, Faculty of Medicine, University of Conakry, Conakry, Guinea (Cancer Registry of Conakry)
DEP/92/16	Barshi Rural Cancer Registry, Ashwini Rural Cancer Research and Relief Society, Barshi, India (Barshi Rural Cancer Registry)
DEP/93/03	Zimbabwe Cancer Registry, Harare, Zimbabwe (Cancer Registry of Zimbabwe)
DEP/93/08	Comprehensive Cancer Centre North, Groningen, Netherlands (European Network of Cancer Registries: mini-fellowships programme)
DEP/94/12	Makerere University Medical School, Kampala, Uganda (Kampala Cancer Registry)
DEP/95/01	Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire (Etablissement d'un registre du cancer du sein de la population d'Abidjan)
DEP/95/06	Christian Fellowship Community Health Centre, Ambilikkai, Tamil Nadu, India (Computerization of the population-based cancer registry in Ambilikkai for monitoring of cancer control)
DEP/95/18	Centre Hospitalier et Universitaire de Brazzaville, Congo (Cancer Registry of Brazzaville)
DEP/96/20	National Cancer Committee, Queen Elisabeth Central Hospital, Blantyre, Malawi (Cancer registration for the city and district of Blantyre)
DEP/97/01	Chittaranjan National Cancer Institute, Calcutta, India (Establishment of a population-based cancer registry in Metropolitan Calcutta)
DEP/97/03	Faculté des Sciences de la Santé, Université de Niamey, Niger (Registre du cancer du Niger)
DEP/97/06	Comprehensive Cancer Centre, Limburg, Netherlands (Survey of European cancer registries)
DEP/98/03	Kilimanjaro Christian Medical Centre, Moshi, Tanzania (Cancer registration in Moshi and Hai districts of Kilimanjaro region)
DEP/98/05	Faculty of Medicine and Pharmacy, University of Aden, Aden, Yemen (Establishment of a population-based cancer registry in Aden)
DEP/98/06	University College Hospital, Department of Pathology, Ibadan, Nigeria (Cancer registration in Ibadan)

DEP/98/07 Hospital de Clinicas, Unidad de Oncologia, La Paz, Bolivia
(Cancer registration in La Paz)

DEP/98/08 Zimbabwe Cancer Registry, Department of Community Medicine, University of Zimbabwe, Harare, Zimbabwe
(Zimbabwe Cancer Registry)

DEP/98/11 Indian Cancer Society, Bombay, India
(Computerization of Bombay cancer registry incidence data, 1976–90)

DEP/99/01 Registro di Tumores, Buenos Aires, Argentina
(Cancer registry of southern Buenos Aires province)

DEP/99/05 Centre Syfed Ouagadougou, Ouagadougou, Burkino Faso
(Registre du Cancer d'Ouagadougou)

DEP/99/09 SEER Program, National Cancer Institute, Bethesda, USA
(International Classification of Diseases for Oncology – Draft Third Edition)

DEP/99/18 Cancer Institute, Faculty of Medicine, Tehran, Iran
(Development of cancer registration in Iran)

DEP/99/19 Faculty of Health Sciences, Moi University, Eldoret, Kenya
(Cancer registration for Uasin Gishu District of Kenya)

Incidence studies

DEP/96/04 Institute of Hematology, Minsk, Belarus
(European childhood leukaemia/lymphoma incidence study (ECLIS))

DEP/96/05 Department of Epidemiology and Cancer Control, National Oncological Centre, Sofia, Bulgaria
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/96/06 Czech National Cancer Registry, Brno, Czech Republic
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/96/07 Department of Pediatrics, National Institute of Child Health, Semmelweis Medical University, Budapest, Hungary
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/96/08 Latvian Cancer Registry, Riga, Latvia
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/96/09 Lithuanian Oncological Centre, Vilnius, Lithuania
(European childhood leukaemia/lymphoma incidence study (ECLIS))

DEP/96/10 Polish Cancer Registry, Maria-Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/96/11 Institute of Hygiene and Public Health, Bucharest, Romania
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/96/12 Research Institute of Pediatric Hematology, Moscow, Russian Federation
(European childhood leukaemia/lymphoma incidence study (ECLIS))

DEP/96/13 Cancer Research Institute, Bratislava, Slovak Republic
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/96/16 Cancer Registry of Slovenia, Institute of Oncology, Ljubljana, Slovenia
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/96/18 Estonian Cancer Registry, Institute of Experimental and Clinical Medicine, Tallinn, Estonia
(European childhood leukaemia/lymphoma incidence study (ECLIS))

DEP/96/19 Petrov Research Institute of Oncology, St Petersburg, Russian Federation
(European childhood leukaemia/lymphoma incidence study (ECLIS))

DEP/96/24 Kyyiv Institute of Haematology and Blood Transfusion, Kiev, Ukraine
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/97/05 Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden
(Cancer attributable to reproductive factors, obesity and physical exercise in the European Union)

DEP/97/08 Department of Community Medicine, University of Cambridge, Cambridge, UK
(Proportion of cancers attributable to genetic factors in European countries)

Studies of cancer survival

DEP/99/02 Indian Cancer Society, Bombay, India
(Stage-specific survival incident cancer cases in Mumbai)

DEP/99/03 Cancer Institute (WIA), Madras, India
(Stage-specific survival incidence cancer cases in Madras)

DEP/99/04 National Institute of Oncology and Radiobiology, Havana, Cuba
(Stage-specific survival incidence cancer cases in Cuba)

DEP/99/07 Cancer Unit, Faculty of Medicine, Khon Kaen, Thailand
(Stage-specific survival incident cancer cases for the years 1993–97 in Khon Kaen)

DEP/99/08 Department of Community, Occupational and Family Medicine, Faculty of Medicine, Singapore, Singapore
(Estimation of population-based survival rates for cancers in the Republic of Singapore)

DEP/99/17 Kampala Cancer Registry, Makerere University Medical School, Kampala, Uganda
(Estimation of population-based cancer survival in Kampala)

Studies on breast cancer

ECP/97/02 Krebsliga St Gallen-Appenzell Cancer Registry, St Gallen, Switzerland
(Case–control study of selected second cancers following breast cancer: influence of tamoxifen and other treatment modalities)

DEP/98/02 Rizal Cancer Registry, Manila, Philippines
(Breast cancer screening in the Philippines: long-term follow-up)

VHC/98/01 Hôpital Cantonal Universitaire de Genève, Genève, Suisse
(Evaluation de la contribution de *BRCA1* and *BRCA2* dans les agrégations familiales du cancer du sein. Rôle possible d'un troisième gène)

Studies on cervical cancer

DEP/95/05 Regional Cancer Centre, Trivandrum, Kerala, India
(Evaluation of unaided visual inspection, cervicoscopy and Pap smear in screening for cervical cancer)

DEP/95/22 Hanoi Cancer Registry, Hanoi Cancer Hospital, Viet Nam
(Prevalence of HPV infection)

FIS/96/01 Centro de Investigaciones en Cancer 'Maes-Heller' Lima, Peru
(Multicentric case–control study on cervical cancer)

FIS/96/02 Departamento de Medicina Preventiva, Faculdade de Medicina Preventiva, São Paulo, Brazil
(Follow-up study to evaluate the role of human papillomavirus in the causation of cervical neoplasia)

FIS/97/01 Institut National de Santé Publique, Algers, Algeria
(Etude cas–témoins multicentres sur le virus du papillome humain et le cancer du col utérin)

FIS/97/09 Instituto Nacional de Salud Publica, Cuernavaca, Morelos, Mexico
(Prevalence of HPV infection)

FIS/97/10 National Cancer Institute, Bangkok, Thailand
(Prevalence of HPV infection)

DEP/98/09 Chittaranjan National Cancer Institute, Calcutta, India
(Comparative inspection of acetic acid, cytology and HPV testing in the early detection of cervical precancers in Calcutta)

FIS/98/01 Children's Hospital and Regional Medical Center, Seattle, USA
(Investigation of herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of cervical cancer)

FIS/98/03 Instituto de Oncologia 'Angel H. Roffo', Buenos Aires, Argentina
(Prevalence of HPV infection)

FIS/98/04 Laboratory Centre for Disease Control, Winnipeg, Canada
(Investigation of *Chlamydia trachomatis* virus-2 as a human papillomavirus cofactor in the etiology of cervical cancer)

FIS/99/03 University of Ibadan, College of Medicine, Ibadan Nigeria
(Prevalence of HPV infection)

FIS/99/11 Department of Pathology, Free University Hospital, Amsterdam, The Netherlands
(Multicentric case–control study on the role of HPV in the etiology of cervical cancer)

DEP/99/11 Aswini Cancer Relief and Research Society, Tata Memorial Centre, Barshi, India
(Evaluation of comparative efficacy of visual inspection with acetic acid (VIA), cytology and HPV testing in cervical cancer prevention)

DEP/99/12 Tata Memorial Centre, Bombay, India
(Evaluation of comparative efficacy of visual inspection with acetic acid (VIA), cytology and HPV testing in cervical cancer prevention)

DEP/99/13 Christian Fellowship Community Health Centre, Ambillikai, India
(Evaluation of comparative efficacy of visual inspection with acetic acid (VIA), cytology and HPV testing in cervical cancer prevention)

DEP/99/14 Chittaranjan National Cancer Institute, Calcutta, India
(Evaluation of comparative efficacy of visual inspection with acetic acid (VIA), cytology and HPV testing in cervical cancer prevention)

DEP/99/15 Regional Cancer Centre, Trivandrum (Kerala), India
(Evaluation of comparative efficacy of visual inspection with acetic acid (VIA), cytology and HPV testing in cervical cancer prevention)

Studies on liver cancer

FIS/87/01 National Cancer Institute, Bangkok, Thailand
(Cohort study of HBsAg carriers in Bangkok)

GHIS/97/02 MRC Laboratories, Fajara, The Gambia
(Epidemiology of viral, environmental and genetic factors in hepatocellular carcinoma – a case–control study in The Gambia)

GHIS/97/03 University of Leeds, Molecular Epidemiology Unit, Leeds, UK
(Hepatocellular carcinoma – a case–control study in The Gambia, West Africa)

GHIS/98/01 MRC Laboratories, Fajara, The Gambia
(Gambia Hepatitis Intervention Study)

DEP/99/06 Qidong Liver Cancer Institute, Jiangsu, China
(Aflatoxin exposure and liver cancer in China)

DEP/99/16 Molecular Epidemiology Unit, Research School of Medicine, University of Leeds, Leeds, UK
(Aflatoxin exposure and liver cancer in China)

Studies on cancer of the gastrointestinal tract

FIS/90/12 Cancer Control Center, San Cristobal, Venezuela
(Etiology and prevention of stomach cancer in Venezuela)

FIS/93/02	Institute of Health Investigations, San José, Costa Rica (Aetiology and prevention of stomach cancer in Costa Rica)
FIS/93/04	First Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan (Serum pepsinogen levels and precancerous lesions of the stomach)
DEP/95/23	Hanoi Cancer Registry, Hanoi Cancer Hospital, Hanoi, Viet Nam (Accuracy of *Helicobacter pylori* antibody tests)
FIS/96/03	Department of Gastroenterology, Azienda Ospedaliera, S. Giovanni Battista di Torino, Turin, Italy (Serological assays on the association of Cag A-positive *H. pylori* with gastric cancer)
FIS/99/04	Instituto Nacional de Cancer, Bogota, Colombia (*Helicobacter pylori* prevalence survey)
FIS/99/06	School of Medicine, Department of Medicine, Harare, Zimbabwe (*Helicobacter pylori* prevalence survey)
FIS/99/07	Cancer Registry, La Paz, Bolivia (*Helicobacter pylori* prevalence survey)
FIS/99/08	National Institute of Public Health, Cuernavaca, Morelos, Mexico (*Helicobacter pylori* prevalence survey)
FIS/99/09	Laboratory of Research in Bacteriology, Faculty of Medicine, Belo Horizonte, Brazil (*Helicobacter pylori* prevalence survey)
FIS/99/10	Costa Rican Institute of Research and Teaching in Nutrition and Health, Tres Rios, Costa Rica (*Helicobacter pylori* prevalence survey)

Studies of brain tumours

RCA/98/05	Cancer Control Information Centre, NSW Cancer Council, Kings Cross, Australia (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/06	Deutsches Krebsforschungszentrum, Heidelberg, Germany (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/07	LRF Centre for Cancer Epidemiology, Leeds, UK (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/08	Orebro Medical Centre, Department of Oncology, Orebro, Sweden (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/09	Institut Armand Frappier, Laval les Rapides, Canada (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/10	Chain Sheba Medical Centre, Tel-Hashomer, Israel (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/11	Hôpital National Saint-Maurice, Saint Maurice, France (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/12	Institut de Médecine de Travail, Lyon, France (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/13	Wellington School of Medicine, University of Otago, Wellington, New Zealand (Feasibility study of the international collaborative case–control study of adult brain tumours)
RCA/98/14	Istituto Superiore di Sanita, Laboratorio di igiene ambientale, Rome, Italy (Feasibility study of the international collaborative case–control study of adult brain tumours)
MPA/99/01	Tehran University of Medical Sciences, Tehran, Iran (Genetic aspects of brain tumors in I.R. Iran)
MPA/99/02	Ludwig Boltzmann Institute of Clinical Neurobiology, Vienna, Austria (Genetic alterations in malignant gliomas)
MPA/99/03	Institut für Neuropathologie, Universitätsklinikum Essen, Essen, Germany (Genetic alterations in malignant gliomas)

RCA/99/01 University of Leeds, Paediatric Epidemiology Group, Leeds, UK
(Development of the CAPI system for the INTERPHONE study)

Studies of oral cancer

DEP/95/09 Regional Cancer Centre, Trivandrum, India
(Evaluation of chemoprevention of oral cancer)

DEP/95/10 Regional Cancer Centre, Trivandrum, India
(Oral cancer screening by mouth examination in Kerala)

FIS/95/03 Regional Cancer Centre, Trivandrum, India
(Multicentric case–control study on oral cancer and HPV)

FIS/95/04 Kidwai Memorial Institute of Oncology, Bangalore, India
(Multicentric case–control study on oral cancer and HPV)

FIS/95/07 Regional Cancer Centre, Madras, India
(Multicentric case–control study on oral cancer and HPV)

FIS/97/02 Cancer Center & M. Sklodowska Curie Institute, Warsaw, Poland
(Multicentric case–control study on oral cancer and HPV)

FIS/97/03 Istituto di Ricerca Farmacologica 'Mario Negri', Milan, Italy
(Multicentric case–control study on oral cancer and HPV)

FIS/97/04 Free University Hospital, Amsterdam, Netherlands
(Multicentric case–control study on oral cancer and HPV)

FIS/97/05 Universidad de Sevilla, Sevilla, Spain
(Multicentric case–control study on oral cancer and HPV)

FIS/97/06 Toombak Research Centre & Oral Cancer Campaign, Khartoum, Sudan
(Multicentric case–control study on oral cancer and HPV)

FIS/97/07 Gruppo Oncologico Clinico Cooperativo del Nord-Est, Aviano, Italy
(Multicentric case–control study on oral cancer and HPV)

FIS/97/08 Cancer Institute (W.I.A.), Chennai, Madras, India
(Multicentric case–control study on oral cancer and HPV)

DEP/98/10 Regional Cancer Center, Trivandrum, India
(Microsatellite instability in oral cancer in India)

FIS/98/02 Institut Català d'Oncologia, L'Hospitalet, Barcelona, Spain
(Multicentric case–control study on oral cancer and HPV)

FIS/98/05 Fundaçao Riograndense Universitaria de Gastroenterologia, Porto Alegre, Brazil
(*Helicobacter pylori* prevalence survey)

FIS/99/01 Deutsches Krebsforschungzentrum, Heidelberg, Germany
(Multicentric case–control study on oral cancer and HPV)

FIS/99/02 Cancer Registry of Granada, Granada, Spain
(Multicentric case–control study on oral cancer and HPV)

FIS/99/05 University of Belfast, Department of Epidemiology and Public Health, Belfast, UK
(Multicentric case–control study on oral cancer and HPV)

Studies of soft-tissue sarcomas and lymphomas

DEP/93/02 Oncology Center of Ho Chi Minh, Viet Nam
(Case–control studies of soft tissue sarcoma and non-Hodgkin's lymphoma in the south of Viet Nam)

DEP/93/06 The 10–80 Committee, Hanoi, Viet Nam
(Case–control studies on soft-tissue sarcoma and non-Hodgkin's lymphoma in Viet Nam: estimation of exposure index)

ECE/99/11 Institute of Occupational Health, Cagliari, Italy
(Multicentre case–control study of lymphoma)

ECE/99/12	German Cancer Research Centre, Division of Epidemiology, Heidelberg, Germany (Multicentre case–control study of lymphoma)
ECE/99/13	University College Dublin, Department of Public Health, Dublin, Ireland (Multicentre case–control study of lymphoma)
ECE/99/14	University of Turin, Unit of Cancer Epidemiology, Turin, Italy (Multicentre case–control study of lymphoma)
ECE/99/15	Oncology Institute, Barcelona, Spain (Multicentre case–control study of lymphoma)

Respiratory tract cancer

ECE/96/05	Dow Medical College, Karachi, Pakistan (Case–control study of environmental risk factors of lung cancer in Karachi)
ECE/99/01	London School of Hygiene and Tropical Medicine, Environmental Epidemiology Unit, London, UK (Genetic, infectious and lifestyle risk factors behind two increasing cancers in central Europe)
ECE/99/02	Akademisch Ziekenhuis, Department of Pathology, Amsterdam, Netherlands (Genetic, infectious and lifestyle risk factors behind two increasing cancers in central Europe)
ECE/99/03	Department of Occupational Health, Specialized State Health Institute, Banska Bystrica, Slovakia (Genetic, infectious and lifestyle risk factors behind two increasing cancers in central Europe)
ECE/99/04	Department of Occupational Health, Institute of Hygiene, Public Health, Health Services and Management, Bucharest, Romania (Genetic, infectious and lifestyle risk factors behind two increasing cancers in central Europe)
ECE/99/05	Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland (Genetic, infectious and lifestyle risk factors behind two increasing cancers in central Europe)
ECE/99/06	J. Fodor National Public health Centre, NIEH, Budapest, Hungary (Genetic, infectious and lifestyle risk factors behind two increasing cancers in central Europe)
ECE/99/07	Nofer Institute of Occupational Medicine, Lodz, Poland (Genetic, infectious and lifestyle risk factors behind two increasing cancers in central Europe)
ECE/99/08	Institute of Carcinogenesis, Moscow, Russian Federation (Genetic, infectious and lifestyle risk factors behind two increasing cancers in central Europe)
ECE/99/09	Institute of Oncology and Radiobiology, Havana, Cuba (Environmental factors of laryngeal cancer)
ECE/99/10	Institute of Tropical Medicine, University of São Paulo, São Paulo, Brazil (Environmental risk factors of laryngeal cancer in South American countries)

Other sites

DEP/96/02	Uganda Cancer Institute, Mulago Hospital, Kampala, Uganda (Epidemiology, morphology and virology of HIV-associated lymphomas in Uganda)
DEP/96/15	Laboratoire d'Immunologie Cellulaire et Tissulaire, URA-CNRS 625, Bobigny, France (Aspects morphologiques, immunologiques, virologiques et moléculaires génétiques des lymphomes associés avec le VIH en Ouganda)
DEP/98/01	Association Naturalia et Biologia, Paris, France (Etude sur les aspects morphologiques, immunologiques, virologiques et moléculaires génétiques des lymphomes associés avec le VIH en Ouganda)
NTR/98/05	Instituto de Oncologia y Radiobiologia, Havana, Cuba (Case–control study on prostate cancer in Cuba)
NTR/98/06	Institut de Recerca epidemiologia i Clinica, Mataro (Barcelona), Spain (Case–control study on prostate cancer in Cuba)

Studies on occupational cancer

AEP/93/33	Hospital Cancer Registry, Tata Memorial Hospital, Bombay, India (Case–control study on the associations between occupational exposure and neoplasms of the lung and the lymphatic and haematopoietic system)
AEP/94/09	Cancer Institute, Adyar, Madras, India (Case–control study on the associations between occupational exposure and neoplasms of the lung and the lymphatic and haematopoietic system)
ECE/96/06	Institute of Occupational Health, Solna, Sweden (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/08	Danish Cancer Society, Copenhagen, Denmark (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/09	Cancer Registry of Norway, Oslo, Norway (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/10	Institute of Occupational Medicine, Edinburgh, UK (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/11	Slovenian Cancer Registry, Institute of Oncology, Ljubljana, Slovenia (Completion of follow-up of the cohort study of mercury miners from Idrija)
ECE/97/01	University of Leeds, Leeds, UK (Collection and analysis of data on occupational cancer among women in the UK)
ECE/97/02	Institut Municipal d'Investigació Mèdica, Barcelona, Spain (Analysis of data on occupational cancer among European women)
ECE/97/04	Institute of Occupational Medicine, Lodz, Poland (Multicentre case–control study of occupational and environmental risk factors of lung cancer in central and eastern Europe)
ECP/97/01	Laboratoire de Microbiologie, Faculté de Pharmacie, Marseille, France (Evaluations des expositions dans les laboratoires de recherche biologique)
ECP/97/03	The Netherlands Cancer Institute, Amsterdam, Netherlands (International study of cancer risk in biology research laboratory workers in Europe: assessment of the record of exposure)
ECP/97/04	Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy (International study of cancer risk in biology research laboratory workers in Europe: assessment of the recording of exposure)
ECE/98/01	London School of Hygiene and Tropical Medicine, London, UK (Occupation, environment and lung cancer in central and eastern Europe)
ECE/98/02	Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland (Occupation, environment and lung cancer in central and eastern Europe)
ECE/98/03	J. Fodor National Public Health Centre, Budapest, Hungary (Occupation, environment and lung cancer in central and eastern Europe)
ECE/98/04	Nofer Institute of Occupational Medicine, Lodz, Poland (Occupation, environment and lung cancer in central and eastern Europe)
ECE/98/05	Institute of Hygiene, Public Health, Health Services and Management, Bucharest, Romania (Occupation, environment and lung cancer in central and eastern Europe)
ECE/98/06	Institute of Carcinogenesis, Moscow, Russia (Occupation, environment and lung cancer in central and eastern Europe)

ECE/98/07	Specialized State Health Institute, Banska Bystrica, Slovakia (Occupation, environment and lung cancer in central and eastern Europe)
ECE/98/08	Faculdade de Saude Publica, São Paulo, Brazil (Occupational factors of laryngeal cancer)
ECE/98/09	Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil (Occupational factors of laryngeal cancer)
ECE/98/10	Faculdade de Medicina, Universidade Federal de Pelotas, Pelotas, Brazil (Occupational factors of laryngeal cancer)
ECE/98/11	Instituto de Oncologia Angel H. Roffo, Buenos Aires, Argentina (Occupational factors of laryngeal cancer)
ECE/98/13	Institut Municipal d'Investigacio Medica, Barcelona, Spain (Occupational factors of laryngeal cancer)
ECE/98/14	Institute of Occupational Health, Helsinki, Finland (Exposure assessment for the international study of cancer risk in asphalt workers)
ECE/98/18	Fundacao de Radioterapia do Rio Grande do Sul, Porto Alegre, Brazil (Occupational factors of laryngeal cancer)
ECP/98/01	Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy (International study of cancer risk in biology research laboratory workers in Europe: further validation of exposure assessment)
ECE/99/16	Palacky University Faculty of Medicine, Olomouc, Czech Republic (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/17	Institute of Experimental and Clinical Medicine, Tallinn, Estonia (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/18	National Institute of Environmental Health, Budapest, Hungary (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/19	Institute of Occupational and Environmental Health, Riga, Latvia (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/20	Kaunus Medical University, Kaunus, Lithuania (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/21	Institute of Occupational Medicine, Lodz, Poland (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/22	Institute of Carcinogenesis, Moscow, Russian Federation (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/23	Specialized State Health Institute, Banska Bystrica, Slovakia (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/24	Institute of Public Health, Ljubljana, Slovenia (Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of Independent States)
ECE/99/25	Masaryk Cancer Institute, Brno, Czech Republic (Pilot study of the feasibility of recruiting kidney and lung cancer cases, in conjunction with the ongoing multicentre case-control study of occupational cancer risk factors in central and eastern Europe)

ECE/99/26 Palacky University Faculty of Medicine, Department of Preventive Medicine, Olomouc, Czech Republic
(Pilot study of the feasibility of recruiting kidney and lung cancer cases, in conjunction with the ongoing multicentre case-control study of occupational cancer risk factors in central and eastern Europe)

ECE/99/27 Institute of Hygiene and Epidemiology, First Faculty of Medicine, Prague, Czech Republic
(Pilot study of the feasibility of recruiting kidney and lung cancer cases, in conjunction with the ongoing multicentre case-control study of occupational cancer risk factors in central and eastern Europe)

Studies on nutrition and cancer

AEP/93/02 Institute of Epidemiological and Clinical Research, Mataró, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/03 Department of Health, Planning and Order, Government of Navarra, Pamplona, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/04 Health Administration of Guipuzcoa San Sebastian, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/05 Andalusian School of Public Health, Granada, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/06 Department of Epidemiology, Health Council, Murcia, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/07 Department of Health Planning, Regional Administration of Public Health, Oviedo, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/09 Imperial Cancer Research Fund, Cancer Epidemiology Unit, Radcliffe Infirmary, Oxford, UK
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/10 German Research Cancer Centre, Division of Epidemiology, Heidelberg, Germany
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/11 Department of Nutrition and Biochemistry, Athens School of Public Health, Athens, Greece
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/12 Department of Epidemiology, University of Utrecht, The Netherlands
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/13 Department of Epidemiology, National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, The Netherlands
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/14 Cancer Epidemiology Research Unit (U.351), National Institute for Health and Medical Research (INSERM), Institut Gustave Roussy, Villejuif, France
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/15 Department of Epidemiology, National Institute for Research and Treatment of Cancer, Milan, Italy
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/16 Ragusa Cancer Registry, Italian League Against Cancer, Ragusa, Sicily, Italy
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/17 Department of Biomedical Sciences and Human Oncology, University of Turin, Turin, Italy
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/20 Unit of Epidemiology, Centre for Preventive Oncology (CSPO), Florence, Italy
(European prospective investigation into cancer and nutrition (EPIC))

NTR/95/01 Malmö Diet and Cancer Study, Malmö, Sweden
(European Prospective Investigation into Nutrition and Cancer (EPIC))

NTR/96/01	Unit of Medical Epidemiology, German Institute of Human Nutrition, Potsdam-Rehbrücke, Germany (European Prospective Investigation into Nutrition and Cancer (EPIC))
NTR/96/02	Department of Community Medicine, University of Cambridge, Cambridge, UK (European Prospective Investigation into Nutrition and Cancer (EPIC))
NTR/96/03	Cancer Epidemiology Research Institute (U.351), Institut Gustave Roussy, Villejuif, France (European Prospective Investigation into Nutrition and Cancer (EPIC))
NTR/96/04	Division for Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (European Prospective Investigation into Nutrition and Cancer (EPIC))
DEP/97/09	Benm vien Institut du Cancer, Hanoi, Viet Nam (Role of diet and *Helicobacter pylori* in gastric cancer in Hanoi)
NTR/97/02	Service de Biochimie, Hôpital de l'Antiquaille, Hospices Civils de Lyon, France (Analyses biochimiques des taux sériques de facteurs hormonaux peptidiques)
NTR/97/03	Department of Nutritional Research, University of Umeå, Sweden (European Prospective Investigation into Nutrition and Cancer (EPIC))
NTR/97/04	Department of Clinical and Experimental Medicine, University of Naples, Italy (European Prospective Investigation into Nutrition and Cancer (EPIC))
DEP/98/12	Cancer Unit, Cancer Committee, Faculty of Médecine, Khon Kaen, Thailand (Role of diet and *Helicobacter pylori* in gastric cancer in Khon Kaen)
NTR/98/01	Laboratoire Central de Biochimie, Hôpital de l'Antiquaille, Lyon, France (Analyses biochimiques des taux sériques de facteurs hormonaux peptidiques)
NTR/98/02	Hôpital de l'Antiquaille, Lyon, France (Mise au point d'un laboratoire d'analyses – installation)
NTR/98/03	Hôpital de l'Antiquaille, Lyon, France (Dosages d'insuline, IGF-1, IGFBP-1 et IGFBP-3)
NTR/98/04	Department of Nuclear Medicine, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy (Nutrition, endogenous hormone profiles and cancer risk)
NTR/99/01	Hospices Civils de Lyon, Lyon, France (Analyses biochimiques de vitamines et autres marqueurs biologiques de l'équilibre antioxidatif cellulaire et plasmatique)
NTR/99/02	Dunn Human Nutrition Unit, Medical Research Council, Cambridge, UK (Laboratory analyses of nitrogen in urine samples collected during the EPIC study)
NTR/99/03	Universita di Napoli, Dipartimento di Medicina Clinica e Sperimentale, Naples, Italy (European prospective investigation of ischaemic heart disease and nutrition)
NTR/99/04	Deutsches Institut für Ernährungsforschung, Bergholz-Rehbrucke, Germany (European prospective investigation of ischaemic heart disease and nutrition)
NTR/99/05	University of Cambridge, School of Clinical Medicine, Cambridge, UK (European prospective investigation of ischaemic heart disease and nutrition)
NTR/99/07	Lund University, Department of Medicine, Malmö, Sweden (European prospective investigation of ischaemic heart disease and nutrition)
NTR/99/08	University of Utrecht, Department of Epidemiology, Utrecht, Netherlands (European prospective investigation of ischaemic heart disease and nutrition)
NTR/99/09	RIVM, Department of Chronic Diseases and Environmental Epidemiology, Bilthoven, Netherlands (European prospective investigation of ischaemic heart disease and nutrition)
NTR/99/10	Danish Cancer Society, Copenhagen, Denmark (EPIC-HEART)

Studies on the effects of active and passive smoking

DEP/97/04 Tata Institute of Fundamental Research, Bombay, India
(Prospective study on tobacco-related cancers and other diseases in the city of Bombay)

ECE/98/15 Institute of Occupational Health, Helsinki, Finland
(Analysis of NAT2 polymorphisms – biomarkers of DNA damage and genetic susceptibility among non-smoking lung cancer cases)

Studies of radiation and cancer

RCA/97/01 Department of Histopathology, Addenbrooke's Hospital, Cambridge, UK
(Study of factors influencing the risk of radiation-induced cancer following the Chernobyl accident)

RCA/97/02 Institute of Endocrinology, University of Pisa, Italy
(Study of factors influencing the risk of radiation-induced cancer following the Chernobyl accident)

RCA/97/03 National Radiological Protection Board, Chilton, UK
(International collaborative study on cancer risk in radiation workers in the nuclear industry)

RCA/97/04 Finnish Centre for Radiation and Nuclear Safety, Helsinki, Finland
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/05 Berufsgenossenschaft der Feinmechanik und Elektrotechnik, Cologne, Germany
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/06 Finnish Cancer Registry, Helsinki, Finland
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/07 Commissariat à l'énergie atomique, Paris, France
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/08 AMYS-UNESA, Madrid, Spain
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/09 Office de Protection contre les Rayonnements Ionisants, Le Vesinet, France
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/10 Deutsches Krebsforschungszentrum, Heidelberg, Germany
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/11 Consejo de Seguridad Nuclear, Madrid, Spain
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/12 Forsmarks Kraftgrupp AB, Osthammar, Sweden
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/13 Studiecentrum voor Kernenergie, Mol, Belgium
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/14 Institut Gustave Roussy, Villejuif, France
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/97/15 Midsweden Research and Development Center, Sundsvall, Sweden
(International collaborative study on cancer risk among radiation workers in the nuclear industry)

RCA/98/01 Medical Radiological Research Centre, Obninsk, Russia
(Genetic and environmental factors influencing the risk of radiation-induced thyroid cancer following the Chernobyl accident)

RCA/98/02 Belorussian Centre for Medical Technologies, Minsk, Belarus
(Genetic and environmental factors influencing the risk of radiation-induced thyroid cancer following the Chernobyl accident)

RCA/98/03 Republican Scientific and Practical Center for Thyroid Tumours, Research Institute of Radiation Medicine and Endocrinology, Minsk, Belarus
(Genetic and environmental factors influencing the risk of radiation-induced thyroid cancer following the Chernobyl accident)

RCA/98/04 University of Cambridge, Department of Pathology, Cambridge, UK
(Genetic and environmental factors influencing the risk of radiation-induced thyroid cancer following the Chernobyl accident)

RCA/98/15 Medical Radiological Research Center, Obninsk, Russian Federation
(Cancer risk following chronic radiation exposure in the nuclear industry in the Russian Federation, Hungary, the Slovak Republic and Lithuania (CANUC))

RCA/98/16 National Radiological Protection Board, Chilton, UK
(Cancer risk following chronic radiation exposure in the nuclear industry in the Russian Federation, Hungary, the Slovak Republic and Lithuania (CANUC))

RCA/98/17 Public Health Institute, Trnava, Slovak Republic
(Cancer risk following chronic radiation exposure in the nuclear industry in the Russian Federation, Hungary, the Slovak Republic and Lithuania (CANUC))

RCA/98/18 Lithuanian Cancer Registry, Vilnius, Lithuania
(Cancer risk following chronic radiation exposure in the nuclear industry in the Russian Federation, Hungary, the Slovak Republic and Lithuania (CANUC))

RCA/98/19 National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary
(Cancer risk following chronic radiation exposure in the nuclear industry in the Russian Federation, Hungary, the Slovak Republic and Lithuania (CANUC))

DEP/99/10 Piedmont Cancer Registry, Turin, Italy
(Estimates of the proportion of skin cancers attributable to UV radiation)

RCA/99/02 Belarussian Center for Medical Technologies, Minsk, Belarus
(Risk of radiation-induced thyroid cancer following the Chernobyl accident)

Other studies of cancer etiology

DEP/97/10 Mekong Institute, Khon Kaen University, Khon Kaen, Thailand
(Cohort study of cancer in rural Thailand)

ECE/98/17 Registro Nacional de Cancer, Montevideo, Uruguay
(Multisite case–control study of cancer and environmental exposures in Uruguay)

Studies on chemical carcinogenesis

CIE/96/01 National Institute of Public Health, Budapest, Hungary
(Carcinogenicity testing of simazine in mice)

CIE/96/02 Institute of Preventive and Clinical Medicine, Bratislava, Federal Republic of Slovakia
(Carcinogenicity testing of simazine in mice)

CIE/98/01 University of Zimbabwe, Harare, Zimbabwe
(Third Pan-African Environmental Mutagen Meeting, Harare, 1–5 March 1999)

ECR/98/01 Institute of Advance Energy, Kyoto University, Kyoto, Japan
(Study on characterization of DNA damage induced by peroxynitrite)

GEI/98/01 Polish Academy of Sciences, Warsaw, Poland
(Exocyclic adducts as new risk markers for DNA damage to man)

GEI/98/02 Institute of Oncology, Sofia, Bulgaria
(Validation of a biomarker of human exposure to ochratoxin A for the assessment of the risk of exposure to this toxin)

CIE/99/01 National Hellenic Research Foundation, Athens, Greece
(Symposium on "Biomarkers and Molecular Epidemiology on Risk Assessment", Athens, 5 September)

Studies on mechanisms of carcinogenesis

MSC/98/01 Netherlands Cancer Institute, Amsterdam, The Netherlands
(The role of *MSH2* gene (mismatch repair) in colon carcinogenesis)

MSC/98/02 National Institute of Occupational Health, Oslo, Norway
(The significance of interplay of genomic instability with environmental agents in carcinogenesis)

Genetics and cancer

GEP/97/01 Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
(Genetic aspects of breast cancer in I.R. of Iran)

GEP/97/02 National Institute of Oncology, Department of Molecular Biology, Budapest, Hungary
(Identification and characterization of germline mutations in breast cancer susceptibility genes in eastern European populations)

GEP/97/03 Icelandic Cancer Society, Molecular & Cell Biology Research Laboratory, Reykjavik, Iceland
(Characterization of germline mutations in breast cancer susceptibility genes in the Icelandic population)

GEP/97/04 Department of Molecular Biology and Genetics, Bilkent University, Bilkent, Ankara, Turkey
(Genetic aspects of breast cancer in Turkey)

GEP/97/05 Centre anti-cancereux Pierre et Marie Curie, Alger, Algeria
(Genetic aspects of breast cancer in Algeria)

ECE/98/16 National Institute of Public Health, Prague, Czech Republic
(Mortality and cancer incidence of subjects monitored for cytogenetic abnormalities in the Czech Republic)

GEP/98/01 Fundacion Jimenez Diaz, Madrid, Spain
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/02 Lund University Hospital, Department of Oncology, Lund, Sweden
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/03 Karolinska Institute, Department of Clinical Genetics, Stockholm, Sweden
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/04 Centre de Génétique Médicale, Département d'Oncogénétique, Gerpinnes (Loverval), Belgium
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/05 Istituto Nazionale Tumori, Division of Experimental Oncology, Milan, Italy
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/06 Odense University Hospital, Department of Clinical Genetics, Odense, Denmark
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/07 German Cancer Research Center, Division of Epidemiology, Heidelberg, Germany
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/08 Universität für Frauenheilkunde, Department of Obstetrics and Gynaecology, Vienna, Austria
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/10 University of Cambridge, Strangeways Research Laboratory, Cambridge, UK
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/11 Netherlands Cancer Institute, Department of Epidemiology, Amsterdam, Netherlands
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/98/12 Institut Gustave Roussy, Villejuif, France
(Enrolment and follow-up of BRCA1/2 mutation carriers into the international BRCA1/2 carrier cohort study)

GEP/99/01 Institute of Cancer Research, Sutton, Surrey, UK
(Genetic epidemiology of multiple primary head and neck cancers)

Courses

DEP/97/07 Cancer Registry of Saarland, Saarbrucken, Germany
(ENCR Course on Cancer Registration, 2–6 March 1998)

DEP/97/11 South African Institute for Medical Research, Johannesburg, South Africa
(Course on cancer registration in Johannesburg)

DEP/98/04 Dipartimento di Scienze Igienistiche e sanitaria Ambientali, Universita di Camerino, Camerino, Italy
(Cours d'enregistrement des cancers, Camerino, 7–11 septembre 1998)

ECE/99/29 National Institute of Environmental Health, Budapest, Hungary
Course on Cancer Epidemiology with emphasis on environmental cancer, March 2000

GCS/98/01 Giannina Gaslini Institute, Genoa, Italy
(Gaslini–IARC course in cancer genetics, 24–29 September 1999)

Annex 6

MEETINGS AND WORKSHOPS ORGANIZED BY IARC

Second meeting of investigators in the study of occupation, environment and lung cancer in central and eastern Europe	Lodz, Poland, 10–12 January 1998
First meeting of coders in the study of occupation, environment and lung cancer in central and eastern Europe	Lodz, Poland, 12–23 January 1998
Meeting on the proposed study of non-Hodgkin lymphoma in Europe	Lyon, 30 January 1998
Meeting of the Organizing Committee of the conference on women's health	Oslo, Norway, 2–3 February 1998
Meeting of industrial hygienists in the study of cancer risk among European asphalt workers	Lyon, 16 February 1998
Monographs working group on re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide	Lyon, 17–24 February 1998
Meeting of investigators in IARC case-control studies of lung cancer	Lyon, 26–27 February 1998
European Network of Cancer Registries (ENCR) course in cancer registration	Saarbrücken, Germany, 2–6 March 1998
Site visit of the EC review committee	Lyon, 9–10 March 1998
Meeting of the EPIC Steering Committee	Lyon, 10–13 March 1998
Meeting on hepatitis B immunization and prevention of cirrhosis and hepatocellular carcinoma in sub-saharan Africa	The Gambia, 11–14 March 1998
GHIS Steering Committee	The Gambia, 14 and 16 March 1998
Course for cancer registrars in sub-Saharan Africa	Johannesburg, South Africa, 16–25 March 1998
European Network of Cancer Registries (ENCR) Steering Committee Meeting	Lyon, 24–25 March 1998
Dosimetry sub-committee meeting for the international collaborative study of cancer risk among radiation workers in the nuclear industry	Lyon, 30–31 March 1998
First meeting of investigators in the study of larynx and oral cavity cancer in South America	São Paulo, Brazil, 14–15 April 1998
First Nordic Institute for Advanced Training in Occupational Health (NIVA)/IARC molecular epidemiology course	Naantali, Finland, 19–24 April 1998
Safe handling of cytostatic drugs for health workers	Lyon, 20–21 April 1998
Fellowships Selection Committee	Lyon, 23–24 April 1998
International BRCA1/2 carrier cohort study	Lyon, 26–27 April 1998
Monographs advisory group on physical agents	Lyon, 27–29 April 1998
Meeting of the Epilymph-Europe Study Group on non-Hodgkin lymphoma	Lyon, 30 April 1998
Summer school on cancer registration and applications in epidemiology	Lyon, 11–29 May 1998
IARC Handbooks on Cancer Prevention working group on vitamin A	Lyon, 13–19 May 1998
Second International Conference on Women's Health	Reykjavik, Iceland, 14–16 May 1998

Meeting of the liaison committee of the study of cancer risk among asphalt workers	Lyon, 19 May 1998
Meeting of the liaison committee of the MMVF lung cancer case–control study	Lyon, 25 May 1998
Monographs working group on hormonal contraception and post-menopausal hormonal therapy	Lyon, 2–9 June 1998
Epidemiology sub-committee meeting for the international collaborative study of cancer risk among radiation workers in the nuclear industry	Lyon, 8–9 June 1998
Editorial meeting, revision of the 2nd edition of *International Classification of Diseases for Oncology*	Lyon, 30 June–2 July 1998
First joint meeting on molecular biology of cancer	Lyon, 1 July 1998
Course for cancer registrars in the Pacific area	Noumea, New Caledonia, 20–29 July 1998
International Conference on Environmental and Occupational Cancer in Developing Countries	Rio de Janeiro, Brazil, 30 July–1 August 1998
International Association of Cancer Registries (IACR) annual meeting	Atlanta, GA, USA, 17–19 August 1998
Meeting for the feasibility study of the international case–control study of adult head and neck tumours and mobile telephones	Lyon, 1–2 September 1998
European Network of Cancer Registries (ENCR) course in cancer registration	Camerino, Italy, 7–11 September 1998
International BRCA1/2 carrier cohort study	Dublin, Ireland, 16 September 1998
Monographs advisory group on priorities for future monographs	Lyon, 16–18 September 1998
Vienna–Lyon collaborative meeting on genomic integrity	Lyon, 18 September 1998
Meeting of joint dosimetry group for the case-control studies of leukaemia, non-Hodgkin's lymphoma and thyroid cancer risk among liquidators in Belarus and Russia and the pilot case–cohort study of haematological diseases among liquidators in Ukraine	Lyon, 21–22 September 1998
European Network of Cancer Registries (ENCR) steering committee meeting	Lyon, 22–23 September 1998
Third Gaslini–IARC course in cancer genetics	Sestri Levante, Italy, 24–29 September 1998
European Network of Cancer Registries (ENCR) statistical course, geographical analysis methods	Lyon, 29 September–2 October 1998
Meeting of the liaison committee of the MMVF lung cancer case–control study	Lyon, 7 October 1998
Editorial meeting, *Cancer in Africa*	Lyon, 8–9 October 1998
Meeting of the Epilymph-Europe Study Group on non-Hodgkin lymphoma	Lyon, 9 October 1998
Second meeting of coders in the study of occupation, environment and lung cancer in central and eastern Europe	Budapest, Hungary, 12–16 October 1998
Monographs working group on some chemicals that cause tumours of the kidney or urinary bladder in rodents, and some other substances	Lyon, 13–20 October 1998

Course for cancer registrars (in French)	Lyon, 19 October–13 November 1998
Meeting on the dose–response analysis of cancer risk in the international study of workers exposed to dioxins	Lyon, 20 October 1998
Meeting of the EPIC working group on cancer genetics	Lyon, 21–22 October 1998
Meeting of the liaison committee of the study of cancer risk among asphalt workers	Lyon, 27 October 1998
Meeting of the working group of the IARC study of cancer risk among asphalt workers	Bremen, Germany, 29–30 October 1998
Second meeting of investigators in the study of larynx and oral cavity cancer in South America	São Paulo, Brazil, 17 November 1998
First meeting of coders in the study of larynx and oral cavity cancer in South America	São Paulo, Brazil, 18–24 November 1998
Course on infections that increase the risk of cancer	Veyrier-du-Lac, France, 13–18 December 1998
Editorial meeting, revision of the 2nd edition of *International Classification of Diseases for Oncology*	Washington, USA, 14–15 December 1998
International symposium on cell adhesion and communication in growth control and cancer	Lyon, 19–21 January 1999
Second joint meeting on molecular biology of cancer	Lyon, 5 February 1999
Meeting of industrial hygienists in the study of cancer risk among European asphalt workers	Lyon, 12 February 1999
European Network of Cancer Registries (ENCR) workshop for cancer registries on evaluation and monitoring of screening	Luxembourg, 18–19 February 1999
Monographs working group on surgical implants, prosthetic devices and foreign bodies	Lyon, 23 February–2 March 1999
Third meeting of investigators in the study of occupation, environment and lung cancer in central and eastern Europe	Bratislava, Slovakia, 2–5 March 1999
Meeting on the Epilymph international case–control study of lymphomas	Lyon, 10 March 1999
Meeting on epidemiological studies in populations of the Newly Independent States exposed after the Chernobyl accident (ENCA)	Lyon, 10–11 March 1999
Meeting on epidemiological studies of thyroid cancer among young people in Belarus and Russia	Lyon, 12–15 March 1999
EACR Executive Committee Meeting,	Lyon, 12 March 1999
EACR-XVI—Scientific Programme Committee Meeting	Lyon, 15 March 1999
Meeting of dosimetrists for the case–control study of liquidators in Belarus and Russia	Lyon, 16–17 March 1999
IARC Handbooks on Cancer Prevention working group on retinoids	Lyon, 24–30 March 1999
Workshop on studies of homocysteine and related factors in EPIC	Lyon, 26 March 1999
Meeting of the EPIC working group on cancer genetics (GenEPIC)	Lyon, 30–31 March 1999
Meeting of investigators in a study of cancer prevention at the workplace	Lyon, 16–17 April 1999
Meeting on exposure assessment in the study of cancer risk among workers in the pulp and paper industry	Vancouver, Canada, 19–23 April 1999

First Institute for Scientific Interchange (ISI)/IARC molecular epidemiology course	Turin, Italy, 19–24 April 1999
ENCR steering committee meeting	Lyon, 20–21 April 1999
Meeting of the Epilymph-Europe study group on non-Hodgkin lymphoma	Lyon, 26 April 1999
Meeting of the liaison committee of the MMVF lung cancer case–control study	Lyon, 26 April 1999
International BRCA 1/2 carrier cohort study	Lyon, 26–27 April 1999
Meeting of industrial hygienists in the study of cancer risk among European asphalt workers	Lyon, 26–30 April 1999
Meeting of the liaison committee of the study of cancer risk among asphalt workers	Lyon, 27 April 1999
Breast Cancer Linkage Consortium – workshop on future projects and funding strategies	Lyon, 27–28 April 1999
Meeting of the EPIC steering committee	Lyon, 27–30 April 1999
Meeting on assessment of occupational exposures in the Epilymph-Europe study on non-Hodgkin lymphoma	Lyon, 27 April–1 May 1999
International case–control study of adult brain, head and neck tumours: meeting of the exposure assessment sub-committee	Lyon, 28–29 April 1999
International case–control study of adult brain, head and neck tumours: meeting of the epidemiology sub-committee	Lyon, 29–30 April 1999
Summer school on cancer registration and applications in epidemiology	Lyon, 3–28 May 1999
Genetic epidemiology studies of squamous cell carcinomas of the head and neck cancer	Lyon, 4–5 May 1999
Fellowships Selection Committee	Lyon, 6–7 May 1999
Collaborative gene mapping project on nasopharyngeal carcinoma	Lyon, 10–11 May 1999
Monographs working group on ionizing radiations, part I, X-rays, γ-rays and neutrons	Lyon, 26 May–2 June 1999
International conference on lead exposure, reproductive toxicity and carcinogenicity	Gargnano, Italy, 7–9 June 1999
Editorial meeting, *Cancer in Africa*	Lyon, 15–17 June 1999
Third meeting of coders in the study of occupation, environment and lung cancer in central and eastern Europe	London, UK, 21–24 June 1999
Merck Research Laboratories/IARC meeting on HPV vaccines	Lyon, 1–2 July 1999
Editorial and consensus meeting on *Pathology and Genetics of Tumours of the Nervous System* (WHO Classification of Tumours)	Lyon, 24–27 July 1999
Occupational hygienists sub-committee meeting for the international case–control study of adult head and neck tumours and mobile telephones	Lyon, 14–15 September 1999
Third joint meeting on molecular biology of cancer	Lyon, 24 September 1999
Curso sobre prevencion y control del cancer	San José, Costa Rica, 27 September–7 October 1999
Fourth Gaslini–IARC course in cancer genetics	Sestri Levante, Italy, 29 September–3 October 1999
International Association of Cancer Registries (IACR) annual meeting	Lisbon, Portugal, 29–30 September 1999

Meeting on conditions of exposure (study of errors in dosimetry within the international collaborative study of cancer risk among radiation workers in the nuclear industry)	Lyon, 30 September–1 October 1999
European Childhood Leukaemia/Lymphoma Incidence Studies meeting	Lisbon, Portugal, 1 October 1999
General meeting of European Network of Cancer Registries (ENCR) members	Lisbon, Portugal, 2 October 1999
European Network of Cancer Registries (ENCR) Steering Committee Meeting	Lisbon, Portugal, 2 October 1999
Meeting of collaborators in project on exocyclic adducts as new risk markers for DNA damage in man	Lyon, 4 October 1999
Editorial meeting, revision of the 2nd edition of *International Classification of Diseases for Oncology*	Lyon, 7–8 October 1999
Monographs working group on some antiviral and antineoplastic agents and some other pharmaceutical drugs	Lyon, 12–19 October 1999
Meeting of the international collaborative group on hormones and cancer	Lyon, 14–16 October 1999
Dosimetry sub-committee meeting for the case–control study of liquidators in Belarus and Russia	Lyon, 25–26 October 1999
Meeting of the dosimetry sub-group for the study of errors in dosimetry within the international collaborative study of cancer risk among radiation workers in the nuclear industry	Lyon, 27–29 October 1999
Editorial and consensus meeting on *Pathology and Genetics of Tumours of the Digestive System* (WHO Classification of Tumours)	Lyon, 24–27 July 1999
Course on cancer registration	Bahrain, 6–11 November 1999
Second Institute for Scientific Interchange (ISI)/IARC molecular epidemiology course	Turin, Italy, 8–13 November 1999
International course on cancer epidemiology—principles and methods	Khon Kaen, Thailand, 15–26 November 1999
Second meeting of coders in the study of larynx and oral cavity cancer in South America	São Paulo, Brazil, 15–19 November 1999
Third meeting of investigators in the study of larynx and oral cavity cancer in South America	Petropolis, Brazil, 18–20 November 1999
Meeting of the liaison committee of the MMVF lung cancer case–control study	Lyon, 23–24 November 1999
Editorial meeting, *Cancer Incidence in Five Continents*, Vol. VIII	Lyon, 25–26 November 1999
Monographs advisory group on the predictive value of rodent tumours of forestomach and of gastric neuroendocrine cell origin for evaluating carcinogenic risks to humans	Lyon, 29 November–1 December 1999
Meeting of the EPIC steering committee	Cambridge, UK, 1–2 December 1999
EPIC workshop on statistical issues in cohort studies	Cambridge, UK, 3–4 December 1999
Meeting of investigators in the follow-up study of vinyl chloride workers	Stockholm, Sweden, 6–7 December 1999
European Network of Cancer Registries (ENCR) statistical course, time trends	Lyon, 8–10 December 1999

Annex 7

SEMINARS PRESENTED AT IARC

The following visitors to IARC presented seminars during the period under review:

Professor H.N. Ananthaswamy, MD Anderson Cancer Centre, Houston, TX, USA
Mechanisms in psoralen and UVA-induced cell death and skin cancer development

Dr P. Anker, University of Geneva, Switzerland
Circulating tumour DNA in plasma of cancer patients, potential for cancer detection

Dr I.I. Arzimanoglou, Lenox Hill Hospital, New York, NY, USA
DNA instability in ovarian cancer

Dr M. Barbacid, Centro Nacionale de Investigaciones Oncologicas Carlos III, Madrid, Spain
Genetic analysis of cell cycle regulators

Dr G. Berke, Weizmann Institute of Science, Rehovot, Israel
The killer lymphocyte: a friend and a foe

Dr P. Boyle, European Institute of Oncology, Milan, Italy
Recent developments in breast cancer and prostate cancer control

Dr D.A. Calderwood, Scripps Research Institute, La Jolla, CA, USA
Characterization of the integrin–talin interaction and its role in regulating integrin function

Dr E. Capelli, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy
Involvement of XRCC1 and Lig III gene products in DNA base excision repair

Dr M. Castellazzi, Unité INSERM de Virologie N° 412, Ecole Normale Supérieure, Lyon, France
Dimerization mutants of v-Jun as a tool for the dissection of the AP1-controlled oncogenic pathway

Dr H. Chaib, Institut Pasteur, Paris, France
Cartographie de gènes responsables de surdité chez l'homme

Dr S. Chang, MD Anderson Cancer Center, Houston, TX, USA
New directions in the hormonal role of body size in carcinogenesis: examples from inflammatory breast and prostate cancers

Dr A. Ciampi, McGill University, Montreal, Canada
Tree growing with RECPAM: a flexible methodology for data analysis in biostatistics

Mr B. Cornillon, Délégué INSERM aux risques biologiques, Montpellier, France
Manipulation des agents biologiques : risques et bonnes procédures de laboratoire

Professor D. Corpet, Ecole nationale vétérinaire/INRA, Toulouse, France
Preventive effects of bacon and polyethylene glycol on colon cancer in rats

Dr A. Covacci, Istituto Ricerche Immunobiologiche, Siena, Italy
Molecular biology of *Helicobacter pylori*

Dr F. Cuzin, INSERM Unité 470, Nice-Sophia Antipolis, France
Meiotic expression of Cre recombinase in the "TAMERE" mouse: a tool for genetic analysis and genomic engineering

Professor M. Di Renzo, Institute for Cancer Research, Candiolo, Italy
The *MET* oncogene in human cancer

Dr M. Dosemeci, National Cancer Institute, Bethesda, MD, USA
Estimating cancer-causing dose in interdisciplinary epidemiological studies

Dr S. Fabre, Ecole Normale Supérieure, Lyon, France
PDZ domains containing proteins: cellular targets of the HTLV-1 tax oncoprotein

Dr E. Felley-Bosco, University of Lausanne, Switzerland
Nitric oxide: role in carcinogenesis

Professor F. Feo, Universita di Sassari, Italy
Controversies on the role of genetic and epigenetic events in hepatocarcinogenesis: a unifying hypothesis and new perspectives for cancer prevention

Professor C. Franceschi, National Institute of Research and Care for Elderly, Ancona, Italy
Immunology and genetics of human longevity
Professor J. Gadek-Wesierski, University of Vienna, Austria
Involvement of p53 in DNA damage signalling and cancer: modulation by PARP
Dr B. Gemmill, University of Colorado Health Sciences Center, Denver, CO, USA
TRC8, a multiple membrane spanning protein implicated in hereditary kidney cancer and early development
Professor E. Greiser, Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany
Leukaemia and malignant lymphoma in northern Germany: an incidence study and a subsequent case–control study
Dr W. Hammerschmidt, Institute for Clinical Molecular Biology and Tumour Genetics, Munich, Germany
Genetics of Epstein–Barr virus: vaccine and vector development
Dr H.R. Harach, St Bartholomew's Hospital, London, UK
Papillary microcarcinoma of the thyroid
Dr C.C. Harris, National Cancer Institute, Bethesda, MD, USA
Etiology and pathobiological consequences of mutations in tumour-suppressor genes
p53, nitric oxide and carcinogenesis
Dr M. Hrabe de Angelis, Institute for Mammalian Genetics, Neuherberg, Germany
Ethylnitrosourea mutagenesis in mice and its relevance for the study of inherited predisposition to disease in humans
Professor U. Hubscher, Institut für Veterinarbiochemie, Zürich, Switzerland
Proliferating cell nuclear antigen as a communicator between DNA replication and DNA repair
Dr E. Imyanitov, N.N. Petrov Research Institute of Oncology, St Petersburg, Russian Federation
Molecular pathogenesis of bilateral breast cancer
Professor T. Ishikawa, University of Tokyo, Japan
Advantage of gene-modulated mice for study of DNA repair and carcinogenesis: experiments with mice modulated with O^6-meGT, XPA and AhR genes
Professor S.P. Jackson, Wellcome/Cancer Research Campaign Institute, Cambridge, UK
The detection and repair of DNA damage
Dr S. Kawanishi, Mie University School of Medicine, Tsu, Japan
Sequence-specific DNA damage by free radicals
Dr G. Keller, National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, USA
Haematopoietic commitment during embryonic development
Dr K. Kiguchi, MD Anderson Cancer Center, Smithville, TX, USA
Role of ErbB family, RTKs and c-SRC in multistage skin carcinogenesis
Dr T. Kuroki, Institute of Molecular Oncology, Tokyo, Japan
Signal transduction pathways mediating terminal differentiation of squamous cell epithelia
Dr R.C. Lee, University of Washington, Seattle, USA
The value of biological information in carcinogen risk management
Dr T. Lindahl, Imperial Cancer Research Foundation Clare Hall Laboratories, Herts, UK
Cancer triggered by endogenous DNA lesions
Dr B. Liu, Institute of Occupational Medicine,Beijing, China
The specific mutational spectra of *p53* and K-*ras* genes in lung cancer of workers exposed to silica
Dr M. Longy, Institut Bergonié, Bordeaux, France
Les altérations du gène *PTEN* dans la maladie de Cowden et les processus tumoraux s'y rapportant
Dr C. Mahe, Institut Gustave Roussy, Villejuif, France
Relapse and death as an endpoint: application to a breast cancer study
Dr B. Malissen, INSERM-CNRS, Marseille, France
Genetic and structural dissections of the T cell antigen receptor
Dr A. Martin, University College London, UK
Structural classification and analysis: databases to link protein sequence, structure and function
Dr M.R. Masjedi, National Research Institute of Tuberculosis and Lung Diseases, Teheran, Iran
Report on 1500 cases of lung cancer from Iran

Dr P. Mehlen, Université Claude Bernard Lyon-I, Villeurbanne, France
The dependence receptors DCC and RET: a new link between tumour suppression, development of the nervous system and apoptosis
Dr A. Metspalu, University of Tartu, Estonia
Oligonucleotide arrays for mutation detection and genome analysis
Dr H. Møller, Danish National Research Foundation, Copenhagen, Denmark
Trends in male : female ratio among newborn infants, male subfertility and testicular cancer: are they connected?
Dr J.J. Moulin, National Institute for Research and Safety, Nancy, France
Quality assurance in epidemiology: the INRS experience of implementation of ISO 9002
Dr B. Muller-Myhsok, Bernard Nocht Institute for Tropical Medicine, Hamburg, Germany
Mapping of a susceptibility locus for Parkinson's disease to human chromosome 2p13
Dr U. Nair, German Cancer Research Center, Heidelberg, Germany
GSTM1 and GSTT1 null genotypes as risk factors for oral leukoplakia in ethnic Indian betel quid tobacco chewers
Dr M. Negishi, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA
Nuclear receptor CAR mediates pleiotropic effects induced by phenobarbital
Professor R.F. Newbold, Brunel University, Uxbridge, UK
Understanding the mechanisms of human cell senescence using functional genetics
Professor T. Nilstun, Lund University, Sweden
Research ethics: how to assess your own study
Ethical assessment of research on the new IARC notification form
Dr J. Nuckols, Colorado State University, Fort Collins, CO, USA
Epidemiologic studies of drinking water contaminants: exposure assessment
Dr P. Oefner, Stanford University, CA, USA
The human genome diversity project: how to find variations of single nucleotides?
Dr E.A. Ostrander, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
BRCA1 and *BRCA2* mutation frequency in women perceived to be at risk
Dr N. Pearce, Wellington School of Medicine, New Zealand
Why is asthma prevalence increasing worldwide?
Dr G. Poirier, CHUL Research Center, Quebec, Canada
The role of poly(ADP-ribose) polymerase in apoptosis and DNA repair
Dr M.C. Poirier, National Cancer Institute, Bethesda, MD, USA
Zidovudine: carcinogenicity in rodents and genotoxicity in rodents, primates and humans
Dr B.S. Polla, UFR Cochin-Port Royal, Paris, France
Heat shock/stress proteins and mitochondrial (de)polarization as novel biomarkers of early responses to environmental pollutants
Professor J. Ponten, University of Uppsala, Sweden
Skin cancer and p53 mutation
Dr D. Queiroz, Faculdade de Medicina/UFMG, Belo Horizonte, Brazil
Gastric carcinoma and *Helicobacter pylori*: a Brazilian experience
Dr F. Rochigneux, Institut de Physique Nucléaire, Villeurbanne, France
Radioactivité et radioprotection
Dr S. Rosso, Registro dei Tumori per il Piemonte e la Valle d'Aosta, Turin, Italy
Prevention of melanoma and non-melanocytic skin cancers and development of a new method for the detection of high-risk groups
Professor F. Saidi, National Research Institute of Tuberculosis and Lung Diseases, Teheran, Iran
Oesophageal cancer screening among the Turkomans. A glimpse into the history of oesophageal cancer
Dr R. Sankila, Finnish Cancer Registry, Helsinki, Finland
Cancer patient survival: a population-based approach
Dr C. Sardet, Institut de Génétique moléculaire, Montpellier, France
Regulation of cyclin E promoter expression

Dr A. Schatzkin and Dr V. Kipnis, National Cancer Institute, Bethesda, MD, USA
How much of nutritional epidemiology can we believe? Empirical evidence of substantial relative risk attention by correlated person-specific biases in dietary assessment methods

Dr G.M. Shah, Hospital Research Center, Université Laval, Quebec, Canada
Effect of niacin deficiency on ultraviolet B radiation-induced skin carcinogenesis: role of NAD and poly(ADP-ribose) polymerase

Dr T. Sobue, National Cancer Center Research Institute, Tokyo, Japan
Japan Public Health Center-based prospective study on cancer and cardiovascular diseases

Dr P. Sommer, Institut de biologie et chimie des protéines, CNRS, Lyon, France
Lysyl oxidases: extracellular and nuclear roles in limiting tumour invasion and reversing the ras-induced phenotype

Professor C. Sonnenschein and Professor A. Soto, Tufts University, Boston, MA, USA
Carcinogenesis and control of cell proliferation: a new perspective

Dr K. Steenland, National Institute of Occupational Safety and Health, Cincinnati, OH, USA
Cytogenetic and thyroid hormone effects among Mexican pesticide applicators

Ms D. Stockton, University of Cambridge, UK
Breast cancer in East Anglia – are we lightening the load?

Professor N. Tomilin, Institute of Cytology, St Petersburg, Russian Federation
DNA repair and cancer susceptibility

Dr D. Toniolo, Istituto di Genetica Biochimica ed Evoluzionistica, Pavia, Italy
A human homologue of the *D. melanogaster* diaphanous gene DIA is involved in ovarian development: evidence for conserved function in oncogenesis and implications for human sterility and cancer

Dr S. Toyokuni, Kyoto University, Japan
Reactive oxygen species-induced molecular damage and carcinogenesis

Dr H. Tsuda, National Cancer Center Research Institute, Tokyo, Japan
Carcinogenesis studies with transgenic rat carrying human Ha-ras proto-oncogene

Dr K. Uchida, University of Tsukuba, Japan
Tissue-specific mRNA in cancer detected in peripheral blood by RT-PCR as a novel tumour marker

Dr T. Ushijima, National Cancer Center Research Institute, Tokyo, Japan
Chromosomal mapping of resistance and susceptibility genes to MNNG-induced stomach cancers

Dr X. Wang, Southwestern Medical Center, Dallas, TX, USA
Searching for the real killer, molecules that cause apoptosis

Dr M. Ward, National Cancer Institute, Bethesda, MD, USA
Epidemiologic studies of drinking water contaminants: recent evidence *re* nitrate and cancer

Dr C. Wesseling, Karolinska Institute, Stockholm, Sweden
Cancer research in Costa Rica

Dr S. Yamamoto, Dr J. Ishihara and Dr M. Kobayashi, National Cancer Center Research Institute, Tokyo, Japan
Japan public health center-based prospective study on cancer and cardiovascular diseases: validity of dietary questionnaires

Annex 8

PUBLICATIONS OF IARC STAFF

1. Ahn, B., Han, B.S., Kim, D.J. & Ohshima, H. (1999) Immunohistochemical localization of inducible nitric oxide synthase and 3-nitrotyrosine in rat liver tumors induced by N-nitrosodiethylamine. *Carcinogenesis*, **20**, 1337–1344
2. Anderson, D., Yu, T.W. & McGregor, D.B. (1998) Comet assay responses as indicators of carcinogen exposure. *Mutagenesis*, **13**, 539–555
3. Armstrong, B.K. & Boffetta, P. (1998) Environmental cancer. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol. 1, 4th ed., Geneva, International Labour Office, pp. 2.8–2.14
4. Atawodi, S.E., Lea, S., Nyberg, F., Mukeria, A., Constantinescu, V., Ahrens, W., Brueske-Hohlfeld, I., Fortes, C., Boffetta, P. & Friesen, M.D. (1998) 4-Hydroxy-1-(3-pyridyl)-1-butanone-hemoglobin adducts as biomarkers of exposure to tobacco smoke: validation of a method to be used in multicenter studies. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 817–821
5. Auricchio, A., Griseri, P., Carpentieri, M.L., Betsos, N., Staiano, A., Tozzi, A., Priolo, M., Thompson, H., Bocciardi, R., Romeo, G., Ballabio, A. & Ceccherini, I. (1999) Double heterozygosity for a RET substitution interfering with splicing and an EDNRB missense mutation in Hirschsprung disease. *Am. J. Hum. Genet.*, **64**, 1216–1221
6. Baan, R.A. & Szyfter, K., eds (1999) Biomarkers in monitoring of occupational and environmental exposure to organic genotoxic substances. *Mutat. Res.*, **445**, 135–293
7. Barbin, A. (1998) Formation of DNA etheno adducts in rodents and humans and their role in carcinogenesis. *Acta Biochim. Pol.*, **45**, 145–161
8. Barbin, A. (1999) Etheno-adduct forming chemicals: from mutagenicity testing to tumour mutation spectra. *Mutat. Res.* (in press)
9. Barbin, A. (1999) The role of etheno DNA adducts in carcinogenesis induced by vinyl chloride in rats. In: Singer, B. & Bartsch, H., eds, *Exocyclic Nucleic Acid Adducts in Carcinogenesis and Mutagenesis* (IARC Scientific Publications No. 150), Lyon, IARC, pp. 303–313
10. Barek, J., Cvacka, J., Zima, J., De Méo, M., Laget, M., Michelon, J. & Castegnaro, M. (1998) Chemical degradation of wastes of antineoplastic agents amsacrine, azathioprine, asparaginase and thiotepa. *Ann. Occup. Hyg.*, **42**, 259–266
11. Bartsch, H., Malaveille, C., Lowenfels, A.B., Maisonneuve, P., Hautefeuille, A., Boyle, P. & International Pancreatic Disease Study Group (1998) Genetic polymorphism of N-acetyltransferases, glutathione S-transferase M1 and NAD(P)H:quinone oxidoreductase in relation to malignant and benign pancreatic disease risk. *Eur. J. Cancer Prev.*, **7**, 215–223
12. Bay, J.O., Uhrhammer, N., Hall, J., Stoppa-Lyonnet, D. & Bignon, Y. J. (1999) Fonctions de la protéine ATM et aspects phénotypiques de l'ataxie-télangiectasie. *Med. Sci.*, **15**, 1086–1095
13. Bay, J.O., Uhrhammer, N., Pernin, D., Presneau, N., Tchirkov, A., Vuillaume, M., Laplace, V., Grancho, M., Verrelle, P., Hall, J. & Bignon, Y. J. (1999) High incidence of cancer in a family segregating a mutation of the ATM gene: possible role of ATM heterozygosity in cancer. *Hum. Mutat.* (in press)
14. Bedwani, R., Renganathan, E., El Kwesky, F., Braga, C., Abu Seif, H.H., Abul Azm, T., Zaki, A., Franceschi, S., Boffetta, P. & La Vecchia, C. (1998) Schistosomiasis and the risk of bladder cancer in Alexandria, Egypt. *Br. J. Cancer*, **77**, 1186–1189
15. Bellander, T., Merler, E., Ceccarelli, F. & Boffetta, P. (1998) Historical exposure to inorganic mercury at the smelter works of Abbadia San Salvatore, Italy. *Ann. Occup. Hyg.*, **42**, 81–90
16. Bhurgri, Y., Bhurgri, A., Hassan, S.H., Zaidi, S.H.M., Rahim, A., Sankaranarayanan, R. & Parkin, D.M. (1999) Cancer incidence in Karachi, Pakistan: first results from Karachi Cancer Registry. *Int. J. Cancer* (in press)
17. Bianchini, F., Donato, F., Faure, H., Ravanat, J.L., Hall, J. & Cadet, J. (1998) Urinary excretion of 5-(hydroxymethyl)uracil in healthy volunteers: effect of active and passive tobacco smoke. *Int. J. Cancer*, **77**, 40–46
18. Bianchini, F., Elmstahl, S., Martinez-Garcia, C., van Kappel, A.L., Donki, T., Cadet, J., Ohshima, H., Riboli, E. & Kaaks, R. (1999) Oxidative DNA damage in human lymphocytes: correlations with plasma levels of alpha-tocopherol and carotenoids. *Carcinogenesis* (in press)
19. Biernat, W., Peraud, A., Wozniak, L. & Ohgaki, H. (1998) p53 Mutations in sweat gland carcinomas. *Int. J. Cancer*, **76**, 317–320
20. Björkqvist, A.M., Husgafvel-Pursiainen, K., Anttila, S., Karjalainen, A., Tammilehto, L., Mattson, K., Vainio, H. & Knuutila, S. (1998) DNA gains in 3q occur frequently in squamous cell carcinoma of the lung, but not in adenocarcinoma. *Genes Chromosomes Cancer*, **22**, 79–82
21. Black, R.J., Parkin, D.M., Masuyer, E., Apjok, E., Barlow, L., Bennett, B.G., Boukhny, A., Merabishvili, V.M., Brewster, D., Stiller, C.A., Coebergh, J.W.W., Bernard, J.L., Carli, P.M., Lacour, B., Ménégoz, F., Schaffer, P., Schraub, S., Hrstkova, H., Crosignani, P., Magnani, C., Terracini, B., Bouchardy, C., Fisch, T., Levi, F.G., Raymond, L., Schüler, G., Torhorst, J., Ivanov, E., Kriauciunas, R., Langgassner, J., Langmark, F.,

Michaelis, J., Moroz, G., Plesko, I., Pompe-Kim, V., Pukkala, E., Rahu, M., Stengrevics, A., Storm, H.H., Tulbure, R., Tzvetansky, C.G. & Zatonski, W. (1999) Incidence of leukaemia in infants in Europe following in utero exposure to radiation from the Chernobyl accident. *Br. J. Cancer* (in press)

22. Black, R.J., Sankaranarayanan, R. & Parkin, D.M. (1999) Interpretation of population-based survival data. In: Sankaranarayanan, R., Black, R.J. & Parkin, D.M., eds, *Cancer Survival in Developing Countries* (IARC Scientific Publications No. 145), Lyon, IARC, pp. 13–17
23. Black, R.J., Simonato, L., Storm, H.H. & Démaret, E., eds (1998) *Automated Data Collection in Cancer Registration* (IARC Technical Reports No. 32), Lyon, IARC
24. Blettner, M., Grosche, B. & Zeeb, H. (1998) Occupational cancer risk in pilots and flight attendants: current epidemiological knowledge. *Radiat. Environ. Biophys.*, **37**, 75–80
25. Blettner, M. & Sauerbrei, W. (1998) Metaanalysen in der Epidemiologie. *Med. Klinik*, **93**, 442–445
26. Bocciardi, R., Mograbi, B., Pasini, B., Borrello, M.G., Pierotti, M.A., Bourget, I., Fischer, S., Romeo, G. & Rossi, B. (1999) The multiple endocrine neoplasia type 2B point mutation switches the specificity of the Ret tyrosine kinase towards cellular substrates that are susceptible to interact with Crk and Nck. *Oncogene* (in press)
27. Boffetta, P. (1998) Cancer chapter. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol.1, 4th Ed., Geneva, International Labour Office, pp. 2.1–2.18
28. Boffetta, P. (1998) Cancer patterns, risk factors and prevention in the Balkans and Middle East, with a note on the use of cancer registries for investigating risk factors. In: Pavlidis, N., Kardamakis, D. & Costa, A., eds, *Cancer Control in the European Mediterranean, Balkans and Middle-East Countries,* European School of Oncology, University of Ioannina, Greece, pp. 23–38
29. Boffetta, P. (1998) Cancer risk from exposure to man-made mineral fibres. *Eur. J. Oncol.*, **3**, 213–220
30. Boffetta, P. (1998) Exposure to man made vitreous fibres and cancer risk: a review of epidemiological studies. In: Peters, G.A. & Peters, B.J., eds, *Current Asbestos Issues (Sourcebook on Asbestos Diseases, Vol.18),* Charlottesville, VA, Lexis Publishing, pp. 191–218
31. Boffetta, P. (1998) Health effects of asbestos exposure in humans: a quantitative assessment. *Med. Lav.*, **89**, 471–480
32. Boffetta, P. (1999) Man-made mineral fibres. In: McDonald, J.C., ed., *Epidemiology of Work-Related Diseases*, 2nd ed., London, BMJ Books (in press)
33. Boffetta, P., Agudo, A., Ahrens, W., Benhamou, E., Benhamou, S., Darby, S.C., Ferro, G., Fortes, C., Gonzalez, C.A., Jöckel, K.H., Krauss, M., Kreienbrock, L., Kreuzer, M., Mendes, A., Merletti, F., Nyberg, F., Pershagen, G., Pohlabeln, H., Riboli, E., Schmid, G., Simonato, L., Trédaniel, J., Whitley, E., Wichmann, H.E., Winck, C., Zambon, P. & Saracci, R., eds (1998) *European Multicentre Case-Control Study of Lung Cancer in Non-smokers. Detailed Results on Exposure to Environmental Tobacco Smoke* (IARC Technical Report No. 33), Lyon, IARC
34. Boffetta, P., Agudo, A., Ahrens, W., Benhamou, E., Benhamou, S., Darby, S.C., Ferro, G., Fortes, C., Gonzalez, C.A., Jöckel, K.H., Krauss, M., Kreienbrock, L., Kreuzer, M., Mendes, A., Merletti, F., Nyberg, F., Pershagen, G., Pohlabeln, H., Riboli, E., Schmid, G., Simonato, L., Trédaniel, J., Whitley, E., Wichmann, H.E., Winck, C., Zambon, P. & Saracci, R. (1998) Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. *J. Natl Cancer Inst.*, **90**, 1440–1450
35. Boffetta, P., Ahrens, W., Nyberg, F., Mukeria, A., Brueske-Hohlfeld, I., Fortes, C., Constantinescu, V., Simonato, L., Batura-Gabryel, H., Lea, S., Gaborieau, V. & Benhamou, S. (1999) Exposure to environmental tobacco smoke and risk of adenocarcinoma of the lung. *Int. J. Cancer*, **83**, 635–639
36. Boffetta, P., Andersen, A., Hansen, J., Olsen, J.H., Plato, N., Teppo, L., Westerholm, P. & Saracci, R. (1999) Cancer incidence among European man-made vitreous fiber production workers. *Scand. J. Work Environ. Health*, **25**, 222–226
37. Boffetta, P., Burdorf, A., Goldberg, M., Merler, E. & Siemiatycki, J. (1998) Workshop report: Towards the coordination of European research on the carcinogenic effects of asbestos. *Scand. J. Work Environ. Health*, **24**, 312–317
38. Boffetta, P., Butler, J., Maynadié, M. & Brennan, P. (1999) Lymphomas. In: Neugut, A.I., Meadows, A.T. & Robinson, E., eds, *Multiple Primary Cancers,* Philadelphia, Lippincott Williams & Wilkins, pp. 277–301
39. Boffetta, P., Fichtinger-Schepman, A.M.J., Weiderpass, E., van Dijk-Knijnenburg, H.C.M., Stoter, G., van Oosterom, A.T., Keizer, H.J., Fossa, S.D., Kaldor, J. & Roy, P. (1998) Cisplatin-DNA adducts and protein-bound platinum in blood of testicular cancer patients. *Anti-Cancer Drugs*, **9**, 125–129
40. Boffetta, P., Garcia-Gomez, M., Pompe-Kim, V., Zaridze, D., Bellander, T., Bulbulyan, M., Caballero, J.D., Ceccarelli, F., Colin, D., Dizdarevic, T., Español, S., Kobal, A., Petrova, N., Sällsten, G. & Merler, E. (1998) Cancer occurrence among European mercury miners. *Cancer Causes Control*, **9**, 591–599
41. Boffetta, P. & Kogevinas, M. (1999) Introduction: Epidemiologic research and prevention of occupational cancer in Europe. *Environ. Health Perspect.*, **107**, 229–231

42. Boffetta, P. & Merler, E. (1999) Occupational cancer in Europe. *Environ. Health Perspect.*, **107**, 227–298
43. Boffetta, P., Nyberg, F., Agudo, A., Benhamou, E., Jockel, K.H., Kreuzer, M., Merletti, F., Pershagen, G., Pohlabeln, H., Simonato, L., Wichmann, H.E. & Saracci, R. (1999) Risk of lung cancer from exposure to environmental tobacco smoke from cigars, cigarillos and pipes (Letter). *Int. J. Cancer*, **83**, 805–806
44. Boffetta, P., Nyberg, F. on behalf of the IARC Study Group (1999) Response to Denson re: Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe (letter). *J. Natl Cancer Inst.*, **91**, 803–804
45. Boffetta, P., Nyberg, F., Saracci, R. on behalf of the IARC Study Group (1999) Response to Lee and Forey re.: Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe (Letter). *J. Natl Cancer Inst.*, 91, 560–561
46. Boffetta, P. & Pearce, N. (1999) Epidemiological studies on genetic polymorphisms: study design issues and measures of occurrence and association. In: Vineis, P., Malats, N., Lang, M., d'Errico, A., Caporaso, N., Cuzick, J. & Boffetta, P., eds, *Metabolic Polymorphisms and Susceptibility to Cancer* (IARC Scientific Publications No. 148), Lyon, IARC, pp. 97–108
47. Boffetta, P., Pershagen, G., Jöckel, K.H., Forastiere, F., Gaborieau, V., Heinrich, J., Jahn, I., Kreuzer, M., Merletti, F., Nyberg, F., Rösch, F. & Simonato, L. (1999) Cigar and pipe smoking and lung cancer risk: a multicenter study from Europe. *J. Natl Cancer Inst.*, **91**, 697–701
48. Boffetta, P., Sali, D., Kolstad, H., Coggon, D., Olsen, J., Andersen, A., Spence, A., Pesatori, A.C., Lynge, E., Frentzel-Beyme, R., Chang-Claude, J., Lundberg, I., Biocca, M., Gennaro, V., Teppo, L., Partanen, T., Welp, E., Saracci, R. & Kogevinas, M. (1998) Mortality of short-term workers in two international cohorts. *J. Occup. Environ. Med.*, **40**, 1120–1126
49. Boffetta, P., Saracci, R. for the IARC Study Group (1998) Reply re. 'Cancer mortality among man-made vitreous fiber production workers' (letter). *Epidemiology*, **9**, 219–220
50. Boffetta, P., Saracci, R., Kogevinas, M., Wilbourn, J. & Vainio, H. (1998) Occupational carcinogens. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol. 1, 4th ed., Geneva, International Labour Office, pp. 2.4–2.8
51. Boffetta, P., Trédaniel, J. & Greco, A. (1999) Exposure to passive smoke from the parents and risk of childhood cancer and adult lung cancer: a meta-analysis. *Environ. Health Perspect.* (in press)
52. Boffetta, P. & Weiderpass, E. (1998) Respiratory cancer. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol.1, 4th Ed., Geneva, International Labour Office, pp. 10.78–10.81
53. Boivin-Angèle, S., LeFrançois, L., Froment, O., Spiethoff, A., Bogdanffy, M.S., Wegener, K., Wesh, H., Barbin, A., Bancel, B., Trépo, C., Bartsch, H., Swenberg, J. & Marion, M.-J. (1999) Ras gene mutations in vinyl chloride-induced liver tumors are carcinogen-specific but vary with cell type and species. *Int. J. Cancer* (in press)
54. Bolino, A., Seri, M., Caroli, F., Eubanks, J., Srinivasan, J., Mandich, P., Schenone, A., Quattrone, A., Romeo, G., Catterall, W.A. & Devoto, M. (1998) Exclusion of the SCN2B gene as candidate for CMT4B. *Eur. J. Hum. Genet.*, **6**, 629–634
55. Bolino, A., Yin, L., Seri, M., Cusano, R., Cinti, R., Coffey, A., Brooksbank, R., Howell, G., Bentley, D., Davis, J.R., Lanyi, A., Huang, D., Stark, M., Creaven, M., Bjorkhaug, L., Heitzmann, F., Lamartine, J., Gaudi, S., Sylla, B.S., Lenoir, G.M., Castagnola, E., Giacchino, R., Porta, G., Franco, B., Zollo, M., Sumegi, J. & Romeo, G. (1998) A new candidate region for the positional cloning of the XLP gene. *Eur. J. Hum. Genet.*, **6**, 509–517
56. Bongarzone, I., Vigano, E., Alberti, L., Borrello, M.G., Pasini, B., Greco, A., Mondellini, P., Smith, D.P., Ponder, B.A.J., Romeo, G. & Pierotti, M.A. (1998) Full activation of MEN2B mutant RET by an additional MEN2A mutation or by ligand GDNF stimulation. *Oncogene*, **16**, 2295–2301
57. Bonnet, P., Binet, S., Brandt, H., Kriech, A.J., Lafontaine, M., Nunge, H., Morele, Y., de Groot, P., Wissel, H. & Castegnaro, M. (1999) Inhalation study on exposure to bitumen fumes. Part 1: Development and validation of the equipment. *Ann. Occup. Hyg.* (in press)
58. Bonnier, P., Bessenay, F., Sasco, A.J., Beedassy, B., Lejeune, C., Romain, S., Charpin, C., Piana, L. & Martin, P.M. (1998) Impact of menopausal hormone-replacement therapy on clinical and laboratory characteristics of breast cancer. *Int. J. Cancer (Pred. Oncol.)*, **79**, 278–282
59. Borresen-Dale, A.L., Lothe, R.A., Meling, G.I., Hainaut, P., Rognum, T.O. & Skovlund, E. (1998) TP53 and long-term-prognosis in colorectal cancer: mutations in the L3 zinc-binding domain predict poor survival. *Clin. Cancer Res.*, **4**, 203–210
60. Bosch, F.X. & Muñoz, N. (1999) Cervical cancer. In: Goldman, M.B. & Hatch, M.C., eds, *Women and Health*, San Diego CA, Academic Press/Goldman, pp. 932–941 (in press)
61. Bosch, F.X., Muñoz, N. & Castellsagué, X. (1998) Epidemiology of cervical dysplasia and neoplasia. In: Luesley, D. & Barrasso, R., eds, *Cancer and Pre-Cancer of the Cervix*, London, Chapman & Hall, pp. 51–68
62. Boturyn, D., Constant, J.-F., Defrancq, E., Lhomme, J., Barbin, A. & Wild, C.P. (1999) A simple and sensitive method for *in vitro* quantitation of abasic sites in DNA. *Chem. Res. Toxicol.*, **12**, 476–482

63. Bouchardy, C., Khlat, M., Wanner, P. & Parkin, D.M., eds (1998) *Mortalité par Cancer des Immigrés en France 1979–1985* (Rapport technique du CIRC No.26), Lyon, IARC
64. Brandt, H., Lafontaine, M., Kriech, A.J., de Groot, P., Bonnet, P., Binet, S., Wissel, H., Morele, Y., Nunge, H. & Castegnaro, M. (1999) Inhalation study on exposure to bitumen fumes. Part 2: Analytical results at two exposure levels. *Ann. Occup. Hyg.* (in press)
65. Brennan, P. (1999) Design and analysis issues in addressing genetic susceptibility case–control studies. In: Vineis, P., Malats, N., Lang, M., d'Errico, A., Caporaso, N., Cuzick, J. & Boffetta, P., eds, *Metabolic Polymorphisms and Susceptibility to Cancer* (IARC Scientific Publications No. 148), Lyon, IARC, pp. 123–132
66. Brennan, P., Bogillot, O., Cordier, S., Greiser, E., Schill, W., Vineis, P., Lopez-Abente, G., Tzonou, A., Chang-Claude, J., Bolm-Audorff, U., Jöckel, K.-H., Donato, F., Serra, C., Wahrendorf, J., Hours, M., Mannetje 't, A., Kogevinas, M. & Boffetta, P. (1999) Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case–control studies. *Int. J. Cancer* (in press)
67. Brennan, P., Coates, M., Armstrong, B., Colin, D. & Boffetta, P. (1999) Second primary neoplasms following non-Hodgkin's lymphoma in New South Wales, Australia. *Br. J. Cancer* (in press)
68. Brennan, P., Fortes, C., Butler, J., Agudo, A., Benhamou, S., Darby, S., Gerken, M., Jöckel, K.-H., Kreuzer, M., Mallone, S., Nyberg, F., Pohlabeln, H., Ferro, G. & Boffetta, P. (1999) A multicenter case–control study of diet and lung cancer among non-smokers. *Cancer Causes Control* (in press)
69. Bringuier, P.P., McCredie, M., Sauter, G., Bilous, M., Stewart, J., Mihatsch, M.J., Kleihues, P. & Ohgaki, H. (1998) Carcinomas of the renal pelvis associated with smoking and phenacetin abuse: p53 mutations and polymorphism of carcinogen metabolising enzymes. *Int. J. Cancer (Pred. Oncol.)*, **79**, 531–536
70. Brunet, J.S., Ghadirian, P., Rebbeck, T.R., Lerman, C., Garber, J.E., Tonin, P.N., Abrahamson, J., Foulkes, W.D., Daly, M., Wagner-Costalas, J., Godwin, A., Olopade, O.I., Moslehi, R., Liede, A., Futreal, P.A., Weber, B.L., Lenoir, G.M., Lynch, H.T. & Narod, S.A. (1998) Effect of smoking on breast cancer in carriers of mutant BRCA1 or BRCA2 genes. *J. Natl Cancer Inst.*, **90**, 761–766
71. Bruno, G., Merletti, F., Boffetta, P., Cavallo-Perin, P., Bargero, G., Gallone, G. & Pagano, G. (1999) Impact of glycaemic control, hypertension and insulin treatment on general and cause-specific mortality: an Italian population-based cohort of Type II (non-insulin-dependent) diabetes mellitus. *Diabetologia*, **42**, 297–301
72. Bulbulyan, M.A. & Boffetta, P. (1999) Occupational cancer in the European part of the Commonwealth of Independent States. *Environ. Health Perspect.*, **107**, Suppl. 2, 283–288
73. Bulbulyan, M.A., Changuina, O.V., Zaridze, D.G., Astashevsky, S.V., Colin, D. & Boffetta, P. (1998) Cancer mortality among Moscow shoe workers exposed to chloroprene (Russia). *Cancer Causes Control*, **9**, 381–387
74. Bulbulyan, M.A., Margaryan, A.G., Ilychova, S.A., Astashevsky, S.V., Uloyan, S.M., Cogan, V.Y., Colin, D., Boffetta, P. & Zaridze, D.G. (1999) Cancer incidence and mortality in a cohort of chloroprene workers from Armenia. *Int. J. Cancer*, **81**, 31–33
75. Burkart, V., Wang, Z.Q., Radons, J., Heller, B., Herceg, Z., Stingl, L., Wagner, E.F. & Kolb, H. (1999) Mice lacking the poly(ADP-ribose) polymerase gene are resistant to pancreatic beta-cell destruction and diabetes development induced by streptozocin. *Nature Med.*, **5**, 314–319
76. Burstyn, I., Kromhout, H. & Boffetta, P. (1999) A literature review of levels and determinants of exposure to potential carcinogens and other agents in the road construction industry. *Am. Ind. Hyg. Assoc.* (in press)
77. Burstyn, I., Kromhout, H., Cruise, P.J. & Brennan, P. (1999) Designing an international industrial hygiene database of exposure among workers in asphalt industry. *Ann. Occup. Hyg.* (in press)
78. Burstyn, I., Kromhout, H., Kauppinen, T., Heikkilä, P., Boffetta, P. & Asphalt Study Group (1999) Statistical modeling of the determinants of historical exposure bitumen and polycyclic aromatic hydrocarbons among paving workers. *Ann. Occup. Hyg.* (in press)
79. Calmels, S., Hainaut, P. & Ohshima, H. (1998) Nitric oxide, p53 and cancer. In: Moncada, S., Nisticò, G., Bagetta, G. & Higgs, E.A., eds, *Nitric Oxide and the Cell – Proliferation, Differentiation and Death*, London, Portland Press, pp. 277–282
80. Canzian, F., Amati, P., Harach, H.R., Kraimps, J.L., Lesueur, F., Barbier, J., Levillain, P., Romeo, G. & Bonneau, D. (1998) A gene predisposing to familial thyroid tumors with cell oxyphilia maps to chromosome 19p13.2. *Am. J. Hum. Genet.*, **63**, 1743–1748
81. Capen, C.C., Dybing, E., Rice, J.M. & Wilbourn, J.D., eds (1999) *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis* (IARC Scientific Publications No. 147), Lyon, IARC
82. Cardis,.E., Amoros, E., Kesminiene, A., Malakhova, I.V., Poliakov, S.M., Piliptsevitch, N.N., Demidchik, E.P., Astakhova, L.N., Ivanov, V.K., Konogorov, A.P., Parshkov, E.M. & Tsyb, A.F. (1999) Observed and predicted thyroid cancer incidence following the Chernobyl accident – Evidence for factors influencing susceptibility to radiation induced thyroid cancer. In: Thomas, G., Kavaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer*, Cambridge, World Scientific Publications, pp. 395–405

83. Cardis, E. & Kilkenny, M. (1999) International case-control study of adult brain, head and neck tumours: results of the feasibility study. *Radiat. Protect. Dosimetry*, **83**, 179–183
84. Cardis, E. & Martuzzi, M. (1998) Improving the estimates of radiation induced cancer risk. *Seguridad Nuclear*, **6**, 31–37
85. Cardis, E. & Martuzzi, M. (1999) L'effet cancérigène des faibles doses d'irradiation – connaissances actuelles et études en cours. *Méd. Nucl.* (in press)
86. Cardis, E., Woodward, A. & Repacholi, M. (1999) Mobile safety. *New Scientist*, **162**, 53–54
87. Cardis, E., Zeise, L., Schwarz, M. & Moolgavkar, S. (1999) Review of specific examples of QEP.In: Moolgavkar, S., Kreski, D., Zeise, L., Cardis, E. & Møller, H., eds, *Quantitative Estimation and Prediction of Human Cancer Risks* (IARC Scientific Publications No. 131), Lyon, IARC, pp. 239–304
88. Castegnaro, M. (1999) Analyse des biomarqueurs d'exposition. In: Pfohl-Leszkowicz, A., ed., *Les Mycotoxines dans l'Alimentation. Evaluation et Gestion du Risque*, Paris, Tec & Doc, pp. 173–196
89. Castegnaro, M. (1999) Risques cancérogènes. In: Pfohl-Leszkowicz, A., ed., *Les Mycotoxines dans l'Alimentation. Evaluation et Gestion du Risque*, Paris, Tec & Doc, pp. 121–140
90. Castegnaro, M., De Méo, M., Laget, M., Michelon, J., Garren, L., Sportouch, M.H. & Hansel, S. (1997) Chemical degradation of wastes of antineoplastic agents. 2. Six anthracyclines: idarubicin, doxorubicin, epirubicin, pirarubicin, aclarubicin, and daunorubicin. *Int. Arch. Occup. Environ. Health*, **70**, 378–384
91. Castegnaro, M. & Dirheimer, G. (1998) Food Additives & Contaminants 13 (1996) Letter to the Editor. *Food Addit. Contam.*, **15**, 123
92. Castegnaro, M., Garren, L., Galendo, D., Gelderblom, W.C.A., Chelule, P., Dutton, M.F. & Wild, C.P. (1998) Analytical method for the determination of sphinganine and sphingosine in serum as a potential biomarker for fumonisin exposure. *J. Chromatogr. B*, **720**, 15–24
93. Castegnaro, M. & McGregor, D. (1998) Carcinogenic risk assessment of mycotoxins. *Rev. Med. Vet.*, **149**, 671–678
94. Castegnaro, M., Mohr, U., Pfohl-Leszkowicz, A., Estève, J., Steinmann, J., Tillmann, T., Michelon, J. & Bartsch, H. (1998) Sex- and strain-specific induction of renal tumors by ochratoxin A in rats correlates with DNA adduction. *Int. J. Cancer*, **77**, 70–75
95. Castegnaro, M., Muranyi-Kovacs, I., Roussille, F. & Brésil, H. (1998) Methods for collection and disposal of mutagenic and carcinogenic waste from research laboratories. In: Marzin, D. & Société Française de Toxicologie Génétique, eds, *Laboratory Handling of Mutagenic and Carcinogenic Products – Training Module No. 2*, Geneva, WHO, pp. 84–106
96. Castegnaro, M., Muranyi-Kovacs, I., Roussille, F. & Brésil, H. (1998) Méthodes de collecte et d'élimination des déchets mutagènes et cancérogènes. In: Marzin, D., Castegnaro, M. & Muranyi-Kovacs, I., eds, *Manipulation de Produits Mutagènes et Cancérogènes*, Paris, INSERM, pp. 81–102
97. Castegnaro, M. & Pfohl-Leszkowicz, A. (1999) Les aflatoxines. In: Pfohl-Leszkowicz, A., ed., *Les Mycotoxines dans l'Alimentation. Evaluation et Gestion du Risque*, Paris, Tec & Doc, pp. 199–247
98. Castellsagué, X., Herrero, R., Muñoz, N., Franceschi, S., Bosch, F.X. & Walboomers, J.M.M. (1998) Human papillomavirus (HPV) and oral cancer: an international study of molecular epidemiology. In: *Head and Neck Oncology (1st World Congress, Madrid, Spain, 29 November–3 December 1998)*, Bologna, Monduzzi Ed., pp. 105–108
99. Castellsagué, X. & Muñoz, N. (1999) Re: Cancer of the oral cavity and pharynx in nonsmokers who drink alcohol and in nondrinkers who smoke tobacco. *J. Natl Cancer Inst.*, **91**, 1336–1337
100. Castellsagué, X., Muñoz, N., De Stefani, E., Victora, C.G., Castelletto, R., Rolon, P.A. & Quintana, M.J. (1999) Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. *Int. J. Cancer*, **82**, 657–664
101. Chajes, V., Hulten, K., van Kappel, A.L., Winkvist, A., Kaaks, R., Hallmans, G., Lenner, P.G. & Riboli, E. (1999) Fatty acid composition in serum phospholipids and risk of breast cancer: a prospective cohort study in Northern Sweden. *Lipids*, **34**, S113
102. Chajès, V., Hultén, K., van Kappel, A.L., Winkvist, A., Kaaks, R., Hallmann, G., Lenner, P. & Riboli, E. (1999) Fatty-acid composition in serum phospholipids and risk of breast cancer: an incident case–control study in Sweden. *Int. J. Cancer*, **83**, 585–590
103. Chaouki, N., Bosch, F.X., Muñoz, N., Meijer, C.J.L.M., El Gueddari, B., El Ghazi, A., Deacon, J., Castellsagué, X. & Walboomers, J.M.M. (1998) The viral origin of cervical cancer in Rabat, Morocco. *Int. J. Cancer*, **75**, 546–554
104. Chappuis-Flament, S., Pasini, A., De Vita, G., Ségouffin-Cariou, C., Fusco, A., Attié, T., Lenoir, G.M., Santoro, M. & Billaud, M. (1998) Dual effect on the RET receptor of MEN 2 mutations affecting specific extracytoplasmic cysteines. *Oncogene*, **17**, 2851–2861
105. Chazotte-Aubert, L., Hainaut, P. & Ohshima, H. (1999) Nitric oxide nitrates tyrosine residues of tumor-suppressor p53 protein in MCF-7 cells. *Biochem. Biophys. Res. Commun.* (in press)
106. Chazotte-Aubert, L., Oikawa, S., Gilibert, I., Bianchini, F., Kawanishi, S. & Ohshima, H. (1999) Co-operative action of nitroxyl anion (NO) and hydrogen peroxide in cytotoxicity and DNA damage. In: Moncada, S., Gustafsson, L., Wiklund,

P. & Higgs, E.A., eds, *The Biology of Nitric Oxide*. Part 7, London, Portland Press (in press)

107. Chazotte-Aubert, L., Oikawa, S., Gilibert, I., Bianchini, F., Kawanishi, S. & Ohshima, H. (1999) Cytotoxicity and site-specific DNA damage induced by nitroxyl anion (NO^-) in the presence of hydrogen peroxide. Implications for various pathophysiological conditions. *J. Biol. Chem.*, **274**, 20909–20915
108. Chemin, I., Ohgaki, H., Chisari, F.V. & Wild, C.P. (1999) Altered expression of hepatic carcinogen metabolizing enzymes with liver injury in HBV transgenic mouse lineages expressing various amounts of hepatitis B surface antigen. *Liver*, **19**, 81–87
109. Chiarelli, I., Porfirio, B., Mattiuz, P.L., Seri, M., Caroli, F., Celli, I., Romeo, G., Volorio, S. & Zollo, M. (1998) A method for point mutation analysis that links SSCP and dye primer fluorescent sequencing. *Mol. Cell. Probes*, **12**, 125–131
110. Chichareon, S., Herrero, R., Muñoz, N., Bosch, F.X., Jacobs, M.V., Deacon, J., Santamaria, M., Chongsuvivatwong, V., Meijer, C.J.L.M. & Walboomers, J.M.M. (1998) Risk factors for cervical cancer in Thailand: a case-control study. *J. Natl Cancer Inst.*, **90**, 50–57
111. Chokunonga, E., Levy, L.M., Bassett, M.T., Borok, M.Z., Mauchaza, B.G., Chirenje, M.Z. & Parkin, D.M. (1999) AIDS and cancer in Africa: the evolving epidemic in Zimbabwe. *AIDS* (in press)
112. Chokunonga, E., Levy, L.M., Bassett, M.T., Mauchaza, B.G., Thomas, D.B. & Parkin, D.M. (1999) Cancer incidence in the African population of Harare, Zimbabwe: second results from the Cancer Registry 1993–1995. *Int. J. Cancer* (in press)
113. Chomarat, P., Rice, J.M., Slagle, B.L. & Wild, C.P. (1998) Hepatitis B virus-induced liver injury and altered expression of carcinogen metabolising enzymes: the role of HBx protein. *Toxicol. Lett.*, **102–103**, 595–601
114. Chomarat, P., Sipowicz, M.A., Diwan, B.A., Fornwald, L.W., Awasthi, Y. C., Anver, M.A., Rice, J.M., Anderson, L.M. & Wild, C.P. (1997) Distinct time courses of increase in cytochromes P450 1A2, 2A5 and glutathione S-transferases during the progressive hepatitis associated with *Helicobacter hepaticus*. *Carcinogenesis*, **18**, 2179–2190
115. Cinti, R., Yin, L., Ilc, K., Berger, N., Basolo, F., Cuccato, S., Giannini, R., Torre, G., Miccoli, P., Amati, P., Romeo, G. & Corvi, R. (1999) *RET* rearrangements in papillary thyroid carcinomas and adenomas detected by interphase FISH. *Cytogenet. Cell Genet.* (in press)
116. Cirenei, N., Colombo, B.M., Mesnil, M., Benedetti, S., Yamasaki, H. & Finocchiaro, G. (1998) In vitro and in vivo effects of retrovirus-mediated transfer of the connexin 43 gene in malignant gliomas: consequences for HSVtk/GCV anticancer gene therapy. *Gene Ther.*, **5**, 1221–1226
117. Coffey, A.J., Brooksbank, R.A., Brandau, O., Oohashi, T., Howell, G.R., Bye, J.M., Cahn, A.P., Durham, J., Heath, P., Wray, P., Pavitt, R., Wilkinson, J., Leversha, M., Huckle, E., Shaw-Smith, C.J., Dunham, A., Rhodes, S., Schuster, V., Porta, G., Yin, L., Serafini, P., Sylla, B., Zollo, M , Franco, B., Bolino, A., Seri, M., Lanyi, A., Davis, J.R., Webster, D., Harris, A., Lenoir, G., de St Basile, G., Jones, A.B., Behloradsky, B.H., Achatz, H., Murken, J., Fassler, R., Sumegi, J., Romeo, G., Vaudin, M., Ross, M.T., Meindl, A. & Bentley, D.R. (1998) Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. *Nature Genet.*, **20**, 129–135
118. Combes, R., Balls, M., Curren, R., Fischbach, M., Fusenig, N., Kirkland, D., Lasne, C., Landolph, J., LeBoeuf, R., Marquardt, H., McCormick, J., Muller, L., Rivedal, E., Sabbioni, E., Tanaka, N., Vasseur, P. & Yamasaki, H. (1999) Cell transformation assays as predictors of human carcinogenicity. The report and recommendations of ECVAM Workshop 39. *ATLA*, **27**, 745–767
119. Consonni, D., Boffetta, P., Andersen, A., Chang-Claude, J., Cherrie, J.W., Ferro, G., Frentzel-Beyme, R., Hansen, J., Olsen, J., Plato, N., Westerholm, P. & Saracci, R. (1998) Lung cancer mortality among European rock/slag wool workers: exposure-response analysis. *Cancer Causes Control*, **9**, 411–416
120. Coursaget, P. & Muñoz, N. (1999) Vaccination against infectious agents associated with human cancer. *Cancer Surv.: Infections and Human Cancer*, **33**, 355–381
121. Courtois, Y., Castegnaro, M. & Beaubestre, C. (1998) Accepting, recording, conditioning, storing and transporting genotoxic, mutagenic and/or carcinogenic products. In: Marzin, D. & Société Française de Toxicologie Génétique, eds, *Laboratory Handling of Mutagenic and Carcinogenic Products – Training Module No. 2*, Geneva, WHO, pp. 46–54
122. Courtois, Y., Castegnaro, M. & Beaubestre, C. (1998) Réception, inventaire, conditionnement, stockage et transports des génotoxiques, mutagènes et/ou cancérogènes. In: Marzin, D., Castegnaro, M. & Muranyi-Kovacs, I., eds, *Manipulation de Produits Mutagènes et Cancérogènes*, Paris, INSERM, pp. 39–46
123. d'Adda di Fagagna, F., Hande, M.P., Tong, W.M., Lansdorp, P.M., Wang, Z.Q. & Jackson, S.P. (1999) Functions of poly(ADP-ribose) polymerase in controlling telomere length and chromosomal stability. *Nature Genet.*, **23**, 76–80
124. d'Errico, A., Malats, N., Vineis, P. & Boffetta, P. (1999) Review of studies of selected metabolic polymorphisms and cancer. In: Vineis, P., Malats, N., Lang, M., d'Errico, A., Caporaso, N., Cuzick, J. & Boffetta, P., eds, *Metabolic Polymorphisms and*

Susceptibility to Cancer (IARC Scientific Publications No. 148), Lyon, IARC, pp. 323–393

125. Daurès, J.P., Gerber, M., Scali, J., Astre, C., Bonifacj, C. & Kaaks, R. (1999) Validation of a food frequency questionnaire using multiple day records and biochemical markers: application of the method of triads. *J. Epidemiol. Biostat.* (in press)
126. Davis, D.L., Axelrod, D., Bailey, L., Gaynor, M. & Sasco, A.J. (1998) Rethinking breast cancer risk and the environment: the case for the precautionary principle. *Environ. Health Perspect.*, **106**, 523–529
127. De Flora, S., Bagnasco, M. & Vainio, H. (1999) Modulation of genotoxic and related effects by carotenoids and vitamin A in experimental models: mechanistic issues. *Mutagenesis*, **14**, 153–172
128. De Miglio, M.R., Canzian, F., Pascale, R.M., Simile, M.M., Muroni, M.R., Calvisi, D., Romeo, G. & Feo, F. (1999) Identification of genetic loci controlling hepatocarcinogenesis on rat chromosomes 7 and 10. *Cancer Res.*, **59**, 4651–4657
129. de SanJosé, S., Bosch, X.F., Muñoz, N., Chichareon, S., Ngelangel, C., Balaguero, L., Jacobs, M.V., Meijer, C.J.L.M. & Walboomers, J.M.M. (1999) Screening for genital HPV. Results from an international validation study on HPV sampling techniques. *Diagn. Mol. Pathol.*, 8, 26–31
130. De Stefani, E., Boffetta, P., Carzoglio, J., Mendilaharsu, M. & Deneo-Pellegrini, H. (1998) Tobacco smoking and alcohol drinking as risk factors for stomach cancer: a case-control study in Uruguay. *Cancer Causes Control*, **9**, 321–329
131. De Stefani, E., Boffetta, P., Deneo-Pellegrini, H., Mendilaharsu, M., Carzoglio, J.C. & Ronco, A. (1999) Carbohydrates and risk of stomach cancer in Uruguay (Letter). *Int. J. Cancer*, **82**, 618–621
132. De Stefani, E., Boffetta, P., Deneo-Pellegrini, H., Mendilaharsu, M., Carzoglio, J.C., Ronco, A. & Olivera, L. (1999) Dietary antioxidants and lung cancer risk: a case-control study in Uruguay. *Nutr. Cancer*, **34**, 100–110
133. De Stefani, E., Boffetta, P., Mendilaharsu, M., Carzoglio, J. & Deneo-Pellegrini, H. (1998) Dietary nitrosamines, heterocyclic amines and risk of gastric cancer: a case-control study in Uruguay. *Nutr. Cancer*, **30**, 158–162
134. De Stefani, E., Boffetta, P., Oreggia, F., Fierro, L. & Mendilaharsu, M. (1998) Hard liquor drinking is associated with higher risk of cancer of the oral cavity and pharynx than wine drinking: a case-control study in Uruguay. *Oral Oncol.*, **34**, 99–104
135. De Stefani, E., Boffetta, P., Oreggia, F., Mendilaharsu, M. & Deneo-Pellegrini, H. (1998) Smoking patterns and cancer of the oral cavity and pharynx: a case-control study in Uruguay. *Oral Oncol.*, **34**, 340–346
136. De Stefani, E., Boffetta, P., Oreggia, F., Ronco, A., Kogevinas, M. & Mendilaharsu, M. (1998) Occupation and the risk of laryngeal cancer in Uruguay. *Am. J. Ind. Med.*, **33**, 537–542
137. De Stefani, E., Deneo-Pellegrini, H., Boffetta, P. & Mendilaharsu, M. (1999) Meat intake and risk of squamous cell esophageal cancer: a case-control study in Uruguay. *Int. J. Cancer*, **82**, 33–37
138. De Stefani, E., Oreggia, F., Boffetta, P., Deneo-Pellegrini, H., Ronco, A. & Mendilaharsu, M. (1999) Tomatoes, tomato-rich foods, lycopene and cancer of the upper aerodigestive tract: a case-control in Uruguay. *Oral Oncol.* (in press)
139. Dcerasamee, S., Martin, N., Sontipong, S., Sriamporn, S., Sriplung, H., Srivatanakul, P., Vatanasapt, V., Parkin, D.M. & Ferlay, J., eds (1999) *Cancer in Thailand.* Vol. II. *1992–1994* (IARC Technical Report No. 34), Lyon, IARC
140. Deharveng, G., Charrondière, U.R., Slimani, N., Southgate, D.A.T. & Riboli, E. (1999) Comparison of nutrients in the food composition tables available in the nine European countries participating in EPIC.*Eur. J. Clin. Nutr.*, **53**, 60–79
141. Deharveng, G., Charrondière, U.R., Slimani, N., Southgate, D.A.T. & Riboli, E. (1999) Carotenoids and retinol-equivalents in food composition tables from European countries (EPIC study) – Letter. *Eur. J Clin. Nutr.* (in press)
142. Demers, P.A. & Boffetta, P., eds (1998) *Cancer Risk from Occupational Exposure to Wood Dust: A Pooled Analysis of Epidemiological Studies* (IARC Technical Report No. 30), Lyon, IARC
143. Demers, P.A., Stellman, S.D., Colin, C. & Boffetta, P. (1998) Nonmalignant respiratory disease mortality among woodworkers participating in the American Cancer Society Cancer Prevention Study II (CPS-II). *Am. J. Ind. Med.*, **34**, 238–243
144. Deneo-Pellegrini, H., De Stefani, E., Boffetta, P., Ronco, A. & Mendilaharsu, M. (1999) Dietary iron and cancer of the rectum: a case-control study in Uruguay. *Eur. J. Cancer Prev.* (in press)
145. Dinse, G.E., Umbach, D.M., Sasco, A.J., Hoel, D.G. & Davis, D.L. (1999) Unexplained increases in cancer incidence in the United States from 1975 to 1994: Possible sentinel health indicators? *Ann. Rev. Publ. Health*, **20**, 173–209
146. Dogliotti, E., Hainaut, P., Hernandez, T., d'Errico, M.R. & DeMarini, D. (1998) Mutation spectra resulting from carcinogenic exposure: from model systems to cancer-related genes. *Recent Results Cancer Res.*, **154**, 97–124
147. Donato, F., Boffetta, P., Fazioli, R., Gelatti, U. & Porru, S. (1998) Reliability of data on smoking habit and coffee drinking collected by personal interview in a hospital-based case-control study. *Eur. J. Epidemiol.*, **14**, 259–267
148. Donato, F., Boffetta, P. & Puoti, M. (1998) A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int. J. Cancer*, 75, 347–354
149. Donato, F., Gelatti, U., Chiesa, R., Albertini, A., Bucella, E., Boffetta, P., Tagger, A., Ribero, M.L., Portera, G., Fasola, M. & Nardi, G. (1999) A case–

control study on family history of liver cancer as a risk factor for hepatocellular carcinoma in North Italy. *Cancer Causes Control*, **10**, 417–421

150. Ducrocq, C., Blanchard, B., Pignatelli, B. & Ohshima, H. (1999) Peroxynitrite: an endogenous oxidizing and nitrating agent. *Cell. Mol. Life Sci.*, **55**, 1068–1077
151. Duflot-Dancer, A., Piccoli, C., Rolland, A., Yamasaki, H. & Mesnil, M. (1998) Long-term connexin-mediated bystander effect in highly tumorigenic human cells in vivo in herpes simplex virus thymidine kinase/ganciclovir gene therapy. *Gene Ther.*, **5**, 1372–1378
152. Eisinger, F., Espié, M., Kuttenn, F., Lasset, C., De Lignières, B., Namer, M., Roché, H., Sasco, A., Serin, D. & Philip, T. (1998) La chimioprévention du cancer du sein – Prise de position au 3 juillet 1998 de la Fédération nationale des centres de lutte contre le cancer (FNCLCC). *Bull. Cancer*, **85**, 725
153. El Ghissassi, F., Barbin, A. & Bartsch, H. (1998) Metabolic activation of vinyl chloride by rat liver microsomes: low-dose kinetics and involvement of cytochrome P450 2E1. *Biochem. Pharmacol.*, **55**, 1445–1452
154. El Ghissassi, F., Verhaegh, G. & Hainaut, P. (1999) Induction of p53 protein activity by the aminothiol WR-2721 (amifostine): a possible mechanism for cytoprotection. *Sem. Cancer Biol.* (in press)
155. Elmståhl, S., Gullberg, B., Riboli, E., Saracci, R. & Lindgärde, F. (1999) The reproducibility of a novel diet history method and an extensive food frequency questionnaire. The Malmö Food Study. *Eur. J. Clin. Nutr.* (in press)
156. Endres, M., Wang, Z.Q., Namura, S., Waeber, C. & Moskowitz, M.A. (1997) Ischemic brain injury is mediated by the activation of poly(ADP-ribose)-polymerase. *J. Cereb. Blood Flow Metab.*, **17**, 1143–1151
157. Espié, M. & Sasco, A. (1998) Risque génétique et épidémiologie du cancer du sein. In: *Risques Héréditaires de Cancers du Sein et de l'Ovaire. Quelle Prise en Charge?*, Paris, Ed. INSERM, pp. 19–55
158. Essers, A.J.A., Alink, G.M., Speijers, G.J.A., Alexander, J., Bouwmeister, P.J., van den Brandt, P.A., Ciere, S., Gry, J., Herrman, J., Kuiper, H.A., Mortby, E., Renwick, A.G., Shrimpton, D.H., Vainio, H., Vittozzi, L. & Koeman, J.H. (1998) Food plant toxicants and safety risk assessment and regulation of inherent toxicants in plant foods. *Environ. Toxicol. Pharmacol.*, **5**, 155–172
159. Essioux, L., Girodet, C., Serova, O., Pagès, S., Eisinger, F., de Résende, S., Maugard, C., Lanoë, D., Longy, M., Bignon, Y.J., Sobol, H., Bonaïti-Pellié, C., Stoppa-Lyonnet, D. & Groupe Génétique et Cancer de la Fédération Nationale des Centre de Lutte contre le Cancer (1999) Marker segregation information in breast/ovarian cancer genetic counselling: is it still useful? *Am. J. Med. Genet.* (in press)
160. Fabiánová, E., Szeszenia-Dabrowska, N., Kjaerheim, K. & Boffetta, P. (1999) Occupational cancer in Central European countries. In: Boffetta, P. & Merler, E., eds, *Occupational Cancer in Europe. Environ.Health Perspect.*, **107**, Suppl. 2, 279–282
161. Ferlay, J., Bray, F., Sankila, R. & Parkin, D.M., eds (1999) *EUCAN: Cancer Incidence, Mortality and Prevalence in the European Union* (CD-ROM), Lyon, IARC
162. Ferlay, J., Parkin, D.M. & Pisani, P., eds (1998) *GLOBOCAN*, Vol. 1: *Cancer Incidence and Mortality Worldwide* (IARC Cancerbase No. 3) (CD-ROM), Lyon, IARC
163. Ford, D., Easton, D.F., Stratton, M., Narod, S., Goldgar, D., Devilee, P., Bishop, D.T., Weber, B., Lenoir, G., Chang-Claude, J., Sobol, H., Teare, M.D., Struewing, J., Arason, A., Scherneck, S., Peto, J., Rebbeck, T.R., Tonin, P., Neuhausen, S., Barkardottir, R., Eyfjord, J., Lynch, H., Ponder, B.A.J., Gayther, S.A., Birch, J.M., Lindblom, A., Stoppa-Lyonnet, D., Bignon, Y., Borg, A., Hamann, U., Haites, N., Scott, R.J., Maugard, C.M., Vasen, H., Seitz, S., Cannon-Albright, L.A., Schofield, A., Zelada-Hedman, M. & Breast Cancer Linkage Consortium (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am. J. Hum. Genet.*, **62**, 676–689
164. Fortuny, J., Kogevinas, M., Chang-Claude, J., Gonzalez, C.A., Hours, M., Jöckel, K.H., Bolm-Audorff, U., Lynge, E., Mannetje 't, A., Porru, S., Ranft, U., Serra, C., Tzonou, A., Wahrendorf, J. & Boffetta, P. (1999) Tobacco, occupation and non-transitional-cell carcinoma of the bladder: an international case-control study. *Int. J. Cancer*, **80**, 44–46
165. Freyer, G., Dazord, A., Schlumberger, M., Conte-Devolx, B., Ligneau, B., Trillet-Lenoir, V. & Lenoir, G.M. (1999) Psychosocial impact of genetic testing in familial medullary-thyroid carcinoma: a multicentric pilot-evaluation. *Ann. Oncol.*, **10**, 87–95
166. Fujisawa, H., Kurrer, M., Reis, R.M., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (1999) Acquisition of the glioblastoma phenotype during astrocytoma progression is associated with loss of heterozygosity on 10q25-qter. *Am. J. Pathol.*, **155**, 387–394
167. Fujisawa, H., Reis, R.M., Nakamura, M., Colella, S., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (1999) Loss of heterozygosity on chromosome 10 is more extensive in primary (*de novo*) than in secondary glioblastomas. *Lab. Invest.* (in press)
168. Garcia-Closas, M., Herrero, R., Bratti, C., Hildesheim, A., Sherman, M.E., Morera, L.A. & Schiffman, M. (1999) Epidemiologic determinants of vaginal pH. *Am. J. Obst. Gynecol.*, **180**, 1060–1066
169. Garcia-Closas, R., Agudo, A., Gonzalez, C.A. & Riboli, E. (1998) Intake of specific carotenoids and flavonoids and the risk of lung cancer in women in Barcelona, Spain. *Nutr. Cancer*, **32**, 154–158

170. Garcia-Closas, R., Gonzalez, C.A., Agudo, A. & Riboli, E. (1999) Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain. *Cancer Causes Control*, **10**, 71–75
171. Geneste, O., Bidaud, C., De Vita, G., Hofstra, R.M.W., Tartare-Deckert, S., Buys, C.H.C.M., Lenoir, G.M., Santoro, M. & Billaud, M. (1999) Two distinct mutations of the RET receptor causing Hirschsprung's disease impair the binding of signalling effectors to a multifunctional docking site. *Hum. Mol. Genet.*, **8**, 1989–1999
172. Genevois, C., Pfohl-Leszkowicz, A., Boillot, K., Brandt, H. & Castegnaro, M. (1998) Implication of cytochrome P-450 1A isoforms and the AH receptor in the genotoxicity of coal-tar fume condensate and bitumen fume condensates. *Environ. Toxicol. Pharmacol.*, **5**, 283–294
173. Giglia, G., Bouffet, E., Jouvet, A., Ohgaki, H., Kleihues, P. & Sarasin, A. (1999) Molecular analysis of glioma and skin-tumour alterations in a xeroderma-pigmentosum child. *Int. J. Cancer*, **81**, 345–350
174. Giraud, S., Zhang, C.X., Serova-Sinilnikova, O., Wautot, V., Salandre, J., Buisson, N., Waterlot, C., Bauters, C., Porchet, N., Aubert, J.P., Emy, P., Cadiot, G., Delemer, B., Chabre, O., Niccoli, P., Leprat, F., Duron, F., Emperauger, B., Cougard, P., Goudet, P., Sarfati, E., Riou, J.P., Guichard, S., Rodier, M., Meyrier, A., Caron, P., Vantyghem, M.C., Assayag, M., Peis, J.L., Pugeat, M., Rohmer, V., Vallotton, M., Lenoir, G., Gaudray, P., Proye, C., Conte-Devolx, B., Chanson, P., Shugart, Y.Y., Goldgar, D., Murat, A. & Calender, A. (1998) Germ-line mutation analysis in patients with multiple endocrine neoplasia type 1 and related disorders. *Am. J. Hum. Genet.*, **63**, 455–467
175. Goldgar, D. (1998) A likelihood-based approach to linkage disequilibrium testing. *Genet. Epidemiol.*, **15**, 516–519
176. Gordon, I., Boffetta, P. & Demers, P.A. (1998) A case-study comparing a meta-analysis and a pooled analysis of studies of sinonasal cancer among wood workers. *Epidemiology*, **9**, 518–524
177. Gratas, C., Tohma, Y., Barnas, C., Taniere, P., Hainaut, P. & Ohgaki, H. (1998) Up-regulation of Fas (APO-1/CD95) ligand and down-regulation of Fas expression in human esophageal cancer. *Cancer Res.*, **58**, 2057–2062
178. Gunnarsdottir, H.K., Kjaerheim, K., Boffetta, P., Rafnsson, V. & Hoar Zahm, S. (1999) Women's health: occupation, cancer, and reproduction. A conference overview. *Am. J. Ind. Med.*, **36**, 1–5
179. Hainaut, P. (1999) Cinq questions essentielles sur le gène suppresseur de tumeurs p53. *Rev. ACOMEN*, **5**, 305–311
180. Hainaut, P., Hernandez, T., Robinson, A., Rodriguez-Tome, P., Flores, T., Hollstein, M., Harris, C.C. & Montesano, R. (1998) IARC database of p53 gene mutations in human tumors and cell lines: updated compilation, revised formats and new visualisation tools. *Nucleic Acids Res.*, **26**, 205–213
181. Hainaut, P. & Hollstein, M. (1999) p53 and human cancer: the first ten thousand mutations. *Adv. Cancer Res.* (in press)
182. Hainaut, P. & Vahakangas, K. (1997) p53 as a sensor of carcinogenic exposures: mechanisms of p53 protein induction and lessons from p53 gene mutations. *Pathol. Biol.*, **45**, 833–844
183. Hainaut, P. & Vähäkangas, K. (1999) Genetic analysis of metabolic polymorphisms in molecular epidemiological studies: social and ethical implications. In: Vineis, P., Malats, N., Lang, M., d'Errico, A., Caporaso, N., Cuzick, J. & Boffetta, P., eds, *Metabolic Polymorphisms and Susceptibility to Cancer* (IARC Scientific Publications No. 148), Lyon, IARC, pp. 395–402
185. Hall, J. & Angèle, S. (1999) Radiation, DNA damage and cancer. *Mol. Med. Today*, **5**, 157–164
186. Harachi, H.R., Lesueur, F., Amati, P., Brown, A., Canzian, F., Kraimps, J.L., Levillain, P., Menet, E., Romeo, G. & Bonneau, D. (1999) Histology of familial thyroid tumours linked to a gene mapping to chromosome 19p13.2. *J. Pathol.*, **189**, 387–393
187. Herceg, Z. & Wang, Z.Q. (1999) Failure of poly-(ADP-ribose) polymerase cleavage by caspases leads to induction of necrosis and enhanced apoptosis. *Mol. Cell. Biol.*, **19**, 5124–5133
188. Hernandez-Boussard, T. & Hainaut, P. (1998) A specific spectrum of p53 mutations in lung cancer from smokers: review of mutations compiled in the IARC p53 database. *Environ. Health Perspect.*, **106**, 385–391
189. Hernandez-Boussard, T., Montesano, R. & Hainaut, P. (1999) Analysis of somatic mutations of the p53 gene in human cancers: a tool to generate hypotheses about the natural history of cancer. In: McGregor, D.B., Rice, J.M. & Venitt, S., eds, *The Use of Short- and Medium-Term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation* (IARC Scientific Publications No. 146), Lyon, IARC, pp. 43–53
190. Hernandez-Boussard, T., Montesano, R. & Hainaut, P. (1999) Sources of bias in the detection and reporting of p53 mutations in human cancer: analysis of the IARC p53 mutation database. *Genet. Anal. Biomol. Eng.*, **14**, 229–233
191. Hernandez-Boussard, T., Rodriguez-Tome, P., Montesano, R. & Hainaut, P. (1999) IARC p53 mutation database: a relational database to compile and analyze p53 mutations in human tumors and cell lines. *Hum. Mutat.*, **14**, 1–8
192. Hernandez, T. & Hainaut, P. (1998) Tumor-specific mutation spectra in the human p53 gene: from carcinogen "fingerprints" to functional consequences. *Environ. Carcinogen. Ecotox. Rev.*, **C16**, 31–45
193. Herrero, R., Hildesheim, A., Bratti, C., Sherman, M., Hutchinson, M., Morales, J., Balmaceda, I., Greenberg, M.D., Alfaro, M., Burk, R.D., Wacholder, S. & Schiffman, M.H. (1999) A population-based study of HPV infection and cervical neoplasia in rural Costa Rica. *J. Natl Cancer Inst.* (in press)

194. Herrero, R. & Muñoz, N. (1999) Human papillomavirus and cancer. *Cancer Surv. – Infections and Human Cancer*, **33**, 75–98
195. Herrero, R., Schiffman, M.H., Bratti, C., Hildesheim, A., Balmaceda, I., Sherman, M.E., Greenberg, M., Cardenas, F., Gomez, V., Helgesen, K., Morales, J., Hutchinson, M., Mango, L., Alfaro, M., Potischman, N.W., Wacholder, S., Swanson, C. & Brinton, L.A. (1997) Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste Project. *Pan Am. J. Publ. Health*, **5**, 362–375
196. Hildesheim, A., Bratti, M.C., Edwards, R.P., Schiffman, M., Rodriguez, A.C., Herrero, R., Alfaro, M., Morera, L.A., Ermatinger, S.V., Miller, B.T. & Crowley-Nowick, P.A. (1998) Collection of cervical secretions does not adversely affect Pap smears taken immediately afterwards. *Clin. Diag. Lab. Immunol.*, **5**, 491–493
197. Hildesheim, A., McShane, L.M., Schiffman, M., Bratti, M.C., Rodriguez, A.C., Herrero, R., Morera, L.A., Cardenas, F., Saxon, L., Bowman, F.P. & Crowley-Nowick, P.A. (1999) Cytokine and immunoglobulin concentrations in cervical secretions: reproducibility of the Weck-cel collection instrument and correlates of immune measures. *J. Immunol. Meth.*, **225**, 131–143
198. Hildesheim, A., Schiffman, M., Brinton, L.A., Fraumeni, J.F., Jr, Herrero, R., Bratti, M.C., Schwartz, P., Mortel, R., Barnes, W., Greenberg, M., McGowan, L., Scott, D.R., Martin, M., Herrera, J.E. & Carrington, M. (1998) p53 polymorphism and risk of cervical cancer. *Nature*, **396**, 530–532
199. Hirvonen, A., Mattson, K., Karjalainen, A., Ollikainen, T., Tammilehto, L., Hovi, T., Vainio, H., Pass, H.I., Di Resta, I., Carbone, M. & Linnainmaa, K. (1999) Simian virus 40 (SV40)-like DNA sequences not detectable in Finnish mesothelioma patients not exposed to SV40-contaminated polio vaccines. *Mol. Carcinog.*, **26**, 93–99
200. Hollstein, M., Hergenhahn, M., Yang, Q., Bartsch, H., Wang, Z.-Q. & Hainaut, P. (1999) New approaches to understanding p53 gene tumor mutation spectra. *Mutat. Res.* (in press)
201. Hooiveld, M., Heederik, D.J.J., Kogevinas, M., Boffetta, P., Needham, L.L., Patterson, D.G.J. & Bueno-de-Mesquita, H.B. (1998) Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. *Am. J. Epidemiol.*, **147**, 891–901
202. Huang, H., Fujii, H., Sankila, A., Mahler-Araujo, B.M., Matsuda, M., Cathomas, G. & Ohgaki, H. (1999) Beta-catenin mutations are frequent in human hepatocellular carcinomas associated with hepatitis C virus infection. *Am. J. Pathol.*, **155**, 1795–1801
203. Huang, H., Mahler-Araujo, B.M., Sankila, A., Chimelli, L., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (1999) APC and beta-catenin mutations in sporadic medulloblastomas. *Am. J. Pathol.* (in press)
204. Huang, H., Reis, R., Yonekawa, Y., Lopes, J.M., Kleihues, P. & Ohgaki, H. (1999) Identification in human brain tumors of DNA sequences specific for SV40 large T antigen. *Brain Pathol.*, **9**, 33–44
205. Husgafvel-Pursiainen, K., Kannio, A., Pylkkänen, L., Karjalainen, A., Sioris, T., Partanen, T., Ojajärvi, A., Anttila, S. & Vainio, H. (1998) Molecular biomarker studies in non-small cell lung cancer. *Lung Cancer*, **22**, 255–263
206. Husgafvel-Pursiainen, K., Karjalainen, A., Kannio, A., Anttila, S., Partanen, T., Ojajarvi, A. & Vainio, H. (1999) Lung cancer and past occupational exposure to asbestos. Role of p53 and K-ras mutations. *Am. J. Respir. Cell Mol. Biol.*, **20**, 667–674
207. Hutchinson, M.L., Zahniser, D.J., Sherman, M.E., Herrero, R., Alfaro, M., Bratti, M.C., Hildesheim, A., Lorincz, A.T., Greenberg, M.D., Morales, J. & Schiffman, M. (1999) Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. *Cancer Cytopathol.*, **87**, 48–55
208. IARC Working Group (1997) *Infection with Epstein-Barr Virus and Human Herpes Viruses* (*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 70), Lyon, IARC
209. IARC Working Group (1999) *Re-Evaluation of some Organic Chemicals, Hydrazine and Hydrogen Peroxide* (*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 71), Lyon, IARC
210. IARC Working Group (1999) *Hormonal Contraception and Post-Menopausal Hormonal Therapy* (*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 72), Lyon, IARC
211. IARC Working Group (1999) *Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and some Other substances* (*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 73), Lyon, IARC
212. IARC Working Group (1999) *Surgical Implants and Other Foreign Bodies* (*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol.74), Lyon, IARC (in press)
213. IARC Working Group (1998) *Carotenoids* (*IARC Handbooks of Cancer Prevention*, Vol. 2), Lyon, IARC
214. IARC Working Group (1998) *Vitamin A* (*IARC Handbooks of Cancer Prevention*, Vol. 3), Lyon, IARC
215. IARC Working Group (1999) *Retinoids* (*IARC Handbooks of Cancer Prevention*, Vol. 4), Lyon, IARC (in press)
216. Iscovich, J., Boffetta, P. & Brennan, P. (1998) Classic Kaposi's sarcoma in Arabs living in Israel, 1970–1993: a population-based incidence study. *Int. J. Cancer*, **77**, 319–321

217. Iscovich, J., Boffetta, P. & Brennan, P. (1999) Classic Kaposi's sarcoma as a first primary neoplasm. *Int. J. Cancer*, **80**, 173–177
218. Iscovich, J., Boffetta, P., Franceschi, S., Azizi, E. & Sarid, R. (1999) Classic Kaposi's sarcoma: epidemiology and risk factors. *Cancer* (in press)
219. Iscovich, J., Boffetta, P., Winkelmann, R. & Brennan, P. (1999) Classic Kaposi's sarcoma as a second primary neoplasm. *Int. J. Cancer*, **80**, 178–182
220. Iscovich, J., Boffetta, P., Winkelmann, R., Brennan, P. & Azizi, E. (1998) Classic Kaposi's sarcoma in Jews living in Israel, 1961–1989: a population-based incidence study. *AIDS*, **12**, 2067–2072
221. Iscovich, J.M. & Parkin, D.M., eds (1998) *The Risk of Cancer in Three Generations of Young Israelis: A Study of Migrants and their Descendants* (IARC Technical Report No. 27), Lyon, IARC
222. Ivanov, V.K., Gorski, A.I., Pitkevitch, V.A., Tsyb, A.F., Cardis, E. & Storm, H. (1999) Risk of radiogenic thyroid cancer in Russia following the Chernobyl accident. In: Thomas, G., Kavaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer*, Cambridge, World Scientific Publishing, pp. 89–96
223. Jefferies, S., Eeles, R., Goldgar, D.E., A'Hern, R., Henk, J.M., Gore, M.J. & Foulkes, W. (1999) The role of genetic factors in predisposition to squamous cell cancer of the head and neck. *Br. J. Cancer*, **79**, 865–867
224. Jongmans, W. & Hall, J. (1999) Cellular responses to radiation and risk of breast cancer. *Eur. J. Cancer*, **35**, 540–548
225. Jongmans, W., Vuillaume, M., Kleijer, W.J., Lakin, N.D. & Hall, J. (1998) The p53-mediated DNA damage response to ionising radiation in fibroblasts from ataxia-without-telangiectasia patients. *Int. J. Radiat. Biol.*, **74**, 287–295
226. Joossens, L. & Sasco, A., eds (1999) *Some Like It "Light". Women and Smoking in the European Union – European Report*, Paris, European Network for Smoking Prevention
227. Joossens, L., Sasco, A., Salvador, T. & Villalbi, J.R. (1999) Las mujeres y el tabaco en la Union Europea. *Rev. Esp. Salud Publ.*, **73**, 3–11
228. Kaaks, R. (1998) Statistical issues in dietary assessment in surveys and etiological studies. *Public Health Rev.*, **26**, 87–88
229. Kaaks, R., Tuyns, A.J., Haelterman, M. & Riboli, E. (1998) Nutrient intake patterns and gastric cancer risk: a case-control study in Belgium. *Int. J. Cancer*, **78**, 415–420
230. Kaaks, R., van Noord, P.A.H., Den Tonkelaar, I., Peeters, P.H.M., Riboli, E. & Grobbee, D.E. (1998) Breast-cancer incidence in relation to height, weight and body-fat distribution in the Dutch "DOM" cohort. *Int. J. Cancer*, **76**, 647–651
231. Kallassy, M., Martel, N., Damour, O., Yamasaki, H. & Nakazawa, H. (1998) Growth arrest of immortalized human keratinocytes and suppression of telomerase activity by $p21^{WAF1}$ gene expression. *Mol. Carcinogen.*, **21**, 26–36
232. Kaplanski, C., Wild, C.P. & Sengstag, C. (1998) Rearrangements in minisatellite sequences induced by aflatoxin B1 in a metabolically competent strain of *Saccharomyces cerevisiae*. *Carcinogenesis*, **19**, 1673–1678
233. Kato, I., Dnistrian, A.M., Schwartz, M., Toniolo, P., Koenig, K., Shore, R.E., Akhmedkhanov, A., Zeleniuch-Jacquotte, A. & Riboli, E. (1999) Serum folate, homocysteine and colorectal cancer risk in women: a nested case-control study. *Br. J. Cancer*, **79**, 1917–1921
234. Kato, I., Dnistrian, A.M., Schwartz, M., Toniolo, P., Koenig, K., Shore, R.E., Zeleniuch-Jacquotte, A., Akhmedkhanov, A. & Riboli, E. (1999) Epidemiologic correlates of serum folate and homocysteine levels among users and non-users of vitamin supplement. *Int. J. Vitam. Nutr. Res.*, **69**, 322–329
235. Kato, I., Dnistrian, A.M., Schwartz, M., Toniolo, P., Koenig, K., Shore, R.E., Zeleniuch-Jacquotte, A., Akhmedkhanov, A. & Riboli, E. (1999) Iron intake, body iron stores and colorectal cancer risk in women: a nested case-control study. *Int. J. Cancer*, **80**, 693–698
236. Kauppinen, T., Toikkanen, J., Pedersen, D., Young, R., Ahrens, W., Boffetta, P., Hansen, J., Kromhout, H., Maqueda Blasco, J., Mirabelli, D., de la Orden-Rivera, V., Pannett, B., Plato, N., Savela, A., Vincent, R. & Kogevinas, M. (1999) Occupational exposure to carcinogens in the European Union. *Occup. Environ. Med.* (in press)
237. Kirk, G.D., Camus-Randon, A.M., Mendy, M., Goedert, J.J., Merle, P., Trepo, C., Brechot, C., Hainaut, P. & Montesano, R. (1999) Ser-230 p53 mutations in plasma DNA from hepatocellular carcinoma patients from Gambia, West Africa. *J. Natl Cancer Inst.* (in press)
238. Kjaerheim, K. (1999) Occupational cancer research in the nordic countries. *Environ. Health Perspect.*, **107**, 233–238
239. Kleihues, P. & Ohgaki, H. (1999) Phenotype versus genotype in the evolution of astrocytic brain tumors. *Toxicol. Pathol.* (in press)
240. Kleihues, P. & Ohgaki, H. (1999) Primary and secondary glioblastomas: from concept to clinical diagnosis. *Neuro-Oncol.*, 44–51
241. Kleihues, P., Wiestler, O.D., Ohgaki, H. & Aguzzi, A. (1998) Animal models of tumors of the nervous system. In: Berger, M. & Wilson, C., eds, *Textbook of Gliomas*, Philadelphia, Saunders, pp. 124–133
242. Kogevinas, M. & Boffetta, P. (1998) Reply re. "Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols and dioxins: an expanded and updated international cohort study" (letter). *Am. J. Epidemiol.*, **147**, 1094–1095
243. Kogevinas, M., Kauppinen, T., Boffetta, P. & Saracci, R., eds (1998) *Estimation of the Burden of Occupational Cancer in Europe – Final Report*,

March 1998, Barcelona, Municipal Institute of Medical Investigation

244. Kogevinas, M., Sala, M., Boffetta, P., Hoar-Zahm, S., Kazerouni, N. & Kromhout, H. (1998) Reply re. "Cancer risk in the rubber industry: a review of recent epidemiological evidence" (letter). *Occup. Environ. Med.*, **55**, 646–647
245. Kogevinas, M., Sala, M., Boffetta, P., Kazerouni, N., Kromhout, H. & Hoar-Zahm, S. (1998) Cancer risk in the rubber industry: a review of the recent epidemiological evidence. *Occup. Environ. Med.*, **55**, 1–12
246. Konstandi, M., Marselos, M., Randon-Camus, A.M., Johnson, E. & Lang, M.A. (1998) The role of stress in the regulation of drug metabolizing enzymes in mice. *Eur. J. Drug Metab. Pharmacokinet.*, **23**, 483–490
247. Kovar, H., Jugovic, D., Melot, T., Zoubek, A., Lenoir, G., Fink, F.M., Philip, I., Turc-Carel, C., Thomas, G. & Zucman-Rossi, J. (1999) Cryptic exons as a source of increased diversity of Ewing tumor-associated EWS-FLI1 chimeric products. *Genomics*, **60**, 371–374
248. Kramarova, E., Kogevinas, M., Anh, C.T., Cau, H.D., Dai, L.C., Stellman, S.D. & Parkin, D.M. (1998) Exposure to Agent Orange and occurrence of soft-tissue sarcomas or non-Hodgkin lymphomas: an ongoing study in Vietnam. *Environ. Health Perspect.*, **106**, 671–678
249. Kreuzer, M., Boffetta, P., Whitley, E., Ahrens, W., Gaborieau, V., Heinrich, J., Jöckel, K.H., Kreienbrock, L., Mallone, S., Merletti, F., Roesch, F., Zambon, P. & Simonato, L. (1999) Gender differences in lung cancer risk by smoking: a multicentre case-control study in Germany and Italy. *Br. J. Cancer* (in press)
250. Krewski, D., Cardis, E., Zeise, L. & Feron, V. (1999) Empirical approaches to risk estimation and prediction. In: Moolgavkar, S., Krewski, D., Zeise, L., Cardis, E. & Møller, H., eds, *Quantitative Estimation and Prediction of Human Cancer Risks* (IARC Scientific Publications No. 131), Lyon, IARC, pp. 131–178
251. Krutovskikh, V. & Yamasaki, H. (1998) Gap junctional intercellular communication as a method to detect and predict carcinogenicity. In: Kitchin, K.T., ed., *Carcinogenicity. Testing, Predicting, and Interpreting Chemical Effects*, New York, Marcel Dekker, pp. 267–287
252. Krutovskikh, V.A., Yamasaki, H., Tsuda, H. & Asamoto, M. (1998) Inhibition of intrinsic gap-junction intercellular communication and enhancement of tumorigenicity of the rat bladder carcinoma cell line BC31 by a dominant-negative connexin 43 mutant. *Mol. Carcinogen.*, **23**, 254–261
253. Laken, S.J., Jackson, P.E., Kinzler, K.W., Vogelstein, B., Strickland, P.T., Groopman, J.D. & Friesen, M.D. (1998) Genotyping by mass spectrometric analysis of short DNA fragments. *Nature Biotechnol.*, **16**, 1352–1356
254. Lakhani, S.R., Jacquemier, J., Sloane, J.P., Gusterson, B.A., Anderson, T.J., van de Vijver, M., Farid, L.M., Venter, D., Antoniou, A., Storfer-Isser, A., Smyth, E., Steel, C.M., Haites, N., Scott, R.J., Goldgar, D., Neuhausen, S., Daly, P.A., Ormiston, W., McManus, R., Scherneck, S., Ponder, B.A.J., Ford, D., Peto, J., Stoppa-Lyonnet, D., Bignon, Y. J., Struewing, J.P., Spurr, N.K., Bishop, D.T., Klijn, J.G.M., Devilee, P., Cornelisse, C.J., Lasset, C., Lenoir, G., Barkardottir, R.B., Egilsson, V., Hamann, U., Chang-Claude, J., Sobol, H., Weber, B., Stratton, M.R. & Easton, D.F. (1998) Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. *J. Natl Cancer Inst.*, **90**, 1138–1145
255. Le Ninivin, A., Guigal, P.M., Sabatier, P., Sasco, A.J., Martinot, S., Fleury, C., Chary, J.F. & Cadoré, J.L. (1998) Descriptive epidemiology of tumors in horses: a questionnaire survey of French equine practitioners. *Riv. SIDI*, **4**, 118–122
256. Lea, C.S., Hertz-Picciotto, I., Andersen, A., Chang-Claude, J., Olsen, J.H., Pesatori, A.C., Teppo, L., Westerholm, P., Winter, P.D. & Boffetta, P. (1999) Gender differences in the healthy worker effect among synthetic vitreous fiber workers. *Am. J. Epidemiol.*, **150**, 1099–1106
257. Lechevrel, M., Casson, A.G., Wolf, C.R., Hardie, L.J., Flinterman, M.B., Montesano, R. & Wild, C.P. (1999) Characterisation of cytochrome P450 expression in human oesophageal mucosa. *Carcinogenesis*, **20**, 243–248
258. Lechevrel, M. & Wild, C.P. (1997) Absence of a differential induction of rat cytochrome P450 2E1 by different alcoholic beverages in rats: implications for the aetiology of human oesophageal cancer. *Arch. Toxicol.*, **71**, 690–695
259. Legoix, P., Legrand, M.F., Ollagnon, E., Lenoir, G., Thomas, G. & Zucman-Rossi, J. (1999) Characterisation of 16 polymorphic markers in the NF2 gene: application to hemizygosity detection. *Hum. Mutat.*, **13**, 290–293
260. Lesueur, F., Stark, M., Ayadi, H., Delisle, M.J., Goldgar, D.E., Schlumberger, M., Romeo, G. & Canzian, F. (1999) Genetic heterogeneity in familial nonmedullary thyroid carcinoma: exclusion of linkage to RET, MNG1, and TCO in 56 families. *J. Clin. Endocrinol. Metab.*, **84**, 2157–2162
261. Li Pira, G., Opezzi, L., Seri, M., Westby, M., Caroli, F., Fenoglio, D., Lancia, F., Ferraris, A., Bottone, L., Valle, M.T., Kunkl, A., Romeo, G., Dalgleish, A.G. & Manca, F. (1998) Repertoire breadth of human CD4+T cells specific for HIV gp120 and p66 (primary antigens) or for PPD and tetanus toxoid (secondary antigens). *Hum. Immunol.*, **59**, 137–148
262. Li, C.Q., Pignatelli, B. & Ohshima, H. (1999) Co-expression of interleukin-8 and inducible nitric oxide synthase in gastric mucosa infected with *cagA*$^+$ *Helicobacter pylori*. *Dig. Dis. Sci.* (in press)

263. Linnainmaa, K., Kivipensas, P. & Vainio, H. (1997) Toxicity and cytogenetic studies of ultrafine titanium dioxide in cultured rat liver epithelial cells. *Toxicol. in Vitro*, **11**, 329–335
264. Linnainmaa, K., Kivipensas, P. & Vainio, H. (1999) Effects of ultrafine titanium dioxide on toxicity and induction of micronuclei in cultured rat liver epithelial cells. *In Vitro Toxicol.* (in press)
265. Livshits, G., Vainder, M., Blettner, M., Graff, E., Wahrendorf, J. & Brunner, D. (1998) Major locus influencing plasma APO-A1 levels also controls plasma HDL3-C concentrations. *Genet. Epidemiol.*, **15**, 237–249
266. Lynch, H.T., Watson, P., Tinley, S., Snyder, C., Durham, C., Lynch, J., Kimarsky, Y., Serova, O., Lenoir, G., Lerman, C. & Narod, S. (1999) An update on DNA-based BRCA1/BRCA2 genetic counseling in hereditary breast cancer. *Cancer Genet. Cytogenet.*, **109**, 91–98
267. Lynch, J.F., Lemon, S.J., Durham, C., Snyder, C., Tonin, P., Lenoir, G., Serova, O., Narod, S., Lerman, C. & Lynch, H.T. (1999) Hereditary breast cancer: DNA-based genetic counseling. In: Utsumomiya, J., Mulvihill, J.J. & Weber, W., eds, *Familial Cancer and Prevention:Molecular Epidemiology: A New Strategy toward Cancer Control*, New York, Wiley-Liss, pp. 441–446
268. Magdinier, F., Ribieras, S., Lenoir, G.M., Frappart, L. & Dante, R. (1998) Down-regulation of BRCA1 in human sporadic breast cancer; analysis of DNA methylation patterns of the putative promoter region. *Oncogene*, **17**, 3169–3176
269. Malaveille, C., Hautefeuille, A., Pignatelli, B., Talaska, G., Vineis, P. & Bartsch, H. (1998) Antimutagenic dietary phenolics as antigenotoxic substances in urothelium of smokers. *Mutat. Res.*, **402**, 219–224
270. Mandir, A.S., Przedborski, S., Jackson-Lewis, V., Wang, Z.-Q., Simbulan-Rosenthal, C.M., Smulson, M.E., Hoffman, B.E., Guastella, D.B., Dawson, V.L. & Dawson, T.M. (1999) Poly(ADP-ribose) polymerase activation mediates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism. *Proc. Natl Acad. Sci. USA*, **96**, 5774–5779
271. Mannetje 't, A., Kogevinas, M., Chang-Claude, J., Cordier, S., Gonzalez, C.A., Hours, M., Jöckel, K.H., Bolm-Audorff, U., Lynge, E., Porru, S., Donato, F., Ranft, U., Serra, C., Tzonou, A., Vineis, P., Wahrendorf, J. & Boffetta, P. (1999) Smoking as a confounder in case-control studies on occupational bladder cancer in women. *Am. J. Ind. Med.*, **36**, 75–82
272. Mannetje 't, A., Kogevinas, M., Chang-Claude, J., Cordier, S., Gonzalez, C.A., Hours, M., Jöckel, K.H., Bolm-Audorff, U., Lynge, E., Porru, S., Donato, F., Ranft, U., Serra, C., Tzonou, A., Vineis, P., Wahrendorf, J. & Boffetta, P. (1999) Occupation and bladder cancer in European women. *Cancer Causes Control*, **10**, 209–217
273. Mannetje 't, A., Kogevinas, M., Luce, D., Demers, P.A., Bégin, D., Bolm-Audorff, U., Comba, P., Gérin, M., Hardell, L., Hayes, R.B., Leclerc, A., Maguani, C., Merler, E., Tobias, A. & Boffetta, P. (1999) Sinonasal cancer, occupation and tobacco smoking in European women and men. *Am. J. Ind. Med.*, **36**, 101–107
274. Martone, T., Airoldi, L., Magagnotti, C., Coda, R., Randone, D., Malaveille, C., Avanzi, G., Merletti, F., Hautefeuille, A. & Vineis, P. (1998) 4-Aminobiphenyl-DNA adducts and p53 mutations in bladder cancer. *Int. J. Cancer*, **75**, 512–516
275. Martone, T., Vineis, P., Malaveille, C. & Terracini, B. (1999) Impact of polymorphisms in xeno(endo)-biotic metabolism on pattern and frequency of p53 mutations in bladder cancer. *Mutat. Res.* (in press)
276. Marzin, D., Castegnaro, M. & Muranyi-Kovacs, I., eds (1998) *Manipulation de Produits Mutagènes et Cancérogènes*, Paris, Editions INSERM
277. Matos, E., Vilensky, M. & Boffetta, P. (1998) Environmental and occupational cancer in Argentina: a case-control study on lung cancer. *Cad. Saude Publica*, **14**, 77–86
278. Matos, E., Vilensky, M., Boffetta, P. & Kogevinas, M. (1998) Lung cancer and smoking: a case–control study in Buenos Aires, Argentina. *Lung Cancer*, **21**, 155–163
279. Mazoyer, S., Puget, N., Perrin-Vidoz, L., Lynch, H.T., Serova-Sinilnikova, O.M. & Lenoir, G.M. (1998) A BRCA1 nonsense mutation causes exon skipping. *Am. J. Hum. Genet.*, **62**, 713–715
280. McCredie, M., Little, J., Cotton, S., Mueller, B., Peris-Bonet, R., Choi, N.W., Cordier, S., Filippini, G., Holly, D.A., Modan, B., Arslan, A. & Preston-Martin, S. (1999) SEARCH international case-control study of childhood brain tumours: role of index pregnancy and birth, and mother's reproductive history. *Pediatr. Perinat. Epidemiol.*, **13**, 325–341
281. McGregor, D. (1998) Diets, food components and human cancer. *Biotherapy*, **11**, 189–200
282. McGregor, D. (1998) Industrial chemicals and human cancer. *Biotherapy*, **11**, 181–188
283. McGregor, D. (1998) Mutagenic chemicals: their significance. *Biotherapy*, **11**, 169–180
284. McGregor, D. & Partensky, C. (1998) Carcinogens and mutagens. In: Rose, J., ed., *Environmental Toxicology – Current Developments*, North Ryde, Australia, Gordon and Breach Science Publishers, pp. 49–78
285. McGregor, D.B. (1998) Carcinogenicity. In: Duffus, J.H. & Worth, H.G.J., eds, *Toxicology for Chemists*, Cambridge, Royal Society of Chemistry, pp. 90–100
286. McGregor, D.B. (1998) Mutagenicity. In: Duffus, J.H. & Worth, H.G.J., eds, *Toxicology for Chemists*, Cambridge, Royal Society of Chemistry, pp. 79–89
287. McGregor, D.B., Partensky, C., Wilbourn, J. & Rice, J.M. (1998) An IARC evaluation of polychlorinated dibenzo-*p*-dioxins and polychlorinated

dibenzofurans as risk factors in human carcinogenesis. *Environ. Health Perspect.*, **106**, 755–760

288. McGregor, D.B., Rice, J.M. & Venitt, S., eds (1999) *The Use of Short- and Medium-Term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation* (IARC Scientific Publications No. 146), Lyon, IARC
289. McKay, J.D., Williamson, J., Lesueur, F., Stark, M., Duffield, A., Canzian, F., Romeo, G. & Hoffman, L. (1999) At least three genes account for familial papillary thyroid carcinoma: *TCO* and *MNG1* excluded as susceptibility loci from a large Tasmanian family. *Eur. J. Endocrinol.*, **141**, 122–125
290. Melchionda, S., Seri, M., Carella, M., Piemontese, M.R., Zhang, X.X., Zelante, L., Romeo, G. & Gasparini, P. (1998) Linkage analysis in two large Italian pedigrees affected with nail patella syndrome. *Eur. J. Hum. Genet.*, **6**, 345–349
292. Merletti, F., Richiardi, L. & Boffetta, P. (1998) Effetti per la salute del fumo passivo. *Med. Lavoro*, **89**, 149–163
293. Mesnil, M. & Yamasaki, H. (1999) Bystander effect in suicide gene therapy of cancers. *Biogenic Amines*, **15**, 39–52
294. Ménégoz, F., Black, R.J., Arveux, P., Magne, V., Ferlay, J., Buémi, A., Carli, P.M., Chapelain, G., Faivre, J., Gignoux, M., Grosclaude, P., Mace-Lesech, J., Raverdy, N. & Schaffer, P. (1999) Cancer incidence and mortality in France in 1975–1995. *Eur. J. Cancer Prev.* (in press)
295. Méplan, C., Mann, K. & Hainaut, P. (1999) Cadmium induces conformational modifications of wild-type p53 and suppresses p53 response to DNA damage in cultured cells. *J. Biol. Chem.*, **274**, 31663–31670
296. Méplan, C., Richard, M.J. & Hainaut, P. (1999) Redox signalling and transition metals in the control of the p53 pathway. *Biochem. Pharmacol.* (in press)
297. Méplan, C., Verhaegh, G.W., Richard, M.J. & Hainaut, P. (1999) Metal ions as regulators of the conformation and function of the tumour suppresssor protein p53: implications for carcinogenesis. *Proc. Nut. Soc.*, **58**, 1–7
298. Miller, A.B. (1998) Chemoprevention of cancer. *Austr. Epidemiologist*, **5.4**, 2–5
299. Mironov, N., Jansen, L.A.M., Zhu, W.B., Aguelon, A.M., Reguer, G. & Yamasaki, H. (1999) A novel sensitive method to detect frameshift mutations in exonic repeat sequences of cancer-related genes. *Carcinogenesis*, **20**, 2189–2192
300. Mitacek, E.J., Brunnemann, K.D., Suttajit, M., Martin, N., Limsila, T., Ohshima, H. & Caplan, L.S. (1999) Exposure to N-nitroso compounds in a population of high liver cancer regions in Thailand: volatile nitrosamine (VNA) levels in Thai food. *Food Chem. Toxicol.*, **37**, 297–305
301. Molinier, B. & Castegnaro, M. (1998) La sécurité lors de l'expérimentation animale. In: Marzin, D., Castegnaro, M. & Muranyi-Kovacs, L, eds, *Manipulation de Produits Mutagènes et Cancérogènes*, Paris, INSERM, pp. 73–79
302. Molinier, B. & Castegnaro, M. (1998) Safety in animal experiments. In: Marzin, D. & Société Française de Toxicologie Génétique, eds, *Laboratory Handling of Mutagenic and Carcinogenic Products – Training Module No. 2*, Geneva, WHO, pp. 78–83
303. Monier, K., Michalet, X., Lamartine, J., Schurra, C., Heitzmann, F., Yin, L., Cinti, R., Sylla, B.S., Creaven, M., Porta, G., Vourc'h, C., Robert-Nicoud, M., Bensimon, A. & Romeo, G. (1998) High-resolution mapping of the X-linked lymphoproliferative syndrome region by FISH on combed DNA. *Cytogenet. Cell Genet.*, **81**, 259–264
304. Montesano, R. (1998) Chemical carcinogenesis. In: *Low Doses of Ionizing Radiation: Biological Effects and Regulatory Control. Invited Papers and Discussions*, Vienna, International Atomic Energy Agency, pp. 37–40
305. Montesano, R. & El Akroud, E. (1999) International Agency for Research on Cancer fellowships programme – over 30 years of experience. *Carcinogenesis*, **20**, 2041–2044
306. Montesano, R. & Hainaut, P. (1998) Molecular precursor lesions in esophageal cancer. *Cancer Surv.*, **32**, 53–68
307. Montesano, R., Hainaut, P. & Wild, C.P. (1997) Hepatocellular carcinoma: from gene to public health. *J. Natl Cancer Inst.*, **89**, 1844–1851
308. Moolgavkar, S., Krewski, D., Zeise, L., Cardis, E. & Møller, H., eds, (1999) *Quantitative Estimation and Prediction of Human Cancer Risks* (IARC Scientific Publications No. 131), Lyon, IARC
309. Moolgavkar, S., Woodward, A., Krewski, D., Cardis, E. & Zeise, L. (1999) Future perspectives, unresolved issues and research needs. In: Moolgavkar, S., Krewski, D., Zeise, L., Cardis, E. & Møller, H., eds, *Quantitative Estimation and Prediction of Human Cancer Risks* (IARC Scientific Publications No. 131), Lyon, IARC, pp. 305–322
310. Morgan, G. (1998) Correspondence re: R. Kim et al. Etiology of Barrett's metaplasia and esophageal adenocarcinoma. Cancer Epidemiol. Biomark. Prev., 6, 369–377, 1997 (Letter to the Editor). *Cancer Epidemiol. Biomarkers Prev.*, 7, 265
311. Morgan, G. & Vainio, H. (1998) Barrett's oesophagus, oesophageal cancer and colon cancer: an explanation of the association and cancer chemopreventive potential of non-steroidal anti-inflammatory drugs. *Eur. J. Cancer Prev.*, 7, 195–199
312. Morrison, C., Smith, G.C.M., Stingl, L., Jackson, S.P., Wagner, E.F. & Wang, Z.Q. (1997) Genetic interaction between PARP and DNA-PK in V(D)J recombination and tumorigenesis. *Nature Genet.*, **17**, 479–482
313. Munnes, M., Patrone, G., Schmitz, B., Romeo, G. & Doerfler, W. (1998) A 5′-CG-3′-rich region in the promoter of the transcriptionally frequently silenced

RET protooncogene lacks methylated cytidine residues. *Oncogene*, **17**, 2573–2583

314. Muñoz, N. (1998) Cáncer gástrico y Helicobacter pylori. In: Pajares Garcia, J.M., Correa, P. & Pérez-Pérez, G.I., eds, *Infeccion por Helicobacter Pylori en Lesiones Gastroduodenales. La Segunda Década,* Barcelona, Prous Science, pp. 199–209
315. Muñoz, N. (1998) Cáncer gástrico y Helicobacter pylori: evidencia epidemiologica y perspectivas para la prevencion (Gastric cancer and "Helicobacter pylori": epidemiological evidence and perspectives for prevention). *Anales Sys. San. Navarra*, **21**, 281–291
316. Muñoz, N. (1999) Gastric cancer and Helicobacter pylori: epidemiological evidence and perspectives for prevention. *Anales Sys. San. Navarra* (in press)
317. Nair, J., Barbin, A., Velic, I. & Bartsch, H. (1999) Etheno DNA-base adducts from endogenous reactive species. *Mutat. Res.*, **424**, 59–69
318. Nakamura, M., Rieger, J., Weller, M., Kim, J., Kleihues, P. & Ohgaki, H. (1999) APO2L/Trail expression in human brain tumors. *Acta Neuropathol.* (in press)
319. Nakazawa, K., Sahuc, F., Damour, O., Collombel, C. & Nakazawa, H. (1998) Regulatory effects of heat on normal human melanocyte growth and melanogenesis: comparative study with UVB. *J. Invest. Dermatol.*, **110**, 972–977
320. Narbonne, J.F., Pfohl-Leszkowicz, A., Castegnaro, M. & Heintz, J.M. (1999) Conclusion et recommandations. In: Pfohl-Leszkowicz, A., ed., *Les Mycotoxines dans l'Alimentation. Evaluation et Gestion du Risque,* Paris, Tec & Doc, pp. 451–456
321. Nei, H., Saito, T., Yamasaki, H., Mizumoto, H., Ito, E. & Kudo, R. (1999) Nuclear localization of beta-catenin in normal and carcinogenic endometrium. *Mol. Carcinogen.*, **25**, 207–218
322. Neuhausen, S.L., Godwin, A.K., Gershoni-Barch, R., Schubert, E., Garber, J., Stoppa-Lyonnet, D., Olah, E., Csokay, B., Serova, O., Lalloo, F., Osorio, A., Stratton, M., Offit, K., Boyd, J., Caligo, M.A., Scott, R.J., Schofield, A., Teugels, E., Schwab, M., Cannon-Albright, L., Bishop, T., Easton, D., Benitez, J., King, M.C. & Goldgar, D. (1998) Haplotype and phenotype analysis of nine recurrent BRCA2 mutations in 111 families: results of an international study. *Am. J. Hum. Genet.*, **62**, 1381–1388
323. Ngelangel, C., Muñoz, N., Bosch, F.X., Limson, G.M., Festin, M.R., Deacon, J., Jacobs, M.V., Santamaria, M., Meijer, C.J.L.M. & Walboomers, J.M.M. (1998) Causes of cervical cancer in the Philippines: a case-control study. *J. Natl Cancer Inst.*, **90**, 43–49
324. Nyberg, F., Agudo, A., Boffetta, P., Fortes, C., Gonzalez, C.A. & Pershagen, G. (1998) A European validation study of smoking and environmental tobacco smoke exposure in nonsmoking lung cancer cases and controls. *Cancer Causes Control*, **9**, 173–182
325. Ohgaki, H. (1999) Carcinogenicity of heterocyclic amines, general, rodents. In: Nagao, M. & Sugimura, T., eds, *Food Borne Carcinogens: Heterocyclic Amines,* New York, Wiley (in press)
326. Ohgaki, H., Hernandez, T., Kleihues, P. & Hainaut, P. (1999) p53 germline mutations and the molecular basis of the Li-Fraumeni syndrome. In: *Molecular Biology in Cancer Medicine,* London, Martin Dunitz, pp. 477–492
327. Ohgaki, H., Watanabe, K., Peraud, A., Biernat, W., von Deimling, A., Yasargil, M.G., Yonekawa, Y. & Kleihues, P. (1999) A case history of glioma progression. *Acta Neuropathol.*, **97**, 525–532
328. Ohshima, H. & Bartsch, H. (1999) Quantitative estimation of endogenous N-nitrosation in humans by monitoring N-nitrosoproline in urine. In: Packer, L., ed., *Methods in Enzymology,* Vol. 301 – *Nitric Oxide* – Part C: *Biological and Antioxidant Activities,* New York, Academic Press, pp. 40–49
329. Ohshima, H., Bianchini, F., Chazotte, L. & Gilibert, I. (1999) DNA damage induced by nitroxyl anion (NO^-). *Proc. Am. Assoc. Cancer Res.*, **40**, 649
330. Ohshima, H., Celan, I., Chazotte, L., Pignatelli, B. & Mower, H.F. (1999) Analysis of 3-nitrotyrosine in biological fluids and protein hydrolyzates by high-performance liquid chromatography using a post-separation, on-line reduction column and electrochemical detection: results with various nitrating agents. *Nitric Oxide Biol. Chem.*, **3**, 132–141
331. Ohshima, H., Gilibert, I. & Bianchini, F. (1999) Induction of DNA strand breakage and base oxidation by nitroxyl anion through hydroxyl radical production. *Free Radical Biol. Med.*, **26**, 1305–1313
332. Ohshima, H. & Masuda, M. (1999) Role of nitric oxide in carcinogenesis (in Japanese). *Exp. Med.*, **17**, 930–934
333. Ohshima, H., Yermilov, V., Yoshie, Y. & Rubio, J. (1998) DNA damage induced by reactive nitrogen species. In: Dizdaroglu, M. & Karakaya, A., eds, *Advances in DNA Damage and Repair,* New York, Plenum Press, pp. 329–340
334. Ohshima, H. & Yoshie, Y. (1998) Formation of peroxynitrite-like oxidant by reaction of nitric oxide with catechol-type compounds (catecholamines, catechol-estrogens). In: Moncada, S., Toda, N., Maeda, H. & Higgs, E.A., eds, *The Biology of Nitric Oxide*, Part 6, London, Portland Press, pp. 286
335. Ohshima, H., Yoshie, Y. & Auriol, S. (1998) Antioxidant and pro-oxidant properties of flavonoids: effects on DNA damage induced by nitric oxide and peroxynitrite. *Proc. Am. Assoc. Cancer Res.*, **39**, 371
336. Ohshima, H., Yoshie, Y., Auriol, S. & Gilibert, I. (1998) Antioxidant and pro-oxidant actions of flavonoids: effects on DNA damage induced by nitric oxide, peroxynitrite and nitroxyl anion. *Free Radical Biol. Med.*, **25**, 1057–1065

337. Ohshima, H., Yoshie, Y. & Gilbert, I. (1999) DNA strand breakage induced by nitric oxide together with catecholamine: its implications for neurodegenerative disease. In: Poli, G., Cadenas, E. & Packer, L., eds, *Free Radicals in Brain Pathophysiology (Oxidative Stress and Diseases Series)*, New York, Marcel Dekker, pp. 229–246
338. Olmsted, E.A., Gannon, F.H., Wang, Z.Q., Grigoriadis, A.E., Wagner, E.F., Zasloff, M.A., Shore, E.M. & Kaplan, F.S. (1998) Embryonic overexpression of the c-Fos protooncogene – a murine stem cell chimera applicable to the study of fibrodysplasia ossificans progressiva in humans. *Clin. Orthopaed.*, **346**, 81–94
339. Olschwang, S., Serova-Sinilnikova, O.M., Lenoir, G.M. & Deletorious, T.G. (1998) Germline mutations of the PTEN gene in juvenile polyposis coli, a disease predisposing to colon cancer. *Nature Genet.*, **18**, 12–14
340. Omori, Y., Duflot-Dancer, A., Mesnil, M. & Yamasaki, H. (1998) Dominant-negative inhibition of connexin-mediated tumor suppression by mutant connexin genes. In: Werner, R., ed., *Gap Junctions*, Amsterdam, IOS Press, pp. 377–381
341. Omori, Y., Duflot-Dancer, A., Mesnil, M. & Yamasaki, H. (1998) Role of connexin (gap junction) genes in cell growth control: approach with site-directed mutagenesis and dominant-negative effects. *Toxicol. Lett.*, 96,97, 105–110
342. Omori, Y. & Yamasaki, H. (1998) Mutated connexin43 proteins inhibit rat glioma cell growth suppression mediated by wild-type connexin 43 in a dominant-negative manner. *Int. J. Cancer*, 78, 446–453
343. Omori, Y. & Yamasaki, H. (1999) Gap junction proteins connexin32 and connexin 43 partially acquire growth-suppressive function in HeLa cells by deletion of their C-terminal tails. *Carcinogenesis*, **20**, 1913–1918
344. Ouhtit, A., Nakazawa, H., Armstrong, B.K., Kricker, A., Tan, E., Yamasaki, H. & English, D.R. (1998) UV-radiation-specific p53 mutation frequency in normal skin as a predictor of risk of basal cell carcinoma. *J. Natl Cancer Inst.*, **90**, 523–531
345. Parkin, D.M. (1998) Epidemiology of cancer: global patterns and trends. *Toxicol. Lett.*, **102–103**, 227–234
346. Parkin, D.M. (1998) The global burden of cancer. *Cancer Biol.*, **8**, 219–235
347. Parkin, D.M., Kramárová, E., Draper, G.J., Masuyer, E., Michaelis, J., Neglia, J., Qureshi, S. & Stiller, C.A., eds (1998) *International Incidence of Childhood Cancer*, Vol. II (IARC Scientific Publications No. 144), Lyon, IARC
348. Parkin, D.M. & Pisani, P. (1999) Gastric cancer. In: Kramer, B.S., Gohagan, J.K. & Prorok, P.C., eds, *Cancer Screening. Theory and Practice*, New York, Marcel Dekker, pp. 515–529
349. Parkin, D.M., Pisani, P. & Ferlay, J. (1999) Estimates of the worldwide incidence of 25 major cancers in 1990. *Int. J. Cancer*, **80**, 827–841
350. Parkin, D.M., Pisani, P., Muñoz, N. & Ferlay, J. (1999) The global health burden of infection associated cancers. *Cancer Surv., Infections and Human Cancer*, **33**, 5–33
351. Parkin, D.M. & Sankaranarayanan, R. (1999) Prevention of cervical cancer in developing countries. *Thai J. Obstet. Gynaecol.*, **11**, 3–20
352. Parkin, D.M., Shanmugaratnam, K., Sobin, L., Ferlay, J. & Whelan, S., eds (1998) *Histological Groups for Comparative Studies* (IARC Technical Report No. 31), Lyon, IARC
353. Parkin, D.M., Wabinga, H., Nambooze, S. & Wabwire-Mangen, F. (1999) AIDS-related cancers in Africa: maturation of the epidemic in Uganda. *AIDS* (in press)
354. Parkin, D.M. & Ziegler, J. (1999) Malignant diseases. In: Strickland, G.T., ed., *Hunters Tropical Medicine*, 8th ed., Philadelphia, W.B.Saunders (in press)
355. Partanen, T., Boffetta, P. & Weiderpass, E. (1998) Leukaemia, malignant lymphomas and multiple myeloma. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol. I, 4th Ed., Geneva, International Labour Office, pp. 1.3–1.5
356. Partanen, T., Boffetta, P. & Weiderpass, E. (1998) Malignant melanoma. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol. I, 4th Ed., Geneva, International Labour Office, pp. 12.8–12.9
357. Partanen, T., Kauppinen, T., Boffetta, P. & Weiderpass, E. (1998) Liver cancer. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol. I, 4th Ed., Geneva, International Labour Office, pp. 4.9
358. Partanen, T., Kauppinen, T., Boffetta, P. & Weiderpass, E. (1998) Pancreatic cancer. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol. I, 4th Ed., Geneva, International Labour Office, pp. 4.10–4.11
359. Partanen, T., Vainio, H., Boffetta, P. & Weiderpass, E. (1998) Renal-urinary cancers. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol. I, 4th Ed., Geneva, International Labour Office, pp. 8.10–8.13
360. Partanen, T., Vasama-Neuvonen, K., Pukkala, E., Weiderpass, E., Welp, E., Kauppinen, T., Paakkulainen, H., Mutanen, P. & Boffetta, P. (1998) Rintasyövällä voi olla työhön liittyviä vaaratekijöitä [Breast cancer may have work-related risk factors]. *Työ ja Ihminen (Work and Man)*, **12**, 161–166
361. Pearce, N., Boffetta, P. & Kogevinas, M. (1998) Introduction to Cancer chapter. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol. I, 4th Ed., Geneva, International Labour Office, pp. 2.2–2.4
362. Pelet, A., Geneste, O., Edery, P., Pasini, A., Chappuis, S., Attié, T., Munnich, A., Lenoir, G.,

Lyonnet, S. & Billaud, M. (1998) Various mechanisms cause RET-mediated signaling defects in Hirschsprung's disease. *J. Clin. Invest.*, **101**, 1415–1423

363. Peluso, M., Airoldi, L., Magagnotti, C., Florini, L., Munnia, A., Hautefeuille, A., Malaveille, C. & Vineis, P. (1999) White blood cell DNA adducts and fruit and vegetable consumption in bladder cancer. *Carcinogenesis* (in press)
364. Peluso, M., Airoldi, L. & Malaveille, C. (1999) Fruit, vegetables, and DNA adducts in bladder cancer. *Proc. Am. Assoc. Cancer Res.*, **40**, 150
365. Peluso, M., Airoldi, L., Munnia, A., Martone, T., Coda, R., Malaveille, C., Giacomelli, G., Terrone, C., Casetta, G. & Vineis, P. (1998) White blood cell DNA adducts, smoking, and NAT2 GSTM1 genotypes in bladder cancer: a case-control study. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 341–346
366. Peraud, A., Watanabe, K., Schwechheimer, K., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (1999) Genetic profile of the giant cell glioblastoma. *Lab. Invest.*, **79**, 123–129
367. Petkova-Bocharova, T., Stoichev, I.I., Chernozemsky, I.N., Castegnaro, M. & Pfohl-Leszkowicz, A. (1998) Formation of DNA adducts in tissues of mouse progeny through transplacental contamination and/or lactation after administration of a single dose of ochratoxin A to the pregnant mother. *Environ. Mol. Mutagen.*, **32**, 155–162
368. Petkova-Bocharova, T., Stoichev, I.I., Chernozemsky, I.N., Castegnaro, M. & Pfohl-Leszkowicz, A. (1998) OTA induces DNA adduct formation in kidney and liver of foetus and offspring mice through transplacental contamination. *Rev. Med. Vet.*, **149**, 661
369. Peyton, C.L., Schiffman, M., Lörincz, A.T., Hunt, W.C., Mielzynska, I., Bratti, C., Aton, S., Hildesheim, A., Morera, L.A., Rodriguez, A.C., Herrero, R., Sherman, M.E. & Wheeler, C.M. (1998) Comparison of PCR- and hybrid capture-based human papillomavirus detection systems by using multiple cervical specimen collection strategies. *J. Clin. Microbiol.*, **36**, 3248–3254
370. Pfohl-Leszkowicz, A. & Castegnaro, M. (1999) L'ochratoxine A. In: Pfohl-Leszkowicz, A., ed., *Les Mycotoxines dans l'Alimentation. Evaluation et Gestion du Risque,* Paris, Tec & Doc, pp. 249–277
371. Pfohl-Leszkowicz, A. & Castegnaro, M. (1999) Les fumonisines. In: Pfohl-Leszkowicz, A., ed., *Les Mycotoxines dans l'Alimentation. Evaluation et Gestion du Risque,* Paris, Tec & Doc, pp. 295–330
372. Pfohl-Leszkowicz, A., Pinelli, E., Bartsch, H., Mohr, U. & Castegnaro, M. (1998) Sex- and strain-specific expression of cytochrome P450s in ochratoxin A-induced genotoxicity and carcinogenicity in rats. *Mol. Carcinogen.*, **23**, 76–85
373. Pfohl-Leszkowicz, A., Pinelli, E., Mohr, U., Bartsch, H. & Castegnaro, M. (1998) Strain and sex specific genotoxic and carcinogenic response of OTA in rats is in part controlled by CYP-mediated metabolic reactions. *Rev. Med. Vet.*, **149**, 659
374. Phillips, D.H. & Castegnaro, M. (1998) Inter-laboratory standardisation and validation of DNA adduct postlabelling methods. *Proc. Am. Assoc. Cancer Res.*, 284–285
375. Phillips, D.H. & Castegnaro, M. (1999) Standardization and validation of DNA adduct postlabelling methods: report of interlaboratory trials and production of recommended protocols. *Mutagenesis*, **14**, 301–315
376. Pieper, A.A., Brat, D.J., Krug, D.K., Watkins, C.C., Gupta, A., Blackshaw, S., Verma, A., Wang, Z.Q. & Snyder, S.H. (1999) Poly(ADP-ribose)polymerase-deficient mice are protected from streptozotocin-induced diabetes. *Proc. Natl Acad. Sci. USA*, **96**, 3059–3064
377. Pignatelli, B., Bancel, B., Estève, J., Malaveille, C., Calmels, S., Correa, P., Patricot, L.M., Laval, M., Lyandrat, N. & Ohshima, H. (1998) Inducible nitric oxide synthase, anti-oxidant enzymes and *Helicobacter pylori* infection in gastritis and gastric precancerous lesions in humans. *Eur. J. Cancer Prev.*, **7**, 439–447
378. Pignatelli, B., Li, C.Q., Bancel, B., Toyokuni, S. & Ohshima, H. (1999) Oxidative stress in the human stomach infected with *Helicobacter pylori*: effect of bacterial eradication. In: Beger, H.G. & Link, K.H., eds, *2nd International Congress on Gastroenterological Carcinogenesis, Ulm, March 25–27, 1999,* Bologna, Italy, Monduzzi Editore, pp. 39–42
379. Pinelli, E., Pipy, B., Castegnaro, M., Miller, D.J. & Pfohl-Leszkowicz, A. (1998) Fumonisin B1 stimulates arachidonic acid cascade by activation of mitogen-activated protein kinase. *Rev. Med. Vet.*, **149**, 651
380. Pinelli, E., Poux, N., Garren, L., Pipy, B., Castegnaro, M., Miller, D.J. & Pfohl-Leszkowicz, A. (1999) Activation of mitogen-activated protein kinase by fumonisin B_1 stimulates $cPLA_2$ phosphorylation, the arachidonic acid cascade and cAMP production. *Carcinogenesis*, **20**, 1683–1688
381. Pingault, V., Bondurand, N., Kuhlbrodt, K., Gehrich, D.E., Préhu, M.O., Puliti, A., Herbarth, B., Hermans-Borgmeyer, I., Legius, E., Matthijs, G., Amiel, J., Lyonnet, S., Ceccherini, I., Romeo, G., Smith, J.C., Read, A.P., Wegner, M. & Goossens, M. (1998) SOX10 mutations in patients with Waardenburg-Hirschsprung disease. *Nature Genet.*, **18**, 171–173
382. Pisani, P., Parkin, D.M., Bray, F. & Ferlay, J. (1999) Estimates of the worldwide mortality of 25 cancers in 1990. *Int. J. Cancer*, **83**, 18–29
383. Preston-Martin, S., Pogoda, J.M., Mueller, B.A., Lubin, F., Modan, B., Holly, E.A., Filippini, G., Cordier, S., Peris-Bonet, R., Choi, W., Little, J. & Arslan, A. (1998) Prenatal vitamin supplementation and paediatric brain tumors: huge international variation in use and possible reduction in risk. *Childs Nerv. Syst.*, **14**, 551–557

384. Preston-Martin, S., Pogoda, J.M., Mueller, B.A., Lubin, F., Modan, B., Holly, E.A., Filippini, G., Cordier, S., Peris-Bonet, R., Choi, W., Little, J. & Arslan, A. (1998) Results from an international case-control study of childhood brain tumors: the role of prenatal vitamin supplementation. *Environ. Health Perspect.*, **106**, 887–892
385. Preston-Martin, S., Pogoda, J.M., Schlehofer, B., Blettner, M., Howe, G.R., Ryan, P., Ménégoz, F., Giles, G.G., Rodvall, Y., Choi, N.W., Little, J. & Arslan, A. (1998) An international case-control study of adult glioma and meningioma: the role of head trauma. *Int. J. Epidemiol.*, 27, 579–586
386. Puget, N., Sinilnikova, O.M., Stoppa-Lyonnet, D., Audoynaud, C., Pages, S., Lynch, H.T., Goldgar, D., Lenoir, G.M. & Mazoyer, S. (1999) An *Alu*-mediated 6-kb duplication in the *BRCA1* gene: a new founder mutation? *Am. J. Hum. Genet.*, **64**, 300–302
387. Puget, N., Stoppa-Lyonnet, D., Sinilnikova, O.M., Pagès, S., Lynch, H.T., Lenoir, G.M. & Mazoyer, S. (1999) Screening for germ-line rearrangements and regulatory mutations in BRCA1 led to the identification of four new deletions. *Cancer Res.*, **59**, 455–461
388. Puliti, A., Cinti, R., Betsos, N., Romeo, G. & Ceccherini, I. (1999) HOX11L1, a gene involved in peripheral nervous system development, maps to human chromosome 2p13.1-p12 and mouse chromosome 6C3-D1. *Cytogenet. Cell Genet.*, **84**, 115–117
389. Puliti, A., Cinti, R., Seri, M., Ceccherini, I. & Romeo, G. (1999) Assignment of the mouse Gdnfr-a, the homologue of a new human HSCR candidate gene, to the telomeric region of mouse Chromosome 19. *Cytogenet. Cell Genet.*, **84**, 115–117
390. Quoc, N.M., Hung, C., Kramarova, E. & Parkin, D.M. (1999) Incidence of childhood cancer in Ho Chi Minh City, Vietnam, 1995–1997. *Pediatr. Perinat. Epidemiol.* (in press)
391. Quoc, N.M., Hung, N.C. & Parkin, D.M. (1998) Cancer incidence in Ho Chi Minh City, Viet Nam, 1995–1996. *Int. J. Cancer*, **76**, 472–479
392. Rachet, B., Sasco, A.J., Abrahamowicz, M. & Benyamine, D. (1998) Prognostic factors for mortality in nasopharyngeal cancer, accounting for time-dependence of relative risks. *Int. J. Epidemiol.*, **27**, 772–780
393. Rajower, I., Eichholzer, M., Reinli, K., Sasco, A.J., Charrondière, U.R. & Riboli, E., eds (1998) *Ernährung und Krebs: Epidemiologische Beweislage*, Bern, Schweizerische Krebsliga
394. Rapiti, E., Jindal, S.K., Gupta, D. & Boffetta, P. (1999) Passive smoking and lung cancer in Chandigarh, India. *Lung Cancer*, **23**, 183–189
395. Reis, R.M., Konu-Lebleblicioglu, D., Lopes, J.M., Kleihues, P. & Ohgaki, H. (1999) Genetic profile of the gliosarcoma. *Am. J. Pathol.* (in press)
396. Riboli, E. & Kaaks, R. (1999) The challenge of multi-center cohort studies in the search for diet and cancer links. *Am. J. Epidemiol.* (in press)
397. Rice, J.M. (1999) Carcinogenicity of dioxins in experimental animals and humans: Evaluations by the *IARC Monographs*. *Mutagen. Res.*, **21**, 191–196
398. Rice, J.M., Baan, R.A., Blettner, M., Genevois-Charmeau, C., Grosse, Y., McGregor, D.B., Partensky, C. & Wilbourn, J.D. (1999) Rodent tumors of urinary bladder, renal cortex, and thyroid gland in *IARC Monographs* evaluations of carcinogenic risk to humans. *Toxicol. Sci.*, **49**, 166–171
399. Rieger, J., Ohgaki, H., Kleihues, P. & Weller, M. (1998) Human astrocytic brain tumors express APO2L/TRAIL. *Acta Neuropathol.*, **97**, 1–4
400. Rolon, P.A., Smith, J.S., Muñoz, N., Klug, S.J., Herrero, R., Bosch, X., Llamosas, F., Meijer, C.J.L.M. & Walboomers, J.M.M. (1999) Human papillomavirus infection and invasive cervical cancer in Paraguay. *Int. J. Cancer* (in press)
401. Romeo, G., Canzian, F., Corvi, R., Stark, M. & Yin, L. (1999) The concept of phenotypic diversity and allelic series: the case of mutations of the ret proto-oncogene associated with different diseases. *Forum Trends in Experimental and Clinical Medicine* (in press)
402. Romeo, G., Ceccherini, I., Celli, J., Priolo, M., Betsos, N., Bonardi, G., Seri, M., Yin, L., Lerone, M., Jasonni, V. & Martucciello, G. (1998) Association of multiple endocrine neoplasia type 2 and Hirschsprung disease. *J. Intern. Med.*, **243**, 515–520
403. Ronco, A., De Stefani, E., Boffetta, P., Deneo-Pellegrini, H., Mendilaharsu, M. & Leborgne, F.J. (1999) Vegetables, fruits, related nutrients and risk of breast cancer: a case-control study in Uruguay. *Nutr. Cancer* (in press)
404. Roth, S., Partanen, T., Suitiala, T., Anttila, S., Ojajärvi, A., Hemminki, K., Vainio, H. & Husgafvel-Pursiainen, K. (1997) Molecular analysis of occupational cancer: infrequent p53 and ras mutations in renal cell cancer in workers exposed to gasoline. *Int. J. Cancer*, **73**, 492–496
405. Rouault, J.P., Kuwabara, P.E., Sinilnikova, O.M., Duret, L., Thierry-Mieg, D. & Billaud, M. (1999) Regulation of dauer larva development in *Caenorhabditis elegans* by daf-18, a homologue of the tumour suppressor PTEN. *Curr. Biol.*, **9**, 329–332
406. Saadatian, M., Goudable, J. & Riboli, E. (1999) Lipides et cancer. *Oléagineux Corps Gras Lipides (OCL)*, **6**, 242–252
407. Saarikoski, S.T., Husgafvel-Pursiainen, K., Hirvonen, A., Vainio, H., Gonzalez, F.J. & Anttila, S. (1998) Localization of CYP1A1 mRNA in human lung by in situ hybridization: comparison with immunohistochemical findings. *Int. J. Cancer*, **77**, 33–39
408. Saarikoski, S.T., Reinikainen, M., Anttila, S., Karjalainen, A., Vainio, H., Husgafvel-Pursiainen, K. & Hirvonen, A. (1999) Role of NAT2 deficiency

in susceptibility to lung cancer among asbestos-exposed individuals. *Pharmacogenetics* (in press)

409. Saarikoski, S.T., Voho, A., Reinikainen, M., Anttila, S., Karjalainen, A., Malaveille, C., Vainio, H., Husgafvel-Pursiainen, K. & Hirvonen, A. (1998) Combined effect of polymorphic GST genes on individual susceptibility to lung cancer. *Int. J. Cancer*, **77**, 516–521
410. Saarikoski, S.T., Voho, A., Reinikeinen, M., Anttila, S., Karjalainen, A., Malaveille, C., Vainio, H., Husgafvel-Pursiainen, K. & Hirvonen, A. (1998) GST polymorphisms as modifiers of individual lung cancer risk. *Proc. Am. Assoc. Cancer Res.*, **39**, 182
411. Sacerdote, C., Peluso, M., Munnia, A., Malaveille, C. & Vineis, P. (1999) The choice of controls in a case-control study on WBC-DNA adducts and metabolic polymorphisms. *Biomarkers* (in press)
412. Saito, T., Schlegel, R., Andresson, T., Yuge, L., Yamamoto, M. & Yamasaki, H. (1998) Induction of cell transformation by mutated 16K vacuolar H^+-ATPase (ductin) is accompanied by down-regulation of gap junctional intercellular communication and translocation of connexin 43 in NIH3T3 cells. *Oncogene*, **17**, 1673–1680
413. Sali, D. & Boffetta, P. (1999) Kidney cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies. *Cancer Causes Control* (in press)
414. Sali, D., Boffetta, P., Andersen, A., Cherrie, J.W., Chang-Claude, J., Hansen, J., Olsen, J.H., Pesatori, A.C., Plato, N., Teppo, L., Westerholm, P., Winter, P. & Saracci, R. (1999) Non-neoplastic mortality of European workers who produce man-made vitreous fibres. *Occup. Environ Med.*, **56**, 612–617
415. Sankaranarayanan, R. (1998) Health care auxiliaries in the detection and prevention of oral cancer. *Eur. J. Cancer*, **33**, 149–154
416. Sankaranarayanan, R., Babu, M., Binu, J.J., Gigi, T., Thara, S., Pisani, P., Manoj, P., Najeeb, K.R., Abraham, E., Sebestian, P., Iqbal, A., Sreedevi, A., Nair, M.K. & Parkin, D.M. (1999) Early findings from a community based cluster randomized controlled oral cancer screening trial in Kerala, India. *Cancer* (in press)
417. Sankaranarayanan, R., Becker, N. & Démaret, E., eds (1999) *Directory of On-Going Research in Cancer Prevention*, Lyon, IARC
418. Sankaranarayanan, R., Black, R.J. & Parkin, D.M., eds (1999) *Cancer Survival in Developing Countries* (IARC Scientific Publications No. 145), Lyon, IARC
419. Sankaranarayanan, R., Black, R.J., Swaminathan, R. & Parkin, D.M. (1999) An overview on cancer survival in developing countries. In: Sankaranarayanan, R., Black, R.J. & Parkin, D.M., eds, *Cancer Survival in Developing Countries* (IARC Scientific Publications No. 145), Lyon, IARC, pp. 135–157
420. Sankaranarayanan, R., Démaret, E., Becker, N. & Wahrendorf, J. (1999) Directory of on-going research in cancer prevention. *Int. J. Cancer* (in press)
421. Sankaranarayanan, R., Masuyer, E., Swaminathan, R., Ferlay, J. & Whelan, S. (1998) Head and neck cancer: a global perspective on epidemiology and prognosis. *Anticancer Res.*, **18**, 4779–4786
422. Sankaranarayanan, R., Shyamalakumari, B., Wesley, R., Amma, N.S., Parkin, D.M. & Krishnan Nair, M. (1998) Visual inspection with acetic acid in the early detection of cervical cancer and precursors. *Int. J. Cancer*, **80**, 161–163
423. Sankaranarayanan, R., Wesley, R., Somanathan, T., Dhakad, N., Shyamalakumari, B., Sreedevi, A.N., Parkin, D.M. & Krishnan Nair, M. (1998) Performance of visual inspection after acetic acid application (VIA) in the detection of cervical carcinoma precursors. *Cancer*, **83**, 2150–2156
424. Sankaranarayanan, R., Wesley, R., Somanathan, T., Dhakad, N., Shyamalakumary, B., Amma, N.S., Parkin, D.M. & Nair, M.K. (1998) Visual inspection of the uterine cervix after the application of acetic acid in the detection of cervical carcinoma and its precursors. *Cancer*, **83**, 2150–2156
425. Saracci, R. (1999) Epidemiology in progress: thoughts, tensions and targets. *Int. J. Epidemiol*, **28**, S997-S999
426. Sasaki, K., Mironov, N., Yilmaz, A., Lahm, H., Odartchenko, N. & Yamasaki, H. (1998) Malignant transformation of simian virus 40 – immortalized human milk epithelial cells by chemical carcinogenesis accompanied by loss of heterozygosity on chromosome 1 but not microsatellite instability. *Mol. Carcinogen.*, **23**, 20–24
427. Sasco, A. (1999) Epidémiologie descriptive: les chiffres. Facteurs de risque. Approche épidémiologique du cancer bronchique. *Rev. Mal. Respir.*, **16**, 3S44–3S45
428. Sasco, A. (1999) Politique européenne anti-tabac. In: Delpierre, A., Scagliotti, G.V., Quoix, E. & Tonato, M., eds, *Le Cancer Bronchique Non à Petites Cellules*, Paris, Ed. Ecole Européenne d'Oncologie - Expression Française, pp. 95–99
429. Sasco, A.J. (1998) Le rôle du mode de vie et de l'environnement. *ADSP*, **25**, 27–30, 52
430. Sasco, A.J. (1998) Lung cancer prevention: the point of view of a public health epidemiologist. In: Martinet, Y., Hirsch, F.R., Martinet, N., Vignaud, J.M. & Mulshine, J.L., eds, *Clinical and Biological Basis of Lung Cancer Prevention*, Basel, Birkhäuser Verlag, pp. 297–304
431. Sasco, A.J. (1998) Tamoxifen, a human carcinogen or the share of common risk factors? *Eur. J. Cancer*, **34**, S43-S44
432. Sasco, A.J. (1998) Validity issues in study design. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, 4th ed., Geneva, International Labour Office, pp. 28.19–28.22
433. Sasco, A.J. (1999) Epidémiologie et facteurs de la carcinogenèse mammaire et utérine. In: Boiron, M. & Marty, M., eds, *Eurocancer 99 – Compte rendu*

du XIIe Congrès, 2–4 Juin 1999, Paris, Paris, John Libbey Eurotext, pp. 27–28

434. Sasco, A.J. (1999) Evaluation of the carcinogenicity of selected antiestrogens: the IARC Monographs classification. *Primary Care Cancer*, **Suppl. 2**, 33–39
435. Sasco, A.J. (1999) Evolution of smoking among women in Europe. In: Lang, P. & Greiser, E., eds, *European Symposium on Smoking and Pregnancy,* Bremen, Bremen Institute for Prevention Research and Social Medicine, pp. 13–22
436. Sasco, A.J. (1999) Passive smoking, a methodological challenge, a public health reality. In: Sasco, A.J. & Dubois, G., eds, *Passive Smoking, the Health Impact. A European Report,* Paris, Europe against Cancer Programme, pp. 9–22
437. Sasco, A.J. (1999) Pharmacoprévention du cancer du sein par tamoxifène: devons-nous encore nous poser la question? *Rev. Epidemiol. Santé Publ.*, **47**, 279–285
438. Sasco, A.J. (1999) Tamoxifène et cancer de l'endomètre: un lien démontré, quelles implications? *Réf. Gynecol. Obstet.*, **No. Special**, 8–11
439. Sasco, A.J. (1999) Women's smoking: health consequences. In: Joossens, L. & Sasco, A.J., eds, *Some Like It "Light". Women and Smoking in the European Union. European Report,* Europe against Cancer; European Network for Smoking Prevention, pp. 9–22
440. Sasco, A.J., Ahlbom, A., Berrino, F., Bums, P.A., Chilvers, C., van Leeuwen, F., Teissier, C. & Vecchio, D. (1998) Exposure to selected viruses in research laboratories (EVIL programme). In: Baig, S.S., ed., *Cancer Research Supported Under BioMed I,* Amsterdam, IOS Press, pp. 297–299
441. Sasco, A.J., Berrino, F., Bouchardy, C., Fisch, T., Hardell, L., Iscovich, J. & Schaffer, P. (1998) A multicentric case-control study of selected second cancers following breast cancer. EuroDeucaTam Study. In: Baig, S.S., ed., *Cancer Research Supported Under Biomed I,* Amsterdam, IOS Press, pp. 294–296
442. Sasco, A.J. & Dubois, G., eds (1999) *Passive Smoking, the Health Impact. A European Report.* Paris, Europe againt Cancer Programme
443. Sasco, A.J. & Gendre, I. (1998) Epidémiologie actuelle des cancers de la vulve. *Contracept. Fertil. Sex.*, **26**, 858–864
444. Sasco, A.J., Gendre, I. & Couris, C. (1998) Epidémiologie du cancer du pancréas ou la recherche étiologique au service de la clinique. *Cahiers Oncol.*, **7**, 189–203
445. Sasco, A.J., Gendre, I., Verbier-Naneix, C., Soulier, J.L., Raffi, F., Satgé, D. & Robert, E. (1998) Neonatal neuroblastoma and in utero exposure to progestagens. *Int. J. Risk Safety Med.*, **11**, 121–128
446. Sasco, A.J. & Kleihues, P. (1998) Data protection in biomedical research – an international perspective with special emphasis on cancer registries and multicentric international epidemiological studies. *Commission d'Experts du Secret Professionnel en Matière de Recherche Médicale,* **Janvier**, 39–46
447. Sasco, A.J., Mélihan-Cheinin, P., Ah-Song, R. & Hirsch, A. (1998) Evaluation et comparaison de la législation de contrôle du tabagisme dans les Etats membres de l'Union Européenne. *Rev. Epidemiol. Santé Publ.*, **46**, 523–531
448. Sasco, A.J. & Rachet, B. (1998) Le point sur l'étude du C.I.R.C. sur le risque de cancer pour les personnels des laboratoires publics de recherche dans les domaines biologique, médical et agronomique en Europe. *Bull. Inform. Assoc. Natl Med. Trav. Ergonom. Person. Hop.*, **33**, 18–19
449. Sasco, A.J. & Rice, J.M. (1998) IARC evaluation of the carcinogenicity of antioestrogens. Basic facts and rationale for appropriate use in medicine (editorial). *Presentations in Focus,* Medical Education Network, pp. 3–6
450. Sasco, A.J. & Vainio, H. (1999) From in utero and childhood exposure to parental smoking to childhood cancer: a possible link and the need for action. *Hum. Exper. Toxicol.*, **18**, 192–201
451. Satarug, S., Haswell-Elkins, M.R., Sithithaworn, P., Bartsch, H., Ohshima, H., Tsuda, M., Mairiang, P., Mairiang, E., Yongvanit, P., Esumi, H. & Elkins, D.B. (1998) Relationships between the synthesis of N-nitrosodimethylamine and immune responses to chronic infection with the carcinogenic parasite, *Opisthorchis viverrini,* in men. *Carcinogenesis*, **19**, 485–491
452. Satgé, D., Sasco, A.J., Carlsen, N.L.T., Stiller, C.A., Rubie, H., Hero, B., de Bernardi, B., de Kraker, J., Coze, C., Kogner, P., Langmark, F., Hakvoort-Cammel, F.G.A.J., Beck, D., von der Weid, N., Parkes, S., Hartmann, O., Lippens, R.J.J., Kamps, W.A. & Sommelet, D. (1998) A lack of neuroblastoma in Down syndrome: A study from 11 European countries. *Cancer Res.*, **58**, 448–452
453. Satgé, D., Sasco, A.J., Geneix, A. & Malet, P. (1998) Another reason to look for tumor suppressor genes on chromosome 21. *Genes Chromosom. Cancer*, **21**, 1
454. Satgé, D., Sasco, A.J. & Little, J. (1998) Neonatal tumours and drug use in pregnancy. *Pediatr. Perinat. Epidemiol.*, **12**, 84–117
455. Satgé, D.L.C., Jaubert, F., Nishi, M., Sasco, A.J. & Vekemans, M.J.J. (1998) Analysis of germ cell tumors in Down syndrome. *Am. J. Hum. Genet.*, **63**, A85
456. Satia, J.A., Patterson, R.E., Herrero, R., Jin, F., Dai, Q., King, I.B., Chen, C., Kristal, A.R., Prentice, R.L. & Rossing, M.A. (1999) Study of diet, biomarkers and cancer risk in the United States, China and Costa Rica. *Int. J. Cancer*, **82**, 28–32
457. Sauerbrei, W., Blettner, M., Schmoor, C., Bojar, H. & Schumacher, M. (1998) The effect of oral contraceptive use on the prognosis of node positive breast cancer patients. *Eur. J. Cancer*, **34**, 1348–1351

458. Scheppach, W., Bingham, S., Boutron-Ruault, M.C., Gerhardsson de Verdier, M., Moreno, V., Nagengast, F.M., Reifen, R., Riboli, E., Seitz, H.K. & Wahrendorf, J. (1999) WHO consensus statement on the role of nutrition in colorectal cancer. *Eur. J. Cancer Prev.*, **8**, 57–62

459. Schiffman, M., Herrero, R., Hildesheim, A., Sherman, M.E., Bratti, M., Wacholder, S., Alfaro, M., Hutchinson, M., Morales, J. & Lorincz, A.T. (1999) HPV DNA testing with hybrid capture for cervical cancer screening: Results from the 9000 women in the NCI Guanacaste Project. *J. Am. Med. Assoc.* (in press)

460. Schiffman, M.H., Liaw, K.L., Herrero, R., Sherman, M.E. & Hildesheim, A. (1998) Epidemiologic support for a simplified view of cervical carcinogenesis. *Eurogin – Genital Infections & Neoplasia Update*, **1**, 2–6

461. Schlehofer, B., Blettner, M., Preston-Martin, S., Niehoff, D., Wahrendorf, J., Arslan, A., Ahlbom, A., Choi, W.N., Giles, G.G., Howe, G.R., Little, J., Ménégoz, F. & Ryan, P. (1999) The role of medical history in brain tumour development. Results from the International Adult Brain Tumour Study. *Int. J. Cancer*, **82**, 155–160

462. Schmid, G., Wang, Z.Q. & Wesierska-Gadek, J. (1999) Compensatory expression of p73 in PARP-deficient mouse fibroblasts as response to a reduced level of regularly spliced wild-type p53 protein. *Biochem. Biophys. Res. Commun.*, **255**, 399–405

463. Schneider, D.L., Herrero, R., Bratti, C., Greenberg, M.D., Hildesheim, A., Sherman, M.E., Morales, J., Hutchinson, M.L., Sedlacek, T.V., Lorincz, A., Mango, L., Wacholder, S., Alfaro, M. & Schiffman, M. (1999) Cervicography screening for cervical cancer among 8460 women in a high-risk population. *Am. J. Obst. Gynecol.*, **180**, 290–298

464. Schorpp-Kistner, M., Wang, Z.Q., Angel, P. & Wagner, E.F. (1999) JunB is essential for mammalian placentation. *EMBO J.*, **18**, 934–948

465. Schuffenecker, I., Virally-Monod, M., Brohet, R., Goldgar, D., Conte-Devolx, B., Leclerc, L., Chabre, O., Boneu, A., Caron, J., Houdent, C., Modigliani, E., Rohmer, V., Schlumberger, M., Eng, C., Guillausseau, P.J., Lenoir, G.M. & Groupe d'Etude des Tumeurs à Calcitonine (1998) Risk and penetrance of primary hyperparathyroidism in multiple endocrine neoplasia type 2A families with mutations at codon 634 of the RET proto-oncogene. *J. Clin. Endocrinol. Metab.*, **83**, 487–491

466. Scott, H.S., Heino, M., Peterson, P., Mittaz, L., Lalioti, M.D., Betterle, C., Cohen, A., Seri, M., Lerone, M., Romeo, G., Collin, P., Salo, M., Metcalfe, R., Weetman, A., Papasavvas, M.P., Rossier, C., Nagamine, K., Kudoh, J., Shimizu, N., Krohn, K.J.E. & Antonarakis, S.E. (1998) Common mutations in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients of different origins. *Mol. Endocrinol.*, **12**, 1112–1119

467. Scotto, C., Mély, Y., Ohshima, H., Garin, J., Cochet, C., Chambaz, E. & Baudier, J. (1998) Cysteine oxidation in the mitogenic S100B protein leads to changes in phosphorylation by catalytic CKII-alpha subunit. *J. Biol. Chem.*, **273**, 3901–3908

468. Seri, M., Cusano, R., Forabosco, P., Cinti, R., Caroli, F., Picco, P., Bini, R., Brescia Morra, V., De Michele, G., Lerone, M., Silengo, M., Pela, I., Borrone, C., Romeo, G. & Devoto, M. (1999) Genetic mapping to 10q23.3-q24.2, in a large Italian pedigree, of a new syndrome showing bilateral cataracts, gastroesophageal reflux, and spastic paraparesis with amyotrophy. *Am. J. Hum. Genet.*, **64**, 586–593

469. Seri, M., Martucciello, G., Paleari, L., Bolino, A., Priolo, M., Salemi, G., Forabosco, P., Caroli, F., Cusano, R., Tocco, T., Lerone, M., Cama, A., Torre, M., Guys, J.M., Romeo, G. & Jasonni, V. (1999) Exclusion of the *Sonic Hedgehog* gene as responsible for Currarino syndrome and anorectal malformations with sacral hypodevelopment. *Hum. Genet.*, **104**, 108–110

470. Seri, M., Melchionda, S., Dreyer, S., Marini, M., Carella, M., Cusano, R., Piemontese, M.R., Caroli, F., Silengo, M., Zelante, L., Romeo, G., Ravazzolo, R., Gasparini, P. & Lee, B. (1999) Identification of *LMX1B* gene point mutations in Italian patients affected with nail-patella syndrome. *Int. J. Mol. Med.*, **4**, 285–290

471. Seri, M., Puliti, A., Bocciardi, R., Patrone, G., Yin, L., Pasini, B., Bolino, A., Lerone, M., Silengo, M., Martucciello, G., Devoto, M., Ceccherini, I. & Romeo, G. (1998) Mappatura e clonaggio di geni che causano malattie congenite frequenti ad ereditarietà complessa: il caso della malattia di Hirschsprung [Mapping and cloning of genes responsible for congenital disorders with complex inheritance: the example of Hirschsprung disease]. *Gaslini*, **30**, 127–137

472. Settimi, L., Comba, P., Carrieri, P., Boffetta, P., Magnani, C., Terracini, B., Andrion, A., Bosia, A., Ciapini, C., De Santis, M., Desideri, E., Fedi, A., Luccoli, L., Maiozzi, C.P., Masina, A., Perazzo, P.L. & Axelson, O. (1999) Cancer risk among female agricultural workers: a multi-site case-control study. *Am. J. Ind. Med.*, **36**, 135–141

473. Shen, N., Weiderpass, E., Anttila, A., Goldberg, M.S., Vasama-Neuvonen, K.M., Boffetta, P., Vainio, H.U. & Partanen, T.J. (1998) Epidemiology of occupational and environmental risk factors related to ovarian cancer. *Scand. J. Work Environ. Health*, **24**, 175–182

474. Sherman, M.E., Schiffman, M., Herrero, R., Kelly, D., Bratti, C., Mango, L.J., Alfaro, M., Hutchinson, M.L., Mena, F., Hildesheim, A., Morales, J., Greenberg, M.D., Balmaceda, I. & Lorincz, A.T. (1998) Performance of a semiautomated Papanicolaou smear screening system: results of a population-based study conducted in Guanacaste, Costa Rica. *Cancer Cytopathol.*, **84**, 273–280

475. Sherman, M.E., Schiffman, M.H., Lorincz, A.T., Herrero, R., Hutchinson, M.L., Bratti, C., Zahniser, D., Morales, J., Hildesheim, A., Helgesen, K., Kelly, D., Alfaro, M., Mena, F., Balmaceda, I., Mango, L. & Greenberg, M. (1999) Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. *Cancer Cytopathol.* (in press)

476. Shiao, Y. H., Rice, J.M., Anderson, L.M., Diwan, B.A. & Hard, G.C. (1998) von Hippel-Lindau gene mutations in N-nitrosodimethylamine-induced rat renal epithelial tumors. *J. Natl Cancer Inst.*, **90**, 1720–1723

477. Shieh, W.M., Amé, J.C., Wilson, M.V., Wang, Z.Q., Koh, D.W., Jacobson, M.K. & Jacobson, E.L. (1998) Poly(ADP-ribose) polymerase null mouse cells synthesize ADP-ribose polymers. *J. Biol. Chem.*, **273**, 30069–30072

478. Shugart, Y. & Goldgar, D.E. (1999) Multipoint genomic scanning for quantitative loci: effects of map density, sibship size and computational approach. *Eur. J. Hum. Genet.*, **7**, 103–109

479. Shugart, Y.Y. & Goldgar, D.E. (1997) The performance of MIM in comparison with MAPMAKER/SIBS to detect QTLs. *Genet. Epidemiol.*, **14**, 897–902

480. Siemiatycki, J. & Boffetta, P. (1998) Invited commentary: Is it possible to investigate the quantitative relation between asbestos and mesothelioma in a community-based study? *Am J. Epidemiol.*, **148**, 143–147

481. Sierra, R., Salas, P., Mora-Zuniga, F., Sanabria, M., Chinnock, A., Peña, S., Quiros, E., Mora, W., Mena, F., Altman, R. & Muñoz, N. (1998) Erradicacion de *Helicobacter pylori* en una poblacion de alto riesgo de cancer gastrico. *Acta Med. Costarricense*, **40**, 30–35

482. Silengo, M., Silvestro, L., Capizzi, G., Lerone, M., Seri, M., Rosaia, L. & Romeo, G. (1998) Ectodermal dysplasia, primary hypothyroidism, and agenesis of the corpus callosum: variable expression of a single syndrome? *J. Med. Genet.*, **35**, 157–158

483. Simbulan-Rosenthal, C.M., Haddad, B.R., Rosenthal, D.S., Weaver, Z., Coleman, A., Luo, R.B., Young, H.M., Wang, Z.-Q., Ried, T. & Smulson, M.E. (1999) Chromosomal aberrations in PARP$^{-/-}$ mice: genome stabilization in immortalized cells by reintroduction of poly(ADP-ribose) polymerase cDNA. *Proc. Natl Acad. Sci. USA*, **96**, 13191–13196

484. Simonato, L., Ballard, T., Bellini, P. & Winkelmann, R. (1998) Avoidable mortality in Europe 1955–1994: a plea for prevention. *J. Epidemiol. Commun. Health*, **52**, 624–630

485. Simonato, L., Zambon, P., Ardit, S., Della Sala, S., Guglielmo, F., Gaborieau, V., Gallo, G., Magarotto, G., Mazzini, R., Pasini, L. & Stracca Pansa, V. (1999) Lung cancer risk in Venice. A population-based case-control study. *Eur. J. Cancer Prev.* (in press)

486. Sinilnikova, O.M., Egan, K.M., Quinn, J.L., Boutrand, L., Lenoir, G.M., Stoppa-Lyonnet, D., Desjardins, L., Levy, C., Goldgar, D. & Gragoudas, E.S. (1999) Germline *brca2* sequence variants in patients with ocular melanoma. *Int. J. Cancer*, **83**, 325–328

487. Sioris, T., Husgafvel-Pursiainen, K., Karjalainen, A., Anttila, A., Kannio, A., Salo, J.A., Perhoniemi, V., Heikkilä, L. & Vainio, H. (1999) Survival in operable non-small cell lung cancer: role of p53 mutations, tobacco smoking and asbestos exposure. *Int. J. Cancer* (in press)

488. Sipowicz, M.A., Chomarat, P., Diwan, B.A., Anver, M.A., Awasthi, Y.C., Ward, J.M., Rice, J.M., Kasprzak, K.S., Wild, C.P. & Anderson, L.M. (1997) Increased oxidative DNA damage and hepatocyte overexpression of specific cytochrome P450 isoforms in livers of mice infected with *Helicobacter hepaticus*. *Am. J. Pathol.*, **151**, 933–941

489. Slimani, N., Deharveng, G., Charrondière, R.U., van Kappel, A.L., Ocké, M.C., Welch, A., Lagiou, A., van Liere, M., Agudo, A., Pala, V., Brandstetter, B., Andren, C., Stripp, C., van Staveren, W.A. & Riboli, E (1999) Structure of the standardized computerized 24-h diet recall interview used as reference method in the 22 centers participating in the EPIC project. *Comput. Meth. Progr. Biomed.*, **58**, 251–266

490. Sorlie, T., Martel-Planche, G., Hainaut, P., Lewalter, J., Holm, R., Borresen-Dale, A.L. & Montesano, R. (1998) Analysis of p53, p16^{MTS}, p21^{WAFI} and H-ras in archived bladder tumours from workers exposed to aromatic amines. *Br. J. Cancer*, **77**, 1573–1579

491. Stellman, S.D., Demers, P.A., Colin, D. & Boffetta, P. (1998) Cancer mortality and wood dust exposure among participants in the American Cancer Society Cancer Prevention Study-II (CPS-II). *Am. J. Ind. Med.*, **34**, 229–237

492. Sun, Y., Eluf-Neto, J., Bosch, F.X., Muñoz, N., Walboomers, J.M.M., Meijer, C.J.L.M., Shah, K.V., Clayman, B. & Viscidi, R.P. (1999) Serum antibodies to human papillomavirus 16 proteins in women from Brazil with invasive cervical carcinoma. *Cancer Epidemiol. Biomarkers Prev.*, **8**, 935–940

493. Sure, U., Tachibana, O., Biernat, W., von Ammon, K., Yonekawa, Y., Ohgaki, H., Kleihues, P. & Hegi, M.E. (1999) p53 Mutations are involved in the development of primary pediatric glioblastoma. *J. Neuropathol. Exp. Neurol.* (in press)

494. Sylla, A., Diallo, M.S., Castegnaro, J.J. & Wild, C.P. (1999) Interactions between hepatitis B virus infection and exposure to aflatoxins in the development of hepatocellular carcinoma: a molecular epidemiological approach. *Mutat. Res*, **428**, 187–196

495. Sylla, B.S., Hung, S.C., Davidson, D.M., Hatzivassiliou, E., Malinin, N.L., Wallach, D.,

Gilmore, T.D., Kieff, E. & Mosialos, G. (1998) Epstein-Barr virus-transforming protein latent infection membrane protein 1 activates transcription factor NF-kB through a pathway that includes the NF-kB-inducing kinase and the IkB kinases IKKalpha and IKKbeta. *Proc. Natl Acad. Sci. USA*, **95**, 10106–10111

496. Szabo, C. & Ohshima, H. (1997) DNA damage induced by peroxynitrite: subsequent biological effects. *Nitric Oxide Biol. Chem.*, **1**, 373–385
497. Tagger, A., Donato, F., Ribero, M.L., Chiesa, R., Portera, G., Gelatti, U., Albertini, A., Fasola, M., Boffetta, P. & Nardi, G. for the Brescia HCC Study (1999) Case–control study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: the role of HCV genotypes and the synergism with hepatitis B virus and alcohol. *Int. J. Cancer*, **81**, 695–699
498. Takahashi, M., Iwashita, T., Santoro, M., Lyonnet, S., Lenoir, G.M. & Billaud, M. (1999) Co-segregation of MEN2 and Hirschsprung's disease: the same mutation of *RET* with both gain and loss-of-function? *Hum. Mutat.*, **13**, 331–336
499. Talmud, J., Sasco, A., Commandré, F., Bence, Y. & Malberti, R. (1999) Comportement des sportifs vis-à-vis du tabac. *Med. Sport*, **73**, 19–20
500. Teschke, K., Ahrens, W., Andersen, A., Boffetta, P., Fincham, S., Finkelstein, M., Henneberger, P., Kauppinen, T., Kogevinas, M., Korhonen, K., Liss, G., Liukonnen, T., Osvoll, P., Savela, A., Szadkowska-Stanczyk, I., Westberg, H. & Widerkiewics, K. (1999) Occupational exposure to chemical and biological agents in the nonproduction departments of pulp, paper, and paper product mills: an international study. *Am. Ind. Hyg. Assoc. J.*, **60**, 73–83
501. Thulke-Gross, M., Hergenhahn, M., Tilloy-Ellul, A., Lang, M. & Bartsch, H. (1998) Pyrazole-inducible proteins in DBA/2 mouse liver bind with high affinity to the 3'-untranslated regions of the mRNAs of coumarin hydroxylase (CYP2A5) and c-jun. *Biochem. J.*, **331**, 473–481
502. Tilloy-Ellul, A., Raffalli-Mathieu, F. & Lang, M.A. (1999) Analysis of RNA-protein interactions of mouse liver cytochrome P4502A5 mRNA. *Biochem. J.*, **339**, 695–703
503. Tohma, Y., Gratas, C., Biernat, W., Peraud, A., Fukuda, M., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (1998) PTEN (MMAC1) mutations are frequent in primary (de novo) but not in secondary glioblastomas. *J. Neuropathol. Exp. Neurol.*, **57**, 684–689
504. Tohma, Y., Gratas, C., van Meir, E.G., Desbaillets, I., Tenan, M., Tachibana, O., Kleihues, P. & Ohgaki, H. (1998) Necrogenesis and Fas/APO-1(CD95) expression in primary (de novo) and secondary glioblastomas. *J. Neuropathol. Exp. Neurol.*, **57**, 239–245
505. Tong, W.M., Bises, G., Sheinin, Y., Ellinger, A., Genser, D., Potzi, R., Wrba, F., Wenzl, E., Roka, R., Neuhold, N., Peterlik, M. & Cross, H.S. (1998) Establishment of primary cultures from human colonic tissue during tumor progression: vitamin-D responses and vitamin-D receptor expression. *Int. J. Cancer*, **75**, 467–472
506. Tong, W.M., Ellinger, A., Sheinin, Y. & Cross, H.S. (1998) Epidermal growth factor receptor expression in primary cultured human colorectal carcinoma cells. *Br. J. Cancer*, **77**, 1792–1796
507. Tong, W.M., Hofer, H., Ellinger, A., Peterlik, M. & Cross, H.S. (1999) Mechanism of antimitogenic action of vitamin D in human colon carcinoma cells: relevance for suppression of epidermal growth factor-stimulated cell growth. *Oncol. Res.*, **11**, 77–84
508. Tong, W.M., Kallay, E., Hofer, H., Hulla, W., Manhardt, T., Peterlik, M. & Cross, H.S. (1998) Growth regulation of human colon cancer cells by epidermal growth factor and 1,25-dihydroxyvitamin D_3 is mediated by mutual modulation of receptor expression. *Eur. J. Cancer*, **34**, 2119–2125
509. Tong, W.M. & Wang, F. (1998) Alterations in rat pancreatic islet beta cells induced by Keshan disease pathogenic factors: protective action of selenium and vitamin E. *Metabolism*, **47**, 415–419
510. Toniolo, P., Kaaks, R. & Lukanova, A. (1999) Steroid hormones, insulin and breast cancer. *J. Natl Cancer Inst. Monogr.* (in press)
511. Toniolo, P., van Kappel, A.L., Akhmedkhanov, A., Ferrari, P., Kato, I., Shore, R.E. & Riboli, E. (1999) Serum carotenoids and breast cancer. *Am. J. Epidemiol.* (in press)
512. Tonnesen, P., Paoletti, P., Gustavsson, G., Russell, M.A., Saracci, R., Gulsvik, A., Rijcken, B. & Sawe, U. (1999) Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. *Eur. Respir. J.*, **13**, 238–246
513. Touzé, A., El Mehdaoui, S., Sizaret, P.Y., Mougin, C., Muñoz, N. & Coursaget, P. (1998) The L_1 major capsid protein of human papillomavirus type 16 variants affects the yield of virus-like particles produced in an insect cells expression system. *J. Clin. Microbiol.*, **36**, 2046–2051
514. Ung, A., Kramer, T.R., Schiffman, M., Herrero, R., Bratti, M.C., Burk, R.D., Swanson, C.A., Sherman, M.E., Hutchinson, M.L., Alfaro, M., Morales, J., Balmaceda, I. & Hildesheim, A. (1999) Soluble interleukin 2 receptor levels and cervical neoplasia: results from a population-based case-control study in Costa Rica. *Cancer Epidemiol. Biomarkers Prev.*, **8**, 249–253
515. Vainio, H. (1998) Biomarkers in metabolic subtyping – relevance for environmental cancer control. *Arch. Toxicol.*, **Suppl. 20**, 303–310
516. Vainio, H. (1998) Use of biomarkers – new frontiers in occupational toxicology and epidemiology. *Toxicol Lett.*, **102–103**, 581–589
517. Vainio, H. (1999) Biomarkers in identification of susceptible subgroups and individuals. In: *Biomarkers and Risk Assessment in Environmental Health (Swedish Environmental Protection Agency,*

Report No. 4982), Swedish Environmental Protection Agency, pp. 58–63

518. Vainio, H. (1999) Biomarkers in the identification of risks, especially with regard to susceptible persons and subgroups [editorial]. *Scand. J Work Environ. Health*, **25**, 1–3
519. Vainio, H. (1999) Chemoprevention of cancer: a controversial and instructive story. *Br. Med. Bull.*, **55**, 593–599
520. Vainio, H. (1999) Fruits, vegetables and pesticides--do we know what we are eating? [editorial]. *Scand. J. Work Environ. Health*, **25**, 161–162
521. Vainio, H. & Morgan, G. (1997) Aspirin for the second hundred years: new uses for an old drug. *Pharmacol. Toxicol.*, **81**, 151–152
522. Vainio, H. & Morgan, G. (1998) Cyclo-oxygenase 2 and breast cancer prevention. Non-steroidal anti-inflammatory agents are worth testing in breast cancer [editorial]. *Br. Med. J.*, **317**, 828
523. Vainio, H. & Morgan, G. (1998) Non-steroidal anti-inflammatory drugs and the chemoprevention of gastrointestinal cancers. *Scand. J. Gastroenterol.*, **33**, 785–789
524. Vainio, H. & Rautalahti, M. (1998) An international evaluation of the cancer preventive potential of carotenoids. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 725–728
525. Vainio, H. & Rautalahti, M. (1998) Onko syöväntorjunnassa edistytty? [Any progress in cancer prevention?]. *Syöpä – Cancer*, **3**, 4–6
526. Vainio, H. & Rautalahti, M. (1999) An international evaluation of the cancer preventive potential of vitamin A. *Cancer Epidemiol. Biomarkers Prev.*, **8**, 107–109
527. Vainio, H., Rosenberg, C., Hirvonen, A. & Norppa, H. (1999) International workshop on biomarkers for isocyanates. *Scand. J Work Environ. Health*, **25**, 157–159
528. van Zeeland, A.A., de Groot, A.J.L., Hall, J. & Donato, F. (1999) 8-Hydroxydeoxyguanosine in DNA from leukocytes of healthy adults: relationship with cigarette smoking, environmental tobacco smoke, alcohol and coffee consumption. *Mutat. Res.*, **439**, 249–257
529. Vasama-Neuvonen, K., Pukkala, E., Paakkulainen, H., Mutanen, P., Weiderpass, E., Boffetta, P., Shen, N., Kauppinen, T., Vainio, H. & Partanen, T. (1999) Ovarian cancer and occupational exposures in Finland. *Am. J. Ind. Med.*, **36**, 83–89
530. Vena, J., Boffetta, P., Becher, H., Benn, T., Bueno-de-Mesquita, H.B., Coggon, D., Colin, D., Flesch-Janys, D., Green, L., Kauppinen, T., Littorin, M., Lynge, E., Mathews, J.D., Neuberger, M., Pearce, N., Pesatori, A.C., Saracci, R., Steenland, K. & Kogevinas, M. (1998) Exposure to dioxin and non-neoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. *Environ. Health Perspect.*, **106**, 645–653
531. Verhaegh, G.W., Parat, M.O., Richard, M.J. & Hainaut, P. (1998) Modulation of p53 protein conformation and DNA-binding activity by intracellular chelation of zinc. *Mol. Carcinogen.*, **21**, 205–214
532. Viani, F., Siegrist, H.H., Pignatelli, B., Cederberg, C., Idstrom, J.P., Verdu, E.F., Fried, M., Blum, A.L. & Armstrong, D. (1999) The effect of intra-gastric acidity and flora on the concentration of N-nitroso compounds in the stomach. *Eur. J. Gastroenterol. Hepatol.* (in press)
533. Vineis, P., d'Errico, A., Malats, N. & Boffetta, P. (1999) Overall evaluation and research perspectives. In: Vineis, P., Malats, N., Lang, M., d'Errico, A., Caporaso, N., Cuzick, J. & Boffetta, P., eds, *Metabolic Polymorphisms and Susceptibility to Cancer* (IARC Scientific Publications No. 148), Lyon, IARC, pp. 403–408
534. Vineis, P., Kogevinas, M., Simonato, L., Brennan, P. & Boffetta, P. (1999) Levelling-off of the risk of lung and bladder cancer in heavy smokers: an analysis based on multicentric case-control studies and a metabolic interpretation. *Mutat. Res.* (in press)
535. Vineis, P., Malats, N. & Boffetta, P. (1999) Why study metabolic susceptibility to cancer? In: Vineis, P., Malats, N., Lang, M., d'Errico, A., Caporaso, N., Cuzick, J. & Boffetta, P., eds, *Metabolic Polymorphisms and Susceptibility to Cancer* (IARC Scientific Publications No. 148), Lyon, IARC, pp. 1–3
536. Vineis, P., Malats, N., Lang, M., d'Errico, A., Caporaso, N., Cuzick, J. & Boffetta, P., eds (1999) *Metabolic Polymorphisms and Susceptibility to Cancer* (IARC Scientific Publications No. 148), Lyon, IARC
537. Vineis, P., Peluso, M., Airoldi, L. & Malaveille, C. (1999) Fruit, vegetables, and DNA adducts in bladder cancer. *Proc. Am. Assoc. Cancer Res.*, **40**, 150
538. Virag, L., Scott, G.S., Antal-Szalmas, P., O'Connor, M., Ohshima, H. & Szabo, C. (1999) Requirement of intracellular calcium mobilization for peroxynitrite-induced poly(ADP-ribose) synthetase (PARS) activation and cytotoxicity. *Mol. Pharmacol.*, **56**, 824–833
539. Vital, A., Bringuier, P.P., Huang, H., San Galli, F., Rivel, J., Ansoborlo, S., Cazauran, J.M., Taillandier, L., Kleihues, P. & Ohgaki, H. (1998) Astrocytomas and choroid plexus tumors in two families with identical p53 germline mutations. *J. Neuropathol. Exp. Neurol.*, **57**, 1061–1069
540. Viviani, S., Jack, A., Hall, A.J., Maine, N., Mendy, M., Montesano, R. & Whittle, H.C. (1999) Hepatitis B vaccination in infancy in The Gambia: protection against carriage at 9 years of age. *Vaccine*, **17**, 2946–2950
541. Vizcaino, A.P., Moreno, V., Bosch, F.X., Muñoz, N., Barros-Dias, X.M., Borras, J. & Parkin, D.M. (1999) International trends in incidence of cervical cancer: II. Squamous cell carcinoma. *Int. J. Cancer* (in press)

542. Vizcaino, A.P., Moreno, V., Bosch, F.X., Muñoz, N., Barros-Dias, X.M. & Parkin, D.M. (1998) International trends in the incidence of cervical cancer: I. Adenocarcinoma and adenosquamous cell carcinomas. *Int. J. Cancer*, **75**, 536–545

543. Vogel, E.W., Barbin, A., Lohman, P.H.M., Nivard, M.J.M., Stack, F.H. & Waters, M.D. (1998) Heritable and cancer risks of exposures to anticancer drugs: inter-species comparisons of covalent deoxyribonucleic acid-binding agents. *Mutat. Res.*, **400**, 509–540

544. Voss, S., Charrondière, U.R., Slimani, N., Kroke, A., Riboli, E., Wahrendorf, J. & Boeing, H. (1998) EPIC-SOFT, ein europäisches Computer-programm für 24-Stunden-Erinnerungsprotokolle. *Z. Ernährungswiss.*, **37**, 227–233

545. Wabinga, H.R., Parkin, D.M., Wabwire-Mangen, F. & Nambooze, S. (1999) Temporal variation in the incidence of cancer in an African population of Kyadondo County, Uganda, 1960–1997. *Br. J. Cancer* (in press)

546. Wagner, E.F. & Wang, Z.-Q. (1999) Genetically modified mice as tools for cancer research. In: Russo, E., Cove, D., Edgar, L., Jaenisch, R. & Salamini, F., eds, *Development – Genetics, Epigenetics and Environmental Regulation*, Heidelberg, Springer-Verlag, pp. 471–485

547. Walboomers, J.M.M., Jacobs, M.V., Manos, M.M., Bosch, F.X., Kummer, J.A., Shah, K.V., Snijders, P.J.F., Peto, J., Meijer, C.J.L.M. & Muñoz, N. (1999) Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J. Pathol.*, **189**, 12–19

548. Watanabe, K., Peraud, A., Gratas, C., Wakai, S., Kleihues, P. & Ohgaki, H. (1998) p53 and PTEN gene mutations in gemistocytic astrocytomas. *Acta Neuropathol.*, **95**, 559–564

549. Weiderpass, E., Partanen, T. & Boffetta, P. (1998) Nonmelanocytic skin cancer. In: Stellman, J.M., ed., *Encyclopaedia of Occupational Health and Safety*, Vol.I, 4th Ed., Geneva, International Labour Office, pp. 12.6–12.8

550. Weiderpass, E., Partanen, T., Kaaks, R., Vainio, H., Porta, M., Kauppinen, T., Ojajarvi, A., Boffetta, P. & Malats, N. (1998) Occurrence, trends and environment etiology of pancreatic cancer. *Scand. J Work Environ. Health*, **24**, 165–174

551. Weiderpass, E., Pukkala, E., Kauppinen, T., Mutanen, P., Paakkulainen, H., Vasama-Neuvonen, K., Boffetta, P. & Partanen, T. (1999) Breast cancer and occupational exposures in women in Finland. *Am. J. Ind. Med.*, **36**, 48–53

552. Weidmann, C., Black, R.J., Masuyer, E. & Parkin, D.M. (1999) Incidence of non-Hodgkin's lymphoma in children between 1970 and 1990 in nine European countries. *Eur. J. Cancer*, **35**, 1235–1237

553. Weller, M., Kleihues, P., Dichgans, J. & Ohgaki, H. (1998) CD95 ligand: lethal weapon against malignant glioma? *Brain Pathol.*, **8**, 285–293

554. Welp, E.A., Weiderpass, E., Boffetta, P., Vainio, H., Vasama-Neuvonen, K., Petralia, S. & Partanen, T.J. (1998) Environmental risk factors of breast cancer. *Scand. J. Work Environ. Health*, **24**, 3–7

555. Wennborg, H., Yuen, J., Axelsson, G., Ahlbom, A., Gustavsson, P. & Sasco, A.J. (1999) Mortality and cancer incidence in biomedical laboratory personnel in Sweden. *Am. J. Ind. Med.*, **35**, 382–389

556. Wesierska-Gadek, J., Wang, Z.Q. & Schmid, G. (1999) Reduced stability of regularly spliced but not alternatively spliced p53 protein in PARP-deficient mouse fibroblasts. *Cancer Res.*, **59**, 28–34

557. Wild, C.P., Castegnaro, M., Ohgaki, H., Garren, L., Galendo, D. & Miller, J.D. (1997) Absence of a synergistic effect between fumonisin B_1 and N-nitrosomethylbenzylamine in the induction of oesophageal papillomas in the rat. *Natural Toxins*, **5**, 126–131

558. Wild, C.P., Daudt, A.W. & Castegnaro, M. (1998) The molecular epidemiology of mycotoxin-related disease. In: Miraglia, M., van Egmond, H.P., Brera, C. & Gilbert, J., eds, *Mycotoxins and Phycotoxins – Developments in Chemistry, Toxicology and Food Safety*, Fort Collins, Colorado, Alaken, pp. 213–231

559. Wild, C.P. & Pisani, P. (1998) Carcinogen–DNA and –protein adducts as biomarkers of human exposure in environmental cancer epidemiology. *Cancer Detect. Prev.*, **22**, 273–283

560. Winkelmann, R.A., Okeanov, A., Gulak, L., Remennik, L., Rahu, M. & Storm, H.H., eds (1998) *Cancer Registration Techniques in the New Independent States of the former Soviet Union* (IARC Technical Report No. 35), Lyon, IARC

561. Wolff, H., Saukkonen, K., Anttila, S., Karjalainen, A., Vainio, H. & Ristimaki, A. (1998) Expression of cyclooxygenase-2 in human lung carcinoma. *Cancer Res.*, **58**, 4997–5001

562. Wünsch-Filho, V., Moncau, J.E., Mirabelli, D. & Boffetta, P. (1998) Occupational risk factors of lung cancer in Sao Paulo, Brazil. *Scand. J. Work Environ. Health*, **24**, 118–124

563. Wynder, E., Hamm, J., Holli, K., Osborne, C.K., Powles, T.J. & Sasco, A.J. (1999) Breast cancer prevention interventions and concerns. *Primary Care Cancer*, Suppl. 2, 47–49

564. Yamakage, K., Omori, Y., Piccoli, C. & Yamasaki, H. (1998) Growth control of 3T3 fibroblast cell lines established from connexin 43-deficient mice. *Mol. Carcinogen.*, **23**, 121–128

565. Yamasaki, H., Krutovskikh, V., Mesnil, M., Tanaka, T., Zaidan-Dagli, M.L. & Omori, Y. (1999) Role of connexin (gap junction) genes in cell growth control and carcinogenesis. *C. R. Acad. Sci. Paris Sciences de la Vie*, **322**, 151–159

566. Yamasaki, H., Omori, Y., Krutovskikh, V., Zhu, W., Mironov, N., Yamakage, K. & Mesnil, M. (1999) Connexins in tumour suppression and cancer therapy. In: *Gap Junction-Mediated Intercellular Signalling in Health and Disease*, New York, Wiley, pp. 241–260

567. Yamasaki, H., Omori, Y., Zaidan-Dagli, M.L., Mironov, N., Mesnil, M. & Krutovskikh, V. (1999) Genetic and epigenetic changes of intercellular communication genes during multistage carcinogenesis. *Cancer Detect. Prev.*, **23**, 273–279
568. Yeole, B.B., Sankaranarayanan, R. & Jussawalla, D.J. (1998) Long-term survival from uterine cervical cancer in Mumbai (Bombay), India. *Int. J. Cancer*, **78**, 394–395
569. Yin, L., Ferrand, V., Laboué, M.F., Hayoz, D., Philippe, N., Seri, M., Giacchino, R., Hodgson, S., Sylla, B.S. & Romeo, G. (1999) SH2D1A mutation analysis for diagnosis of XLP in typical and atypical patients. *Hum. Genet.* (in press)
570. Yoshie, Y. & Ohshima, H. (1998) Synergistic induction of DNA strand breakage by catechol-estrogen and nitric oxide: implications for hormonal carcinogenesis. *Free Radical Biol. Med.*, **24**, 341–348
571. Zaridze, D., Maximovitch, D., Zemlyanaya, G., Aitakov, Z. N. & Boffetta, P. (1998) Exposure to environmental tobacco smoke and risk of lung cancer in non-smoking women from Moscow, Russia. *Int. J. Cancer*, **75**, 335–338
572. Zeeb, H. & Blettner, M. (1998) Adult leukaemia: what is the role of currently known risk factors ? *Radiat. Environ. Biophys.*, **36**, 217–228
573. Zeise, L., Cardis, E., Hemminki, K. & Schwarz, M. (1999) Quantitative estimation and prediction of cancer risk: review of existing activities. In: Moolgavkar, S., Krewski, D., Zeise, L., Cardis, E. & Møller, H., eds, *Quantitative Estimation and Prediction of Human Cancer Risks* (IARC Scientific Publications No 131), Lyon, IARC, pp. 11–59
574. Zeleniuch-Jacquotte, A., Chajès, V., van Kappel, A.L., Riboli, E. & Toniolo, P. (1999) Long-term within- and between-subject variability of fatty acid composition in human serum phospholipids. *Eur. J. Clin. Nutr.* (in press)
575. Zhang, Z., Diwan, B.A., Anderson, L.M., Logsdon, D., Olivero, O.A., Haines, D.C., Rice, J.M., Yuspa, S.H. & Poirier, M.C. (1998) Skin tumorigenesis and Ki-ras and Ha-ras mutations in tumors from adult mice exposed in utero to 3′-azido-2′,3′-dideoxy-thymidine. *Mol. Carcinogen.*, **23**, 45–51
576. Zhu, W., Yamasaki, H. & Mironov, N. (1998) Frequency of HPRT gene mutations induced by N-methyl-N′-nitro-N-nitrosoguanidine corresponds to replication error phenotypes of cell lines. *Mutat. Res.*, **398**, 93–99
577. Ziegler, A., Kastner, C. & Blettner, M. (1998) The generalised estimating equations: an annotated bibliography. *Biometr. J.*, **40**, 115–139
578. Zielinski, J.M., Krewski, D., Ashmore, P. & Cardis, E. (1999) The use of national registers of radiation exposure in occupational radiation risk assessment. *Eur. J. Cancer* (in press)
579. Zucman-Rossi, J., Legoix, P., Der Sarkissian, H., Cheret, G., Sor, F., Bernardi, A., Cazes, L., Giraud, S., Ollagnon, E., Lenoir, G. & Thomas, G. (1998) NF2 gene in neurofibromatosis type 2 patients. *Hum. Mol. Genet.*, **7**, 2095–2101

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