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WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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The Netherlands

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Sweden

Switzerland

The United Kingdom of Great Britain and Northern Ireland

The United States of America

Introduction

This Biennial Report is the first of the new millennium, covering the period from January 2000 to December 2001. It describes current and newly initiated projects and provides a complete list of publications, books and electronic databases that appeared during the period. It reflects the exceptional scientific productivity of IARC research units and their collaborators. During the past biennium, IARC staff published a total of 544 research articles. Of these 90% were published or are in press in peer-reviewed journals including many with a high international profile and impact. IARC staff also contributed to 42 book chapters and edited 11 books.

This edition of the Biennial Report appears in a new three-column format, which provides greater flexibility for structuring the text and inserting illustrations in a range of formats. We are confident that these changes will make the report more readable and interesting. We have also given greater prominence to the Research Units and Groups and their staff by highlighting their programmes and work in a special section of the Report (pages 105–128).

Cancer surveillance

The work of the Agency in the domain of cancer surveillance is largely based on a close and productive collaboration with cancer registries worldwide. The collaboration with the European Network of Cancer Registries has been particularly fruitful, providing excellent data on the incidence, mortality and survival of cancer patients in Europe. The results are now available through the new edition of the EUCAN electronic database, which is a very user-friendly and increasingly popular resource. The Network has also made successful efforts to reduce the time between recording of cancer data and publication. Key data are now regularly updated and can be downloaded from the Internet.

In North American and some European countries, a significant reduction in cancer mortality is now evident. Worldwide, however, the disease burden is still increasing, and this is reflected in the new edition of the GLOBOCAN electronic database. Although more difficult to interpret, information on the survival of cancer patients has become increasingly important for public health authorities, since it provides a measure of achievements in cancer control that can be more easily communicated to the public. While the collection of reliable data is now well established in most industrialized countries, this task is more difficult in developing countries. Nevertheless, IARC epidemiologists have made considerable progress in this field, and a new edition of *Cancer Survival in Developing Countries* will be published during the next biennium. IARC scientists collaborated in and had a considerable impact on the revision of WHO's International Classification of Diseases for Oncology (ICD-O), which has been implemented from January 2001.

Causes of human cancer

A primary mission of the Agency is to carry out studies on cancer etiology. In 2000, the *IARC Monographs* programme published five volumes – on industrial chemicals, on antineoplastic drugs, on ionizing radiation from internally deposited radionuclides and on thyrotropic chemicals that cause thyroid tumours in rodents. For this last group of compounds, the Working Group concluded that there is no evidence of excess thyroid cancer risk in humans exposed to any of these agents. Studies of occupational carcinogenesis have indicated that while workers employed in the man-made vitreous fibres industry do not appear to have an increased risk of lung cancer, workers exposed to bitumen fumes do appear to have an increased mortality from the disease. The potential carcinogenic risk from exposure to diesel exhaust is of much public concern and IARC scientists have launched a large study in central and eastern European countries, including the Russian Federation.

An important Monograph meeting is scheduled for 2002, to re-evaluate cancer causation by tobacco smoking, including passive smoking. This review of tobacco-associated cancers will provide an invaluable, unbiased scientific basis for tobacco control and is expected to play an important supportive role in the development of the framework convention on tobacco, a major public health initiative of the Director-General of WHO. Tobacco remains the most important preventable cause of human cancer and this is evident in results from an IARC-funded cohort study in Mumbai (Bombay, India), in which nearly 100 000 subjects participated. Preliminary results show a 39% excess of deaths among cigarette smokers and a 92% excess among bidi (a locally produced cigarette) smokers. These results contradict speculation that Asian populations are protected, either genetically or through nutritional habits, from the adverse effects of tobacco consumption.

The Unit of Radiation and Cancer is co-ordinating a large international project on possible adverse health effects of radiofrequency electromagnetic fields emitted by mobile telephones.

Although there is currently no evidence that such exposure contributes to the human cancer burden, the public is greatly concerned, and it was decided that this should be addressed in a well conducted international study, which is funded by the European Union. Supplementary funding for part of the study is being provided indirectly by a consortium of mobile telephone manufacturers and operators. This support is channelled through UICC and safeguards have been included in the agreement to ensure the integrity and independence of the study.

Infection and cancer remains a topic of major importance. This is underlined by the recent conclusion that chronic infection with human papillomavirus (HPV) is not a contributing but an essential factor in the development of cervical cancer. The Unit of Field and Intervention Studies, with its new chief, Dr Silvia Franceschi, is continuing its worldwide analytical and intervention studies to estimate the role of chronic infections in the development of human cancer. This includes preparatory studies for future HPV vaccination trials and a search for new infectious agents that may be involved in the etiology of human cancer, particularly in malignant lymphomas.

The Unit of Molecular Pathology has identified DNA from simian virus 40 (SV40) in a substantial proportion of brain tumours from Switzerland. A likely source of this infection is the SV40-contaminated polio vaccines given to millions of people in the late 1950s. SV40-contaminated vaccine was not used in Finland and brain tumours from Finnish patients did not contain SV40 sequences. However, the incidence of brain tumours does not differ significantly from that in Switzerland, the United States and other countries. This suggests that some tumours, including brain tumours, sarcomas and mesotheliomas, have a microenvironment that favours the replication of SV40 in individuals with silent infections, but there is currently no epidemiological evidence that this infection plays a significant role in the etiology of these neoplasms.

Cancer of the oesophagus is usually of the squamous cell type in western countries and is due mainly to excessive smoking and alcohol consumption. However, in some countries such as Iran and some areas in China, other, still unknown, factors are responsible for a high incidence of this disease. Following analytical epidemiological studies in 1970s, the Agency has resumed collaboration with scientists in Iran to conduct genetic studies which may provide clues as to the origins of these tumours. In western countries, the incidence of adenocarcinoma of the oesophagus is increasing sharply, largely as a result of reflux oesophagitis. The genetic profile of this neoplasm is essentially different from that of squamous cell carcinomas and points to endogenous mutations as being responsible for the development of these tumours. It remains to be shown why white men in highly industrialized countries are particularly susceptible.

The Gambia Hepatitis Intervention Study remains an excellent resource for detailed studies on the etiology and pathogenesis of liver cancer in a high-prevalence country. The Molecular Carcinogenesis Group published a very interesting report in 2000 showing that *TP53* mutations that are largely specific for exposure to aflatoxin B_1 can be detected in serum DNA in a substantial proportion of patients with liver cancer, and also in patients with cirrhosis and some individuals who do not show clinical evidence of cirrhosis or cancer. This study may provide a method for early detection of these otherwise incurable tumours.

Nutrition and Cancer

The European Prospective Investigation into Nutrition and Cancer (EPIC) has now entered a crucial stage, since there is a considerable inflow of data on cancer diagnosis in individuals participating in the study. The number of tumours diagnosed for several cancer sites is already sufficient to allow initiation of preliminary investigations into the role of dietary components. Among the first results is confirmation that an increased risk for colorectal cancer is associated with consumption of processed meats, while regular intake of fruits and vegetables reduces the risk of developing this cancer. At the same time, laboratory studies have yielded interesting insights into the mechanisms by which a western-style diet affects the evolution of cancers, such as those of the colon, breast and prostate. Several studies point to a key role of insulin-like growth factor 1 (IGF-1). Elevated serum levels seem to reflect an increased risk for these cancer types.

Genetic cancer susceptibility

There is increasing evidence that genetic susceptibility to cancer may affect a substantial proportion of the population through interactions of several genes, in addition to people affected by inherited cancer syndromes caused by a single gene mutation. This possibility is now being explored within the framework of the EPIC studies, as well as in projects on head and neck cancer, breast cancer and a variety of other human neoplasms. It is well established that *BRCA1* and *BRCA2* germline mutations play a major role in familial breast cancer, but the contribution of mutations in the ataxia telangiectasia (*ATM*) gene is still unclear. Studies by the DNA Repair Group in humans and *in vitro* have led to identification of several *ATM* mutations in radiosensitive breast cancer patients. The Unit of Genetic Epidemiology is focusing on gene–environment interactions in patients with inherited *BRCA1* or *BRCA2* mutations; in addition, there appear to be families

with a clear genetic trait that do not carry mutations in either of these genes. This is the focus of an international consortium searching for a third breast cancer susceptibility gene. Scientists from the Unit of Genetic Cancer Susceptibility are members of another consortium that identified the gene for X-linked lymphoproliferative disease (XLP) and have collaborated with the Unit of Gene–Environment Interactions to generate knock-out mice for the *SH2D1A* gene. This has led to an intensive effort to characterize the functions of the gene. This report also presents preliminary results on the identification of new loci for genes predisposing to thyroid cancer.

Mechanisms of carcinogenesis

Progress has been made in elucidating the mechanisms involved in development of tumours that are not induced by exogenous carcinogenic agents. Chronic infections including gastritis and ulcerative colitis confer an increased cancer risk, and the Unit of Endogenous Cancer Risk Factors has identified DNA and protein modifications resulting from oxidative stress which may contribute to the pathogenesis of these neoplasms. Its studies are also helping to clarify the role of nitric oxide synthase in carcinogenesis.

The Unit of Multistage Carcinogenesis has made excellent contributions to our understanding of cell–cell interactions and the loss of these communicative pathways in malignant transformation. Several publications have resulted from studies on the role of connexin gene expression in intercellular communication and apoptosis. Following the departure of Dr Yamasaki and closure of the Unit, most of these studies have been concluded. The search for connexin gene mutations in human neoplasms is being continued by Dr Krutovskikh. These studies and those on genomic instability are now carried out in the Unit of Gene–Environment Interactions. Dr Wang and his collaborators use poly(ADP)ribose polymerase (PARP) knock-out mice to study the role of this enzyme in signalling pathways related to apoptosis and in the maintenance of genomic integrity. In collaboration with Dr Monica Hollstein (DKFZ, Heidelberg), the unit generated a transgenic mouse strain in which the murine DNA-binding domain of the *TP53* gene is substituted by the homologous human *TP53* sequence. First results with this animal model show that carcinogens produce a spectrum of *TP53* mutations similar to those observed in humans, thus providing a new approach to the study of links between DNA alterations and environmental exposures.

Cancer prevention

Among newly initiated projects, the large intervention study on early detection and treatment of cervical cancer in India and Africa is particularly noteworthy. This programme is generously supported by the Bill and Melinda Gates Foundation. It involves several hundred thousand women and its aim is to develop more effective approaches to reducing the burden of cervical cancer, which is still a major source of mortality in many countries. This programme will have a considerable public health impact in addition to achieving its research objectives, as it could lead to a reduction of mortality from cervical cancer of up to 50% among the participants. First results of the study indicate that visual inspection of the cervix after application of acetic acid may evolve as an alternative to cytological (Pap) screening.

The Unit of Cancer Chemoprevention organized a workshop on Biomarkers in Cancer Prevention at the German Cancer Research Center in Heidelberg (published as IARC Scientific Publication No. 154). The Unit also organized a working group meeting to evaluate the preventive effects of sunscreens. It was concluded that the use of sunscreens can reduce the incidence of squamous cell carcinoma and basal cell carcinoma of the skin, while evidence for reduction of the incidence of melanoma is still lacking. However, there seems to be a strong tendency for users of sunscreens to expose themselves for greater periods of time to sunlight, thereby counteracting most of the protective effects. The result of these evaluations was published in the series of IARC Handbooks of Cancer Prevention.

IARC Communications

A new Unit, IARC Communications, headed by Dr Nicolas Gaudin, has been created following an earlier recommendation by the Governing Council. This brings together and coordinates a number of Agency activities – public relations, IARCPress and the translation service. Combining these activities has markedly increased the effectiveness with which scientific information is disseminated. The library and information services will be integrated into IARC Communications in 2003.

IARC Press. Most of the original scientific results generated at the Agency are published in the general scientific literature, principally in peer-reviewed journals, but the Agency also has a long tradition of publishing books itself. These are marketed and distributed by the Agency and, in partnership, with WHO Headquarters and Oxford University Press. IARC Press sales have increased substantially over the past five years and contribute significantly to the Governing Council Special Fund. The Governing Council has made a pledge to return 50% of the gross revenues to the programme as an incentive to further expansion. This has allowed the Agency to expand into research domains not previously covered by IARCPress.

Washington office. In order to promote and disseminate IARC publications more effectively in North America, an office has been established in Washington, DC, in a building which houses branches of several United Nations agencies. The IARCPress office opened in January 2001 and is run by Ms Donna Flint. This has already led to a marked increase in orders from the United States, which can now be met more quickly and at lower cost than through shipment from Lyon. The office also plays an important role in preparations for sales and exhibitions of IARC books at major cancer research meetings.

The Agency has assumed responsibility for the preparation and publication of the *WHO Classification of Tumours*, in collaboration with WHO Headquarters. This series constitutes the third edition of the *WHO Blue Book* series. In contrast to the previous edition, which was restricted to histological criteria, the new edition also includes genetic factors necessary for the more precise identification and characterization of human tumours. In addition, it incorporates epidemiological and clinical data and information on predictive factors and contains the code numbers of the recently published third edition of the International Classification of Disease Oncology (ICD-O). This provides a particularly useful link between pathologists and cancer registries. This book series has become very popular, with 10 000 copies being printed of each volume. The first volume was Pathology and Genetics of Tumours of the Nervous System (February 2000), the second on Tumours of the Digestive System (October 2000), and the third on Tumours of Haematopoietic and Lymphoid Tissues (July 2001). It is planned to complete the WHO Classification of Tumours by the end of 2003, covering all human neoplasms in ten volumes.

Five volumes have been published in the series of *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (see above). This programme is generously supported by the National Cancer Institute of the United States, and continues to play an important role in the estimation of carcinogenic risks from a scientific and public health point of view.

In addition to conventional paper publications, the Agency makes increasing use of electronic means for the dissemination of information, particularly for epidemiological data. *GLOBOCAN 2000*, the fifth volume of the CancerBase series, is a highly successful graphics-oriented software package. It provides easy access to data on the worldwide incidence and prevalence of, and mortality from, 26 major cancers. Its ease of use and the facility which enables individuals to customize the layout has made this CD-ROM one of the best-sellers in the IARCPress programme. Several databases can be accessed directly through the IARC Internet site, including a summary of the results in the *IARC Monographs*, cancer epidemiology and the IARC database of *TP53* mutations in human neoplasms.

Fellowships and training courses

The Agency provides funds for approximately eleven IARC Research Training Fellowships each year, which are awarded on a competitive basis. The Fellowships Selection Committee includes renowned scientists from different countries and is currently headed by Dr David Goldgar, Chief of the Unit of Genetic Epidemiology. Awardees may work in a laboratory of their choice and follow-up has shown that for many of them the fellowship is an important (and often the initiating) event in the development of a long-term career in cancer research. In addition, the Agency has created a fellowship programme for those who wish to work at the Agency. Approximately six postdoctoral fellows are selected in this programme, again through a competitive selection process.

Several international courses on cancer epidemiology were organized by the Agency, both in Lyon and internationally, including courses in Africa and Latin America. Attendance at these courses was often facilitated by fellowships from WHO Regional Offices. They have proved to be very effective, playing an important role in the development and support of cancer registries. Dr Giovanni Romeo, Chief of the Unit of Genetic Cancer Susceptibility was responsible for IARC courses in cancer genetics, which were held in Sestri Levante, September 2000 and in Bertinoro, November 2001, in collaboration with the Gaslini Institute in Genoa. These courses have become increasingly popular due to the excellence of the faculty and a growing interest in cancer genetics, particularly in the counselling of families with inherited cancer syndromes.

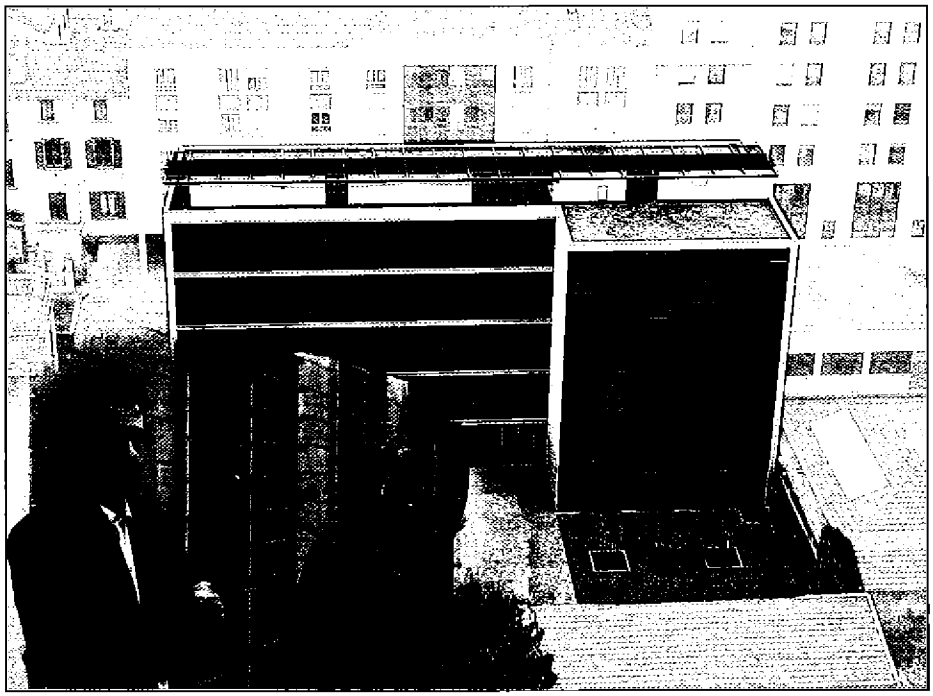
Staff and visitors

At the end of the biennium, a total of 290 people worked at IARC, of whom 131 were fixed-term and 70 short-term staff members. These numbers demonstrate that a considerable portion of the work of the Agency is carried out by doctoral students, postdoctoral fellows and, in particular, visiting scientists. During 2000/2001, the IARC Visiting Scientist Awards were held by Dr Patricia A. Buffler (University of California, Berkeley, USA), Dr H. Gilbert Welsch (Veterans' Administration Medical Centre, Vermont, USA) and Dr Leslie D. Stayner (National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA), enabling them to spend a year at the Agency. In turn, Dr Paola Pisani, of the Unit of Descriptive Epidemiology, left the Agency in the autumn of 2001 for a sabbatical at the University of Leeds, United Kingdom, and Dr E. Bah commenced a period of study leave in Finland.

The year 2000 was marked by the restructuring of certain units and programmes at the Agency following the retirement of Dr Ruggero Montesano (in 1999) and Dr Nubia Muñoz. Despite a significant reduction in the budget for 2000/2001, the shifting of funds from administrative functions to research programmes has allowed us to maintain a high level of scientific productivity. Five new staff scientists joined the Agency during the biennium, Dr Silvia Franceschi (to head the Unit of Field and Intervention Studies) Dr Marilys Corbex (Unit of Genetic Epidemiology), Dr Elisabete Weiderpass (Unit of Field and Intervention Studies), Dr Kurt Straif (Unit of Carcinogen Identification and Evaluation) and Dr Eric van Dyck (Unit of Gene–Environment Interactions). Three new professional members of the Administrative and Finance staff joined the Agency during the biennium – Ms Valerie Hay as the new Director of Administration and Finance, from WHO Headquarters in Geneva; Mr Raul Thomas as Budget and Finance Officer, formerly of the Budget Office of the Pan American Health Organization (PAHO/WHO, Washington) and Mrs Dorotea Pantua in the Budget and Finance Office, from the Western Pacific Region of WHO.

A total of 27 personnel left the Agency during the biennium. These included a number of professional staff. Among those who departed were seven scientists, Dr Nubia Munoz (Unit of Field and Intervention Studies), Dr Christian Malaveille and Dr Brigitte Pignatelli (Unit of Endogenous Cancer Risk Factors), Dr Hiroshi Yamasaki (Chief of the former Unit of Multistage Carcinogenesis), Dr Douglas McGregor and Mr Julian Wilbourn (Unit of Carcinogen Identification and Evaluation) and Dr Risto Sankila (Unit of Descriptive Epidemiology). Mrs Arlette Escoffier, the IARC Personnel Officer for more than 20 years, has been succeeded by Mrs Raymonde Alloin; Mr Ashok Mitra, former Finance Office, accepted an offer to become Budget and Finance Officer in the WHO Western Pacific Regional Office, Manila.

On behalf of the Agency, I would like to express our gratitude and appreciation for the excellent work carried out by these staff members over many years, together with our best wishes for their future activities.



The new Latarjet Building of IARC; inset, Mr Christian Drevet (architect) and Dr Diana Dunstan (Chair, IARC Governing Council)

Latarjet Building

With generous funding from the Governing Council, we were able to construct a new building along the rue Feuillat, consisting of a basement, ground and four upper floors, providing more than 2000 square metres of space. The building was inaugurated in October 2000 in the presence of the Chair of the Governing Council, Dr Diana Dunstan, the Mayor of our *arrondissement*, Professor Jean-Louis Touraine, now Deputy Mayor of Lyon, and the architect, Mr Christian Drevet. As a result of its excellent design, the building has become a landmark and articles about it have appeared in several architectural reviews.

On the occasion of IARC Day 2001, the new building was officially designated the Latarjet Building, in honour of Raymond Latarjet (1911–98), a renowned scientist who made substantial contributions to radiation research. He played a significant role in the creation of the Agency and was a longstanding supporter of our work as well as that of the French Cancer League, helping to establish fruitful links between the Agency and the French cancer research community. Equally, he was a charismatic, multi-talented man of letters, who wrote both literary and philosophical essays.

The ground floor and two upper floors are fully fitted out and house the Units of Environmental Cancer Epidemiology, Radiation and Cancer and Field and Intervention Studies. In addition, space has been made available for the production team of the WHO Classification of Tumours. It is planned to fit out the remaining two

floors during the coming biennium. The building will provide a base for the majority of the epidemiological and field studies whereas laboratory research, library, communications and administration will continue to be based in the tower building.

IARC Day

This annual event is held in conjunction with the Governing Council meeting and has become a tradition in the life of the Agency and its interactions with scientific, diplomatic and political communities of Lyon. The Roger Sohier Lecture 2000 was presented by Dr Richard Klausner, Director of the United States National Cancer Institute. His visionary talk concentrated on the great opportunities for cancer research following the deciphering of the human genome and our rapidly increasing knowledge of signalling pathways regulating cell growth and differentiation. He predicted that in the future, cancer drug development would be increasingly hypothesis-driven. In 2001, the Roger Sohier Lecture was given by Dr Oliver Brüstle from the University of Bonn, Germany. He is a leading scientist in stem cell research and fascinated the audience by his views on the therapeutic use of human stem cells with specific patterns of differentiation. Although more likely to be applied to neurodegenerative diseases, a role in cancer treatment has also been hypothesized.

Scientific Council

Members of the Scientific Council are elected by the Governing Council on the basis of their expertise in areas of cancer research relevant to the work of the Agency. They review critically the work of IARC scientists and give valuable advice on future research strategies. Our special thanks go to the Chairmen of the Scientific Council, Dr John Hopper (Australia), and Dr Michel Aguet (Switzerland) and its Vice-Chairs Dr Nicholas E. Day (United Kingdom) and Dr Catherine Bonaïti-Pellié (France).

On behalf of the Agency and its scientists, I wish to thank those members who left the Council during the past Biennium: Dr N. Day (United Kingdom), Dr S. Hirohashi (Japan), Dr J. Hopper (Australia), Dr H. van den Berghe (Belgium), Dr L. Aaltonen (Finland), Dr P. Band (Canada), Dr C. Bonaïti-Pellié (France), Dr. V. Khudoley (Russian Federation), Dr E. Matos (Argentina) and Dr G. Suarez Kurtz (Brazil).

Governing Council

The Council noted with much regret that Argentina and Brazil, which joined the Agency only two years ago, had decided to withdraw. This decision created a significant financial deficit, which could only be balanced by painful measures. These included the departure, through a mutual agreement of separation, of a significant number of staff members who had worked at the Agency for many years with skill and dedication; their contribution to the success of the institution is greatly appreciated. At its 42nd session in May 2001, the Governing Council determined the biennial budget for 2002/2003, with a budget slightly lower than that in the previous biennium. Despite this restriction, we are confident that through efficiency measures and by readjusting our strategic objectives, we shall be able not only to maintain the level of scientific activity, but also to expand into new research domains. Following suggestions by the Scientific and Governing Councils, new Units are planned to be established in 2002, on Infection and Cancer, and on Biostatistics/Bioinformatics.

On behalf of the Agency and its staff, I would like to thank the Governing Council for its continuing support, and its Chair, Dr Diana Dunstan, for valuable advice over the past two years.

IARC strategy

The Governing Council formed a working group at its session in May 2001 which was charged with the task of preparing a Medium-Term Strategic Vision for IARC. The Group includes members of the Governing Council, Scientific Council, IARC scientists and a WHO representative, and is headed by the Chair of the Governing Council, Dr Diana Dunstan. A meeting of this Group in early November 2001 allowed a very fruitful exchange on strategic priorities and the future work of the Agency. The resulting document will be presented to the Governing Council for consideration at its session in May 2002.

Interaction with WHO Headquarters

Professional relationships with WHO Headquarters have been further strengthened. Members of the Cluster for Non-communicable Diseases contributed to the book project *Cancer Report 2002*, which we plan to publish on the occasion of the next Governing Council meeting. Dr Cecilia Sepulveda-Bermedo, Head of the WHO Programme on Cancer Control, participated in the working group which formulated the Medium-Term Strategic Vision for IARC. The Director participates in the WHO Global Cabinet meetings with the Director-General, Dr Gro Harlem Brundtland, and the WHO Regional Directors. This provides an excellent opportunity to exchange views and maintain contacts with the Regional Directors, who often support the Agency's work at the national level. These meetings also contribute to a better integration of the work of the Agency into the overall public health agenda of the World Health Organization.

Paul Kleihues, M.D.
Director

Part 1

Cancer occurrence and outcome

IARC provides support for cancer registries in all regions of the world. These registries constitute an essential public health resource for national cancer control programmes and a key activity of the Agency is to ensure that registries use common methods and definitions, so as to ensure comparability of their data. Many studies of cancer causes such as environmental and genetic factors in specific populations are built upon data on prevalence, incidence and outcomes from the cancer registries, as are a range of primary and secondary prevention studies.

Analysis of geographic variation in cancer incidence, trends and outcomes depends on the development of suitable software packages. A major preoccupation is the dissemination of the results through the publication of *Cancer Incidence in Five Continents* and a range of other printed and electronic outputs.

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.

International Association of Cancer Registries (IACR)

D.M. Parkin, S.L. Whelan, S. Haver; in collaboration with D. Forman, Yorkshire, UK; H.H. Storm, Copenhagen, Denmark

IARC provides the secretariat for the International Association of Cancer Registries (IACR), administering collaborative projects, membership applications and subscriptions. In 2001 the association had 440 members in 108 countries, 80% of them cancer registries. Members collaborate actively with IARC in projects using cancer registry data, the preparation of publications presenting data on cancer occurrence worldwide and on cancer registration methodology. The secretariat maintains a library containing over 2000 publications produced by member registries and presenting data on cancer incidence, mortality and prevalence.

Assistance is provided to the hosts of the annual scientific meetings. 280 participants took part in the 2000 meeting, held in Khon Kaen, Thailand. The programme addressed cervix cancer prevention, magnetic and electric fields and cancer, genetic and environmental influences in cancer causation and etiology and control of cancer of selected sites common in Asia. The contributions to a poster session presenting cancer registration results in 18 Asian countries have been published as a supplement to the *Asian Pacific Journal of Cancer Prevention* (Vol. 2, Supplement 1, 2001). In 2001, more than 200 participants from over 50 countries came to the meeting in Havana, Cuba, that focused on evaluation of cancer control programmes; population survival studies; cervix, head and neck, and prostate cancer; geographical and time variations in cancer incidence and mortality, quality control and presentation of research and results from Latin American cancer registries.

The Calum Muir Memorial Fellowship (to help personnel working in cancer registries to spend time in institutions which offer learning opportunities not available in their home institute) was awarded to Mr Sory Kané from the Mali Cancer Registry in 2000. In 2001, two fellowships were awarded to Ms Krittika Suwanrungruang from the Khon Kaen, Thailand, Cancer Registry and to Mr Eric Chokunonga from the Zimbabwe Cancer Registry.

News is updated regularly on the IACR web site (http://www-dep.iarc.fr/iacr.htm). The IACR Newsletter, sent to all members and also available on the web site, gives news of activities and includes articles from cancer registries and national/regional associations of registries. Applications for membership, questionnaires for collaborative projects and registration material for the annual meetings can be downloaded from the site.

European Network of Cancer Registries

D.M. Parkin, R. Sankila, J. Tyczynski, F. Bray, E. Démaret, J. Ferlay, M.T. Valdivieso, E. Riboli; in collaboration with U. Batzler, Stuttgart, Germany; H. Botha, Leicester, UK; D. Brewster, Edinburgh, UK; J.W.W. Coebergh, Eindhoven, Netherlands; J. Faivre, Dijon, France; F. Langmark, Oslo, Norway; C. Martínez Garcia, Granada, Spain; L. Simonato, Padua, Italy; R. Tumino, Ragusa, Italy; 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. The ENCR has 164 member registries (Figure 1). Of these, 97 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 ENCR is guided by a Steering Committee made up of elected members and nominees of cancer registry associations; IARC provides the secretariat. The ENCR Internet home page at http://www-dep.iarc.fr/encr.htm provides comprehensive information on the activities of the ENCR. An *ENCR Newsflash* is published periodically, in English and French.

Establishment of standards and definitions

An ENCR working group has produced recommendations for using the variable 'method of detection' in cancer registries with respect to screen-detected cancers, that were circulated to registries in April 2001. The IARC/IACR confidentiality guidelines have been revised by a Working Group in the light of the EU Directive on 'Protection of individuals with regard to processing of personal data'. The recommendations were finalized in June 2001 and will be circulated to the

registries after endorsement by the Steering Committee. Another working group is reviewing methods for evaluating completeness of cancer registration, in particular to deal with confusion in nomenclature and diversity in practice concerning the use of death certificates. A new working group has prepared instructions and developed a questionnaire to be used in reviews to help registries to improve their performance, and a pilot review has been carried out.

Based upon a field trial completed under the responsibility of Dr T. Möller (Lund, Sweden), recommendations regarding stage (extent) of disease were finalized in February 2001 and circulated to registries. A second working group for coding bladder cancer has been established, under the leadership of Dr C. Martinez (Granada, Spain), to prepare recommendations for coding and tabulating urothelial tumours in a uniform way and to identify any implications for the coding of multiple urothelial tumours. New recommendations on which types of non-melanoma skin cancer to register and how to code multiple primaries, as well as a list of extended subsite topography of the skin were prepared and circulated to registries in November 2000.

Automated cancer registration

A small group was set up in 1999 with the aim of making existing automated systems comparable, reducing the proportion of cases requiring checking of the source records and preparing guidelines for case resolution. A workshop was held in Venice, Italy, in October 2000 to present the results of the comparability tests on different automated incidence software, the quality control tests and how to improve the algorithms for automated registration. A web site on automated cancer registration has been developed.

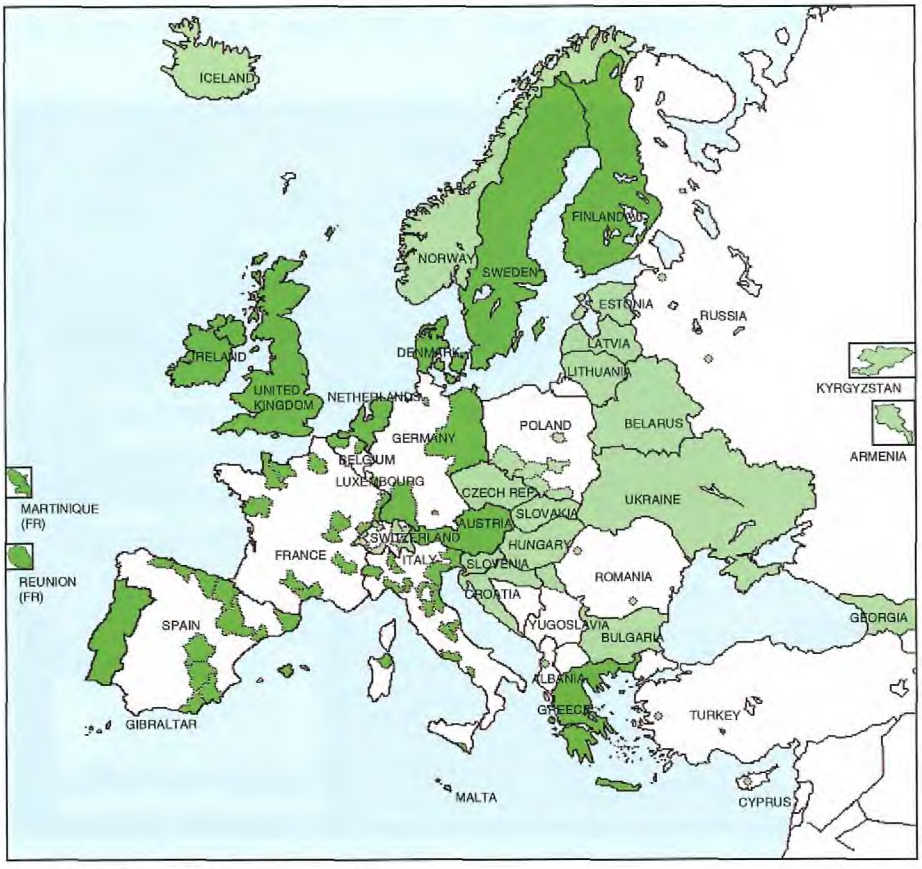


Figure 1. Locations of ENCR member registries

Standard definitions of essential data items in the summarization process, case consolidation, etc., have been established.

Cancer registries and clinical care

With increasing interest in evidence-based medicine, costs of health care and issues relating to the accessibility and quality of care as a major determinant for survival and quality of life of cancer patients, ENCR organized a workshop on the use of cancer registries in the evaluation of clinical care in Rotterdam on 14–15 December 2001.

Training in cancer registration and data analysis methods

Six courses were organized in 2000 and 2001, two on cancer registration methods and four on statistical methods (see Section 7.3). Registry personnel can obtain support to attend ENCR courses or to exchange skills through working visits to other cancer registries. Approximately ten fellowships are available each year.

Consultancy

Cancer registries can request a consultant visit by an experienced person to advise on cancer registration methodology or specific local problems. In 2000 and 2001, ENCR expert consultants visited cancer registries in Georgia, Germany, Poland and Romania.

Provision of information on cancer in Europe

A new version of EUROCIM (4.0) software and an updated EUCAN database and software package have been made available (see Section 1.2). Within the programme of collaborative studies of trends in cancer incidence and mortality in specific countries, in 2000–01 an analysis of cancer incidence and mortality in Portugal was carried out and an analysis of trends in incidence of mesothelioma was begun. A formal assessment is being undertaken of trends in cancer incidence and mortality within the European countries by age, period of diagnosis and birth cohort, using the age–period–cohort

model, and includes short-term predictions of future cancer burden.

Reliability and validity of registry data

International Classification of Diseases

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

The third edition of the *International Classification of Diseases for Oncology* (ICD-O-3), prepared by IARC with the collaboration of an international group of experts, was published by WHO in November 2000, and was implemented in many cancer registries in January 2001. This revision includes many new terms to reflect, in particular, the rapid changes in understanding of and terminology concerning the leukaemias and lymphomas. Conversion programs between the new and existing coding schemes were created during 2000. ICD-O-3 was translated into French during 2001.

International Classification of Childhood Cancer

E. Kramárová, D.M. Parkin; in collaboration with P. Kaatsch, Mainz, Germany; C.A. Stiller, Oxford, UK

Following the publication of ICD-O-3, the International Classification of Childhood Cancer (ICCC) has been revised. While accommodating the latest changes in classification of malignant tumours, continuity between the two latest editions of ICCC was preserved.

Histological Groups for Comparative Studies

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

Histological Groups for Comparative Studies (Parkin *et al.*, 1998, IARC Technical Report No. 31) provides a description of the recognized histological subtypes of the principal cancers, together with the appropriate ICD-O morphology codes. Revision began in 2001, to update the codes to ICD-O-3, and to expand the groups to additional cancer sites.

Computer software for cancer registries

CanReg

D.M. Parkin, A. Cooke

CanReg is a configurable computer program designed for cancer registration in population-based registries. The most recent version—CanReg3—was first released in late 1996 and in the last two years more than 50 new registries have received their own version of the program and been trained in its use.

The program features include a search 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. Easy-to-use analysis options include frequency distributions, reports, incidence tables and an interface into EpiInfo6. 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 Cyprus, Egypt, Israel, Jordan and Palestine.

A new 32-bit Windows NT® version—CanReg4—is planned that will allow integration of Chinese, Thai and Arabic character sets, and working in networked environments (Figure 2). The Bill and Melinda Gates Foundation is providing funding through its support for the cervical cancer prevention project (see Section 5.3).

IARCtools

IARCtools is a Windows®-based package providing 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 the ICD version 9 and 10, and a new

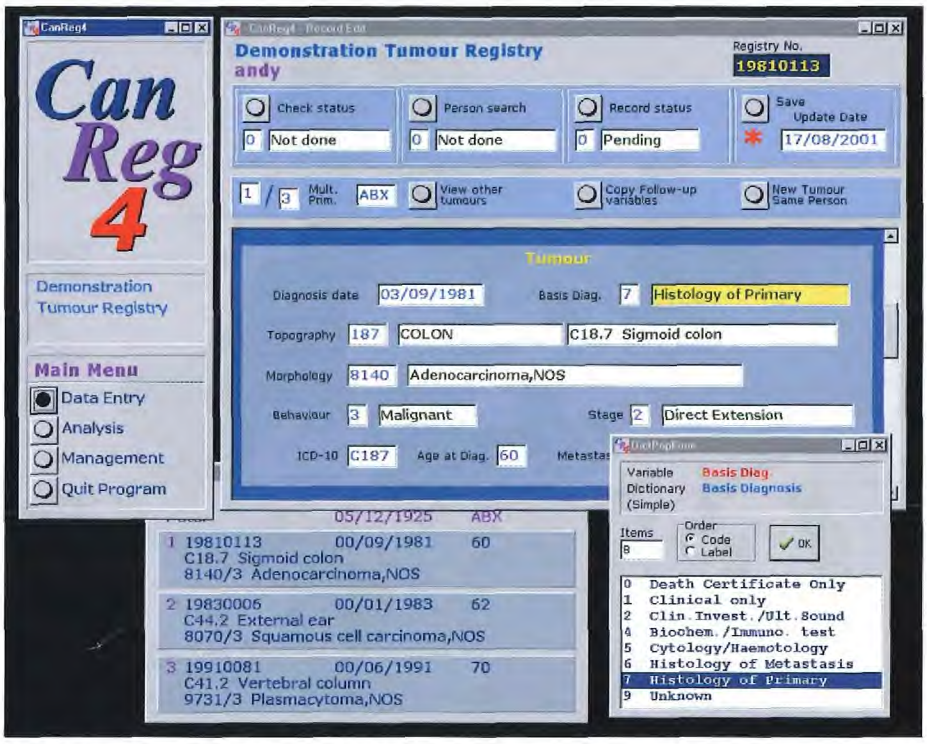


Figure 2. Demonstration screen display of CanReg4

program to detect multiple primary tumours in an individual. New conversion programs for converting data into the third edition of ICD-O (ICD-O-3) and from ICD-O-3 into ICD-10 are being prepared. In addition, the IARC-CHECK program included in the package will be reviewed. In particular, new histology/site validation rules working with the new ICD-O-3 codification are being defined. The IARCtools package is distributed free from the *CANCERMondial* web site (http://www-dep.iarc.fr/resour/software/iarctools.htm) or on diskettes or CD-ROM on request.

Support to specific cancer registries

D.M. Parkin, P. Pisani, R. Sankaranarayanan, S.L. Whelan, 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 many cancer registries in the course of the biennium, and individuals working in cancer registries have visited the unit for training or discussion. A structured course in cancer registration and applications in epidemiology is held regularly in Lyon and courses on cancer registration methods have been held in Lima, Peru (October 2000), Bamako, Mali (March 2000), Ibadan, Nigeria (February 2001) and Nairobi, Kenya (September 2001) (see Section 7.3).

In September 2001, 27 cancer registries in developing countries were receiving direct support in the form of a collaborative research agreement, to enable them to start activities or to purchase equipment. Several commonly used computer programs are provided to registries (see above).

Close collaboration is maintained with the regional offices of WHO with respect to cancer registry activities. IARC staff provided consultancies on cancer registration and cancer control in several countries. The Unit of Descriptive Epidemiology also provides more direct support and encouragement for cancer registration activities in many countries, often in the form of collaborative research agreements between the registry and IARC. Aid with analyses often leads to joint publications (see Section 1.2).

Algeria: Three registries received assistance: in Mascara (H. Hamdali), Oran (L. Mokhtari and N. Midoun) and Sétif (M. Hamdi-Chérif).

Argentina: Three registries are supported, Bahia Blanca (E. Laura and N. Arias Ondicol), Concordia (M.A. Price), where a plan to extend registration to the whole province of Entre Rios is being implemented and Jujuy province (Mrs C. Bonaldi), for which the histology registry has been expanded to become population-based.

Bahrain (J. Al-Sayyad): Progress was reviewed during a visit.

Belize (H. Leslie and H. Sanchez): A visit was made following a request from the Belize Cancer Society for help in developing a cancer registry.

Bermuda (M. Rego and L. Proctor): One of the registry supervisors attended training courses in Warsaw and Lyon.

Bolivia: Cancer incidence for one year (July 1998–June 1999) in the population of La Paz and El Alto has been analysed (R. Calderon and J. Rios-Dalenz). A hospital-based cancer registry is being expanded to cover the population of the province of Sucre. The pathologist attended the IARC course held in Lima.

Brazil (M.P. Curado, P.R. Grassi, N. Mahayri and A.P. Mirra): A version of CanReg for the Brazilian cancer registries is in preparation. IARC staff attended the annual meeting of the registries in November 2000.

Bulgaria: The cancer registry (S. Danon) covers the entire population. The registry hosted an ENCR course in cancer registry methods in January 2000.

Burkina Faso (B. Sakande): Registration for the city of Ouagadougou commenced in 1998. A review visit by a member of staff was made in March 2000 to assess the first two years of operation.

Cambodia (P. Piseth Raingsey and Khuon Eng Mony): Registration began in 2001, following an initiative of the Preventive Medicine Department of the Ministry of Health.

Cameroon (A. Doh, P. Ndom and G. Enow-Orok): Previous attempts at population-based registration were not successful; conditions for restarting have been studied.

Chile: The supervisors of the registries in Antofagasta (M. Goycolea) and Valdivia (M.E. Flores) attended the IARC course in Lima.

China: After discussions with representatives of cancer registries in November 2000, a formal review visit was made, at the invitation of Dr Lian-di Li to prepare recommendations to the Ministry of Health on development of cancer information systems.

Colombia: A CanReg3 system was developed for the registry of Cali (E. Carrascal) and historical archives were transferred. The registry was invited to participate in an international descriptive study on diagnosis and treatment practices of breast cancer. A network of registries in four other cities (Bucaramanga, Medellin, Cartagena, Pasto) is being developed with technical assistance from the National Cancer Institute (H. Posso) and IARC.

Congo (C. Gombe-Mbalawa and S. Moubie): The Brazzaville registry is supported.

Côte d'Ivoire (A. Echimane and A. Ahnoux): Support to the registry continued.

Cuba: The central registry in Havana (L. Fernandez and Y. Galan) is being decentralized to regional registries. The registry was the host for the annual scientific meeting of the International Association of Cancer Registries (Section 1.1) in 2001. The registry collaborates in the studies of cancer survival (Section 1.4), and has been invited to participate in an international study on diagnosis and treatment practices of breast cancer.

Gabon: A consultant visit is planned, with a view to developing population-based cancer registration.

Gambia: The cancer registry (E. Bah) is the main component of Phase III of the Gambia Hepatitis Intervention Study (see

Section 5.1) and the registry is collaborating in the study of cancer survival (see Section 1.4).

Georgia (V. Tkeshelashvili): A consultant visit was made.

Ghana (B. Awuah): The principal investigator received training in Lyon with a view to initiating cancer registration and a consultant visit was made to review requirements

Guam (R.L. Haddock): Population coverage has been completed with the inclusion of information from private clinics.

Guinea (M. Koulibaly and I. Kabba): Support to the registry continued.

Guyana (W. Chin and P Lane): The Ministry of Health requested assistance in developing cancer registration. A staff member made a visit and prepared a plan of action. The registry supervisor attended a training course in Lyon.

Honduras: Hospital-based registries in Tegucigalpa and San Pedro Sula (J. Figeroa and M.T. Martinez) have been transformed to cover the resident populations of the cities.

India: Numerous registries participate actively in research projects on cervical cancer screening (Ambillikai; J. Cherian and R. Rajkumar; Barshi, B. Nene, K. Jayant and A. Budukh), cancer survival (Bhopal, S. Khassake and R. Dikshit; Mumbai (Bombay), B.B. Yeole; Chennai (Madras), V. Shanta and C.K. Gajalakshmi), oral cancer screening (Trivandrum, K. Nair and C. Varghese) (Section 5.3) and a cohort study focusing on the risks of tobacco use (Mumbai and Trivandrum (Section 2.4). Assistance has been provided for analysis of the results from Ambillikai, Barshi, Bhopal and Calcutta (M. Siddiqi and U. Sen).

Iran: The registries in Teheran (A. Mohagheghi and A. Mosavi) and Shiraz (M.J. Saalabian and J Shamsnia) are being developed to cover wider populations.

Jordan (S. Al-Kayed and B. Qasem-Hijawi): The registry covers the entire country since 1997. Technical support for data management is provided. A staff member attended a training course in Lyon.

Kenya: Progress at the recently established cancer registry in Eldoret (N. Buziba), western Kenya, was evaluated by a consultant in 2000. In Nairobi (G. Mutuma, L. Muchiri, A Nyongo and J. Rajab), plans have been made to develop the old Kenya National Cancer registry (essentially a register of pathology diagnoses in one hospital) into a population-based registry covering the city and its environs (with financial help from the United States National Cancer Institute).

Laos (B. Phouthone and P. Alongkone): Cancer registration has been set up following a request of the Ministry of Health, supported by WHO, and registration began in 2001.

Libya (S. El-Fathali and K. Enowellyi): Registration covering a population of 525 000 in Zawia region of western Libya began in 1998. The cancer registrar received training in Lyon.

Malawi (C. Dzamalala, T. Mijoya and N.G. Liomba): a new registry director was appointed and case finding has improved. The previous supervisor published the results for 1994–98.

Mali (S. Bayo and S. Kané): An analysis of data covering about 14 years, including a review of possible temporal trends for certain cancers, is being prepared.

Mauritania (M. Diop): A visit was made to advise on setting up a population-based registry for Nouakchott and a collaborative research agreement was established.

Mongolia (Munkhtaivan and Ozzi-delger): A staff member attended a training course in Lyon.

Niger (H. Nouhou): Support to the registry continued and a visit was made to evaluate progress.

Nigeria: The Ibadan registry (J.O. Thomas) hosted a training course for Nigerian cancer registry staff in February 2001. It provides the framework for a study of non-Hodgkin lymphoma related to human immunodeficiency virus (HIV), and surveillance of temporal trends in HIV-related related cancers (Section 2.6). A new registry for the city of Lagos (K. Banjo) started in 2000.

Oman (J. Al Lawati): The registry covers the entire country. Staff members received training in Lyon. A consultant visit on behalf of WHO took place to review progress and results. Registry results for 1993–99 have been published.

Pakistan: A population-based registry (Y. Bhurgri) covering the population of the southern part of Karachi is supported.

Panama (M. Valdes): Data collection and processing is continuing.

Paraguay: A staff member from the Asuncion registry (P. Rolón) attended the IARC training course in Lima.

Peru: continuing support was provided for the registry in Trujillo (P.J. Albujar) and the Lima registry (E. Caceres) hosted a training course for staff of Latin American registries in October 2000.

Philippines: The two registries in greater Manila (D. Esteban, A. Laudico and B. Talaver) are active in the follow-up of the breast cancer screening project (Section 5.3). The data of the Manila registry are being used for studies of survival.

Romania (N. Ghilezan, M. Patruleasa and V. Pacurar): Cancer registration is being developed through initiatives in several provinces.

Singapore (H.P. Lee, K.S. Chia and A. Cheow): The registry participated in an analysis of survival (Section 1.4).

Swaziland (S. Okonda): The registry staff received training in Kenya and a collaborative research agreement was established.

Tanzania: A registry in Moshi (E. Moshi) has operated since 1998, covering four surrounding districts of the north of Tanzania. Plans were made for the development of cancer registration in the Ocean Road Cancer Institute (F. Temu-Mbaga), as a first step to population-based registration in the Dar es Salaam area.

Thailand: Five population-based registries (Lampang, Chiang Mai, Khon Kaen, Bangkok and Songkla) (S. Deerasamee, P. Srivatanakul, S. Srisukho, S. Sontipong, S. Sriamporn, H. Sriplung and V. Vatanasapt) collaborated on the preparation of a monograph in cancer in Thailand. Khon Kaen registry provides follow-

up for a population-based study (Section 3.3) and was host for the annual scientific meeting of the International Association of Cancer Registries (Section 1.1) in 2000.

Trinidad & Tobago: Population coverage is complete for the city of Port of Spain, (V. Roach), and extension to the whole island is planned.

Turkey (G. Aydemir, C. Fidaner, and S. Eser): Registration for Izmir province is now complete.

Uganda: The registry (H. Wabinga and S. Nambooze) continues to act as a resource for training in East Africa. It is one of the centres monitoring temporal trends in HIV-related cancers (Section 2.6) and collaborates in the study of survival in Africa (see Section 1.4). The registry results for the period 1960–97 have been published [514]. The registry is providing technical support in development of cancer registration for the district of Mbarara.

Viet Nam: The registry in Hanoi (Pham Hoang Anh, Nguyen Chan Hung, Nguyen Manh Quoc) is supported.

Zimbabwe: The registry in Harare (L. Levy, E. Chokunonga, B. Mauchaza and M. Bassett) continues to act as a resource for training and consultancy in southern Africa. It is one of the centres monitoring temporal trends in HIV-related cancers (Section 2.6) and collaborates in the study of survival in Africa (Section 1.4). The registry results for the period 1993–95 were published [94] and the cancer registrar visited Lyon to undertake an analysis of incidence and survival from cancer in children. A further initiative to re-vitalize the historic registry in Bulawayo (J. Kasese) was undertaken with staff training and financial support, in part from the US National Cancer Institute.

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. Therefore the collation, processing, analysis and presentation of cancer data are important activities. It is also 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 priorities for public health intervention.

Cancer Incidence in Five Continents, Volume VIII

D.M. Parkin, S.L. Whelan, J. Ferlay; in collaboration with L. Teppo, Helsinki, Finland; D. Thomas, Seattle, WA, USA

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 distinct subpopulations (especially ethnic), as a reference source for studies requiring information on international variations in cancer risk. Volume VII (1997) included data on 182 populations in 50 countries.

Over 300 cancer registries were invited to submit data for Volume VIII, to be published in 2002, and by September 2001 data on 269 populations in 76 countries had been received. The data were analysed and checked for validity and coherence in 2000 and 2001, and reviewed during four editorial meetings. The final selection will include several new areas from Africa and from developing countries in Asia.

Over the years successive editors have defined features of a data-set which can help to identify incomplete or invalid registration. Measures of quality include the proportion of cases with histological verification and of notifications based only on a death certificate, the ratio of mortality to incidence, significant changes in rates over time and childhood cancer rates outside the expected range. These editorial checks for data quality were updated and improved during 2000, and the analysis now incorporates editorial flags to highlight problems in the data.

The traditional tables presenting data on incidence have been abbreviated to accommodate the increased number of contributors, and the more detailed data will be provided in electronic format. A new feature will be an analysis of selected histological diagnoses by site.

European cancer incidence and mortality database

EUROCIM

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

EUROCIM is a powerful software package allowing statistical analyses of cancer incidence and mortality data contributed by members of the European Network of Cancer Registries (ENCR: see Section 1.1). The latest version of EUROCIM (Version 4) contains approximately 15 million individual case records held in the database in a tabulated format. In addition to the set of statistical analyses available in the previous Windows version of EUROCIM, a time trends analysis module has been added, that allows the user to fit age–period–cohort models to the registry incidence and mortality data (Figure 3). The user interface has been extensively revised to enhance ease of use. EUROCIM has been distributed on CD-ROM to ENCR members, together with the latest incidence and mortality databases maintained at IARC, containing data from over 100 European cancer registries covering the period 1953 to 1998. Training courses in using EUROCIM for European cancer registry personnel were held in March 2000 and April 2001. The software and database are managed and maintained at IARC, while an external contractor is responsible for the development of the program.

EUCAN

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

The Windows-based EUCAN package provides access to 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 in a tabular format, graphically as line plots, bar or pie charts, or as maps (Figure 4). The presentations can be easily printed or exported to other packages. In addition, the countries and cancer sites can be grouped together according to the user's needs.

The database is updated annually to incorporate the latest incidence and mortality data available. The CD-ROM allows the user to download new versions of the database directly from the ENCR Internet home page. The estimates for 1997 were made available online in 2001. A simplified version of the EUCAN software is available on the ENCR web site. The EUCAN CD-ROM was published by IARC as CancerBase No. 4.

EUROPE 95

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

Estimates of cancer incidence and mortality in 1995 were made for the 38 countries in the four United Nations-defined areas of Europe, using WHO mortality data and published estimates of incidence from national cancer registries [65]. Where national incidence data were not available, estimation involved incorporating the high-quality incidence and mortality data available from the expanding number of population-based cancer registries in Europe. Information on the burden and risk of 25 common cancers in each European country (Figure 5), together with a commentary on the descriptive epidemiology of these cancers, has been published, and a more in-depth analysis is available online on the ENCR web site. The estimated 2.6 million new cases of cancer in Europe in 1995 represented over one quarter of the world burden of cancer. The corresponding number of deaths from cancer was around 1.6 million. Lung cancer, with an estimated 377 000 cases, was the most common cancer in Europe in 1995. Lung cancer, together with cancers of colon and rectum (334 000) and female breast (321 000)

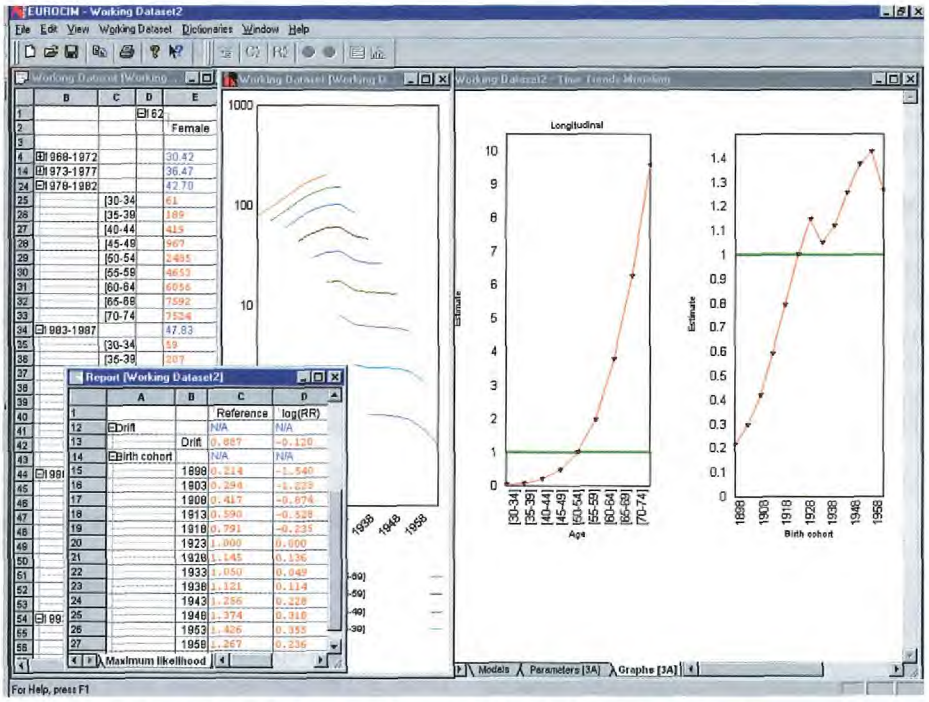


Figure 3. EUROCIM version 4; evaluating the effects of age, period and cohort on lung cancer rates over time

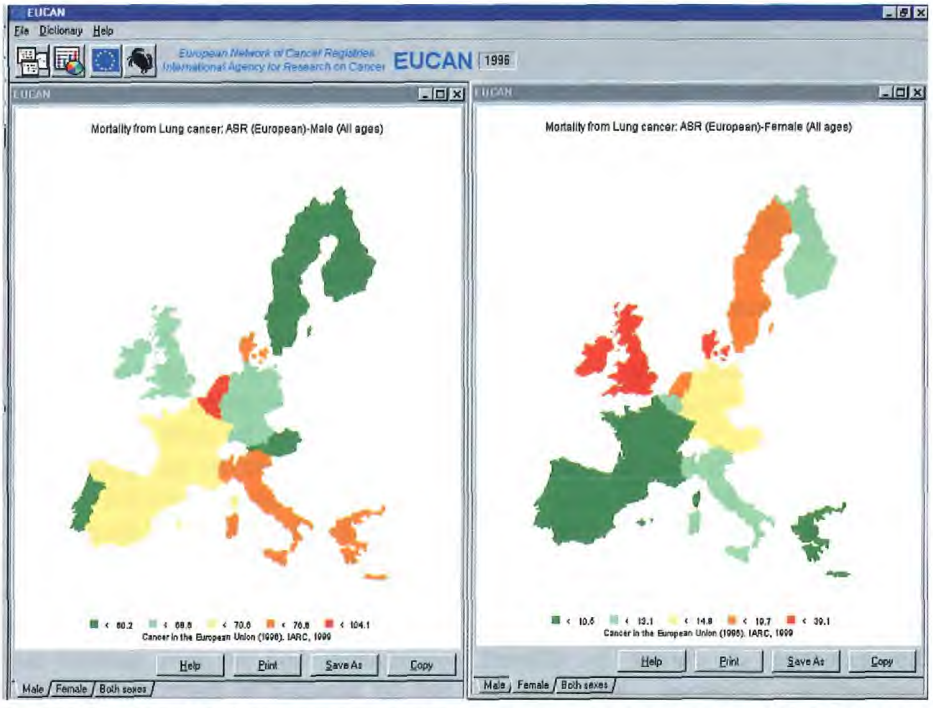


Figure 4. Example of a EUCAN screen display: lung cancer incidence in men (left) and women (right) in the European Union

represented about 40% of new cases in Europe. Lung cancer (330 000) was also the most common cause of death from cancer, accounting for about one fifth of the total number of cancer deaths in Europe in 1995.

Analysis of data from collaborating cancer registries

D.M. Parkin, R. Sankaranarayanan, E. Kramárová, P. Vizcainio, R. Lambert, F. Bray

The results from the cancer registry of Harare, Zimbabwe, for its second three years of operation (1993–95) have been published [94]. For Kampala, Uganda, registry results for a 38-year period (1960–97) were analysed and published [514], together with a study estimating completeness of registration in a recent period (1994–96) [342]. The first results from the cancer registry in Abidjan, Côte d'Ivoire (for 1995–97) were published [130]; they demonstrate that the most common cancers are prostate cancer in men and breast cancer in women. The first results from the Malawi cancer registry (for Blantyre district) for 1994–98 have been published [14]. Almost all other registries in Africa submitted their most recent data in 1999, with a view to their publication in *Cancer in Africa* (see below).

In Asia, results from the cancer registry of Izmir, Turkey [139] show a picture dominated by tobacco-related cancer (in men) and breast cancer (in women). The data from the cancer registry of Karachi South (Pakistan) for the years 1995–97 [22] show high rates of lung, oral cavity and larynx cancers in men and breast and oral cavity cancers in women. Incidence data from the rural population-based cancer registry in Ambillikai, India, for the period 1996–98 [366] show a very high risk of cervical cancer in women and high rates of mouth cancer in both sexes. The profile of childhood cancer in Ho Chi Minh City, Viet Nam, has been described [310].

In Europe, incidence data from cancer registries have been analysed and published within the framework of the European Network of Cancer Registries (ENCR) (see above).

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 were completed or in progress. These include a study of time trends in the incidence of squamous cell carcinomas of the cervix [513], and a comparative analysis of trends in gastric cancer mortality and incidence in Japan (Osaka), the United States (SEER) and Slovenia [243]. An analysis of time trends in the incidence of carcinoma of the

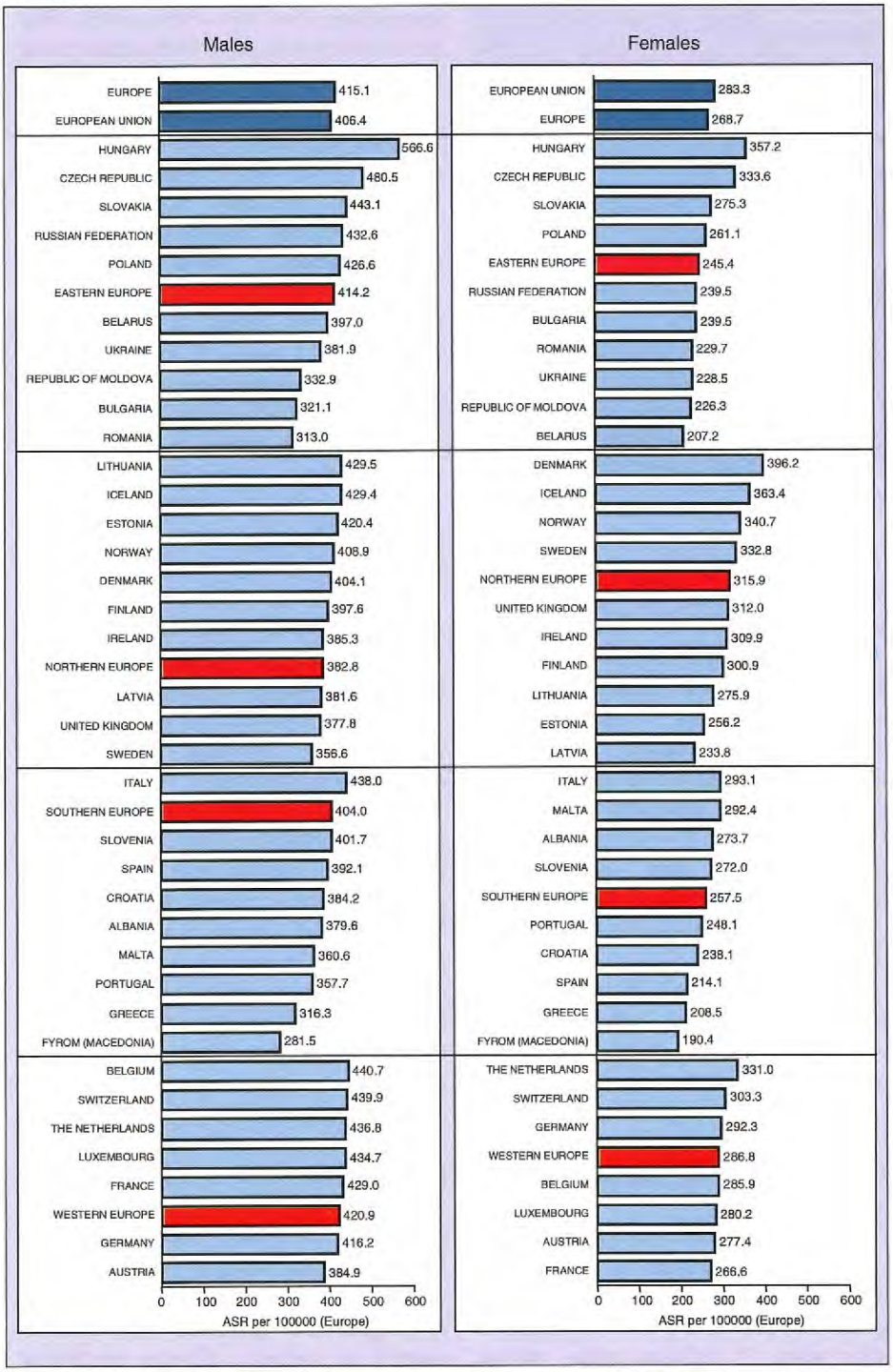


Figure 5. Age-standardized incidence rates by area and country in Europe: all cancers combined (except skin)

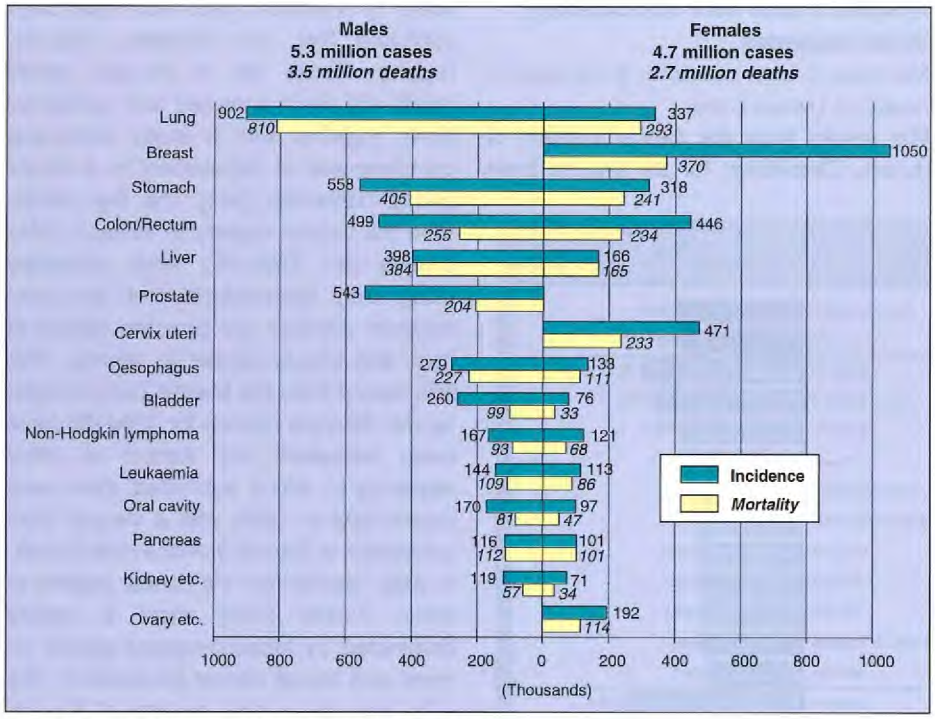


Figure 6. Numbers of cases and deaths worldwide, by cancer site

oesophagus and gastric cardia, by histological type, has been completed.

Survival data from various cancer registries have been analysed and published within the framework of the project on cancer survival (Section 1.4).

Worldwide burden of cancer

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

The global estimates of cancer incidence and mortality for the year 1990 complemented with estimates of cancer prevalence provide the best information on the likely numbers, by country, of cancer patients who are alive one, three and five years after their diagnosis [356].

These estimates of cancer incidence, mortality and prevalence were subsequently updated, using the latest available rates of incidence, mortality and survival from cancer registries and vital statistics departments. The rates obtained were applied to the estimated world population in the year 2000 to provide an estimate of cancer burden at the beginning of the millenium. The results for 25 different cancers, by sex and broad age group, for every country of the world, are presented on the GLOBOCAN 2000 CD-ROM and on the Internet (Section 7.1). There were an estimated 10 million new cases, 6 million deaths and 22 million persons living with cancer in the year 2000. The most common cancers are, in terms of new cases, lung (1.2 million), breast (1.05 million), colon–rectum (945 000), stomach (876 000) and liver (564 000), and in terms of deaths, lung (1 million), stomach (646 000), liver and colon–rectum (489 000 each) (Figure 6). Summaries of these results have been published [335–337].

The profile varies greatly in different populations, and this appears to be mainly a consequence of different lifestyle and environmental factors, which should be amenable to preventive interventions. Figure 7 shows as an example the worldwide incidence patterns for liver cancer.

World population growth and ageing imply a progressive increase in the cancer burden—15 million new cases and 10 million new deaths are to be expected in 2020, even if current rates remain unchanged.

Time trends and projections of cancer mortality

F. Bray, D.M. Parkin, J. Tyczynski, J. Ferlay; in collaboration with H. Botha, Leicester, UK; T. Hakulinen, Helsinki, Finland

This study of time trends in cancer incidence and mortality rates in European populations has two components. The first involves evaluation of the influence of secular and generation effects in retrospective cancer data using the standard age–period–cohort model. Birth cohort effects occur when patterns in rates over time differ in different age groups, possibly reflecting changes in lifestyle factors in those born in successive generations. Period effects imply changes which affect all ages at the same time, as occurs if, at a given time point, a treatment intervention affects all patients regardless of age, or if there is a change in the coding practice of the tumour under investigation. Current studies include (1) an investigation of trends in breast cancer incidence in Europe, comparing countries having national mammographic screening programmes with countries where no such programme has been established; (2) an examination of lung cancer incidence rates by histology in populations with diverse smoking habits, both currently and previously.

The second component relates to the short-term prediction of future cancer incidence and mortality burden. Using a set of simple time-linear models, one can project forward recent cancer trends, yielding a plausible set of estimates of the future number of cases and deaths and age-adjusted rates. The method is being used to supplement the most recent annual estimates available in the EUCAN database (see above), with predictions of incidence and mortality in 2010 and 2020 for 24 cancer sites in the 15 Member States of the European Union. The predictions of breast cancer incidence and lung cancer mortality are of particular interest, and two further projects will investigate the projected estimates in relation to national statistics on breast

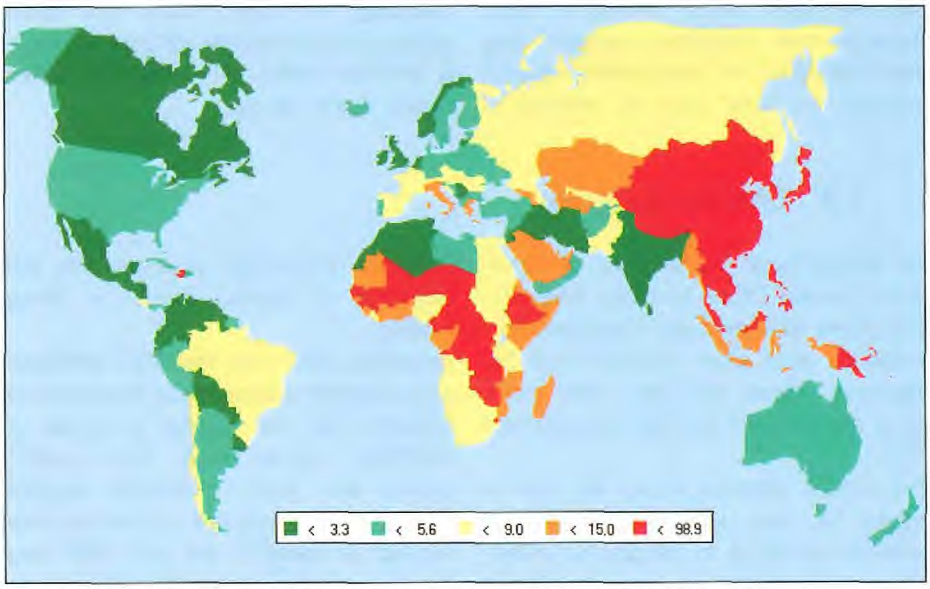


Figure 7. Incidence of liver cancer in males: world age-standardized rates. From GLOBOCAN 2000

screening and on smoking prevalence, respectively.

Cause-attributable cancer

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

Rational planning of preventive interventions requires quantification of the number of cases that can theoretically be prevented by avoiding or reducing exposure to the causative agents. The first comprehensive evaluation of cancer fractions attributable to known causes, by cause and cancer site, was that of Doll and Peto in 1981, which applied to cancer mortality in the United States in 1980. We are now conducting a systematic evaluation of the amount of the cancer burden 'explained' and 'unexplained' by current knowledge.

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 22% of all new cancer cases are due to infection with viruses (hepatitis B and C viruses, some human papillomaviruses, Epstein–Barr virus, human immunodeficiency virus (HIV) and HTLV-I), parasites (*Schistosoma* and liver flukes) or bacteria (*H. pylori*); the corresponding figure in developed areas is estimated at 9%.

With the support of the Europe Against Cancer Programme, detailed numerical results for the countries of the European Union, have been completed for several factors. Figure 8 shows proportions of all cancer cases attributable to selected factors, by sex.

Of all cancers, 33% in men and 6% in women are attributable to active tobacco smoking. Passive exposure of non-smokers to the spouse's smoke in the home is estimated to account for 1% of all lung cancer cases. In the European Union, 5% of all cancers were attributable to excess body weight (3% in men, 6% in women). Among female cancers, 11% are attributable to low parity (less than three children) or delayed first pregnancy (at age 30 years or later) and at least 5% of breast cancer cases are due to excessive alcohol drinking.

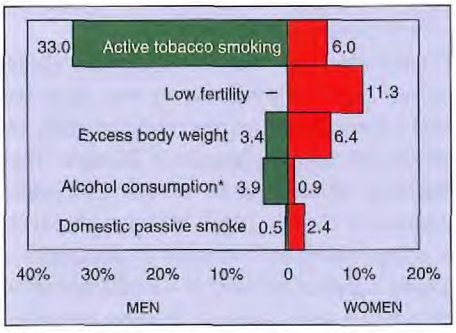


Figure 8. Proportions of all cancer cases in the European Union attributable to selected causes, by sex.

* Excluding breast cancer

Cancer in Africa

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

The publication *Cancer in Africa*, presenting a compendium of data on the incidence or frequency of cancer in Africa for the decade of the 1990s, was prepared during 2000 and 2001; two editorial meetings were held in Lyon. The book will be published in 2002. In addition to tabular material from 30 contemporary cancer registries, a systematic review by country presents all relevant historic data from the scientific literature. A review of the epidemiology of 16 cancers, drawing together studies on the African continent over the last 50 years, is also included. Estimates of incidence and mortality by country for the year 2000 are provided in electronic format.

Cancer genes: from families to epidemiology in world populations

D.E. Goldgar, C. Szabo, O. Sinilnikova; in collaboration with G. Lenoir, Paris, France. Supported in part by the Indo-French Cooperative Research Organization (IFCPAR)

IARC is coordinating a study of mutational patterns and associated risks of known genes which predispose to cancers that are historically common in the industrialized world, but whose incidence is rising in developing nations (MAGIC project). This project focuses on recurrent mutations found in diverse populations, mutations unique to specific populations and transfer of appropriate mutation detection methods to areas where they are not yet available. Collaboration with scientists from Brazil, China, India, Iran,

Mexico, Thailand and Turkey has led to identification of mutations in the *BRCA1* and *BRCA2* genes. In addition, a scientist from Cuba brought DNA samples from 20 high-risk breast cancer families to IARC. Several novel sequence variants have been identified. A collaborative project between the IARC and the Institute of Pathology in Delhi, India, has been established to estimate attributable risk in a defined series of early-onset Indian breast cancer cases.

1.3 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.

Automated Childhood Cancer Information System (ACCIS)

D.M. Parkin, E. Kramárová, N. Mitton, M.T. Valdivieso-Gonzales; in collaboration with F. Berrino, Milan, Italy; J.W.W. Coebergh, Eindhoven, Netherlands; J. Michaelis, Mainz, Germany; C.A. Stiller, Oxford, UK

Although cancer is rare in children, it represents an important cause of death in all age-groups and the proportion of life lost is higher for children than adults. International studies are of value in view of the rarity of childhood cancer, permitting collection of sufficient numbers of cases for analyses of etiological factors and population-based survival.

The objectives of the ACCIS project, co-sponsored by the European Commission (Sanco program), are to constitute a large childhood cancer database, create software for management and presentation of collected data and disseminate and interpret the results.

More than 100 population-based cancer registries in Europe were invited to contribute to this study. Over 100 000 cases under 20 years of age arising from a population at risk of almost 1 000 000 000 over the past 30 years have been compiled in the ACCIS database. Each record contains basic demographic, diagnostic and follow-up information. In collaboration with over 80 population-based European cancer registries, these records have been carefully checked for coding errors and classified according to the International Classification of Childhood Cancer. Of the resulting data-sets, only those with seriously underestimated incidence rates were excluded from the database. Other data-sets with minor flaws are included but with a cautionary note.

The ACCIS software allows the user to create his own subgroups of cancer patients according to geographic provenance, sex, age, tumour groups, period of incidence, vital status or period of death. It allows simple tabular and graphic presentation of data, calculates the incidence rates and survival proportions for user-defined groups of patients and compares statistically the computed indices. It is available on a CD-ROM and distributed free to all data contributors.

The presentation of the ACCIS project on the Internet at http://www-dep.iarc.fr/accis.htm includes a list of registries and the periods included in the ACCIS database and the main results of incidence and survival analyses.

Descriptive studies of cancer in childhood

D.M. Parkin, E. Kramárová, N. Mitton, E. Weiderpass; in collaboration with F. Berrino, G. Gatta, Milan, Italy; E. Chokunonga, Harare, Zimbabwe; J.W.W. Coebergh, Eindhoven, Netherlands; I. Corraziari, M. Santquillani, Rome, Italy; A. Lee, Los Angeles, CA, USA; C. Magnani, S. Viscomi, G. Pastore, Turin, Italy; I. Magrath, Brussels, Belgium; J.R. Mann, Birmingham, UK; P. Pillon, Marseille, France; I. Plesko, Bratislava, Slovakia; J. Reutfors, A. Ahlbom, Stockholm, Sweden; C.A. Stiller, Oxford, UK; C. Wesseling, P. Monge, Heredia, Costa Rica

The database of childhood thyroid cancer cases in Europe has been updated to cover the period 1980–97 with all cases diagnosed at ages 0–19 years in the participating registries. The association between exposure to radioactive iodine from the Chernobyl accident and the incidence of thyroid cancer is being studied.

Extensive data from the IARC database and published sources have been used to estimate the total number of cases of childhood cancer (age 0–14 years) around the world. Previously applied methods were adapted to estimate the number of cases in the year 2000 and incidence rates for some 20 tumour types for regions of the world.

Patterns of childhood cancer incidence and mortality in the world have been reviewed.

Possible reasons for the low occurrence of brain tumours in Costa Rican children, the country with the highest incidence rates worldwide of childhood leukaemia, have been examined.

One chapter of the IARC monograph *Cancer in Africa* (see Section 1.2) is devoted to epidemiology of childhood cancer in Africa.

Occurrence of childhood cancer in Zimbabwe was analysed in collaboration with the Harare Cancer Registry. Possible reasons for underdiagnosis and under-registration, especially in the remote areas of the country, were examined. The study also included the first population-based survival analysis of childhood cancer patients in Africa.

Coordinated by the EUROCARE study group, IARC contributed to the analysis and interpretation of the survival data of childhood cancer patients in Europe. The resulting special issue of the *European Journal of Cancer* (April 2001) represents a comprehensive overview of population-based survival of almost 45 000 children diagnosed with cancer in Europe between 1978 and 1992. Survival improved over this period, the hazard ratios for the period 1990–92 being only 40–75% of

those for 1978–81, depending on diagnostic group. However, potential for improvement was seen in the eastern European countries, with overall five-year survival of 55%, compared with 75% survival in the Nordic countries.

IARC is collaborating with the International Network for Cancer Treatment and Research (INCTR), as well as with WHO and other national and international organizations, in the establishment of the Global Alliance for Cure of Children with Cancer (GACCC), an initiative focused on improvement of conditions of children with cancer in the developing countries.

Some specific childhood tumours

A.J. Sasco; in collaboration with R.C. Rudigoz, Lyon, France; D. Satgé, Tulle, France

The association between genetic conditions and occurrence of cancer may be particularly pertinent for tumours arising early in life. Following a pioneering study of neuroblastoma in Down syndrome, we are exploring the possibility of assessing the occurrence of selected other tumours in children with Down syndrome, particularly retinoblastoma [417].

The earliest tumours occur *in utero* and neonatally. Although such cancers are exceedingly rare, some benign tumours such as angiomas are frequent. 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 for 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.

1.4 Survival from cancer

Population-based cancer survival estimates of unselected groups of cancer patients permit valid and unbiased comparisons between populations. Though such data cannot be used to assess the efficacy of specific treatments (this 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. There are only limited data available on population-based survival from cancer in developing countries, despite the importance of such information for cancer control.

Survival from cancer in developing countries

R. Sankaranarayanan, D.M. Parkin, E. Bah, R. Sankila; in collaboration with: *Algeria*, M. Hamdi-Cherif, Setif Wilaya; *Austria*, V. Levin, Vienna; *China*, J. Chen, Qidong; Fan Jin, Shanghai; *Costa Rica*, M. Sanchez Roja, R. Herrero, San Jose; *Cuba*, A. Lence, L. Fernandez Garrotte, Havana; *India*, D.D. Patel, D.V. Bala, Ahmedabad; J. Cherian, R. Rajkumar, Ambillikai; K. Jayant, B.M. Nene, A.M. Budukh, Barshi; S. Khanare, R. Dikshit, Bhopal; V. Shanta, C.K. Gajalakshmi, R. Swaminathan, Chennai; P. Gangadharan, K. Jayalakshmi, Karunagapppalli; B.B. Yeole, L. Sunny, Mumbai; *Mali*, S. Bayo, A. Dolo, Bamako; *Pakistan*, Y. Bhurgri, Karachi; *Philippines*, D. Esteban, Manila; H. Lee, K. Chia, W. Du, Singapore; *Thailand*, V. Lornvidhaya, S. Srisukho, Chiang Mai; S. Sriamporn, S. Wiangnon, Khon Kaen; *Uganda*, H. Wabinga, S. Nambooze, Kampala; *UK*, R.J. Black, Edinburgh; *Zimbabwe*, L. Levy, M. Bassett, B. Mauchaza, E. Chokunonga, Harare

The first comparable cancer survival data for 1982–91 from 10 registries in developing countries were published by IARC in 1998. Subsequent work has addressed stage-specific survival, prognostic facors, methods to improve follow-up (particularly in sub-Saharan Africa), issues in analysis, interpretation, comparability of data and factors responsible for observed variations in survival. Work is in progress in population-based cancer registries in Algeria, China, Colombia, Costa Rica, Cuba, India, Philippines, Singapore, Thailand and Viet Nam, using a mixture of both passive and a variety of active methods to collect information on vital status. A study of population-based survival in two countries in West Africa (Gambia and Mali) and two in East Africa (Uganda and Zimbabwe) has been initiated with support from the Association for International Cancer Research (United Kingdom) and Association pour la Recherche sur le Cancer, (France). The prognostic importance of concomitant HIV infection is being addressed in Uganda and Zimbabwe. In collaboration with the International Atomic Energy Agency, the relationship between radiotherapy for cervical cancer and survival is being investigated in Uganda and Zimbabwe.

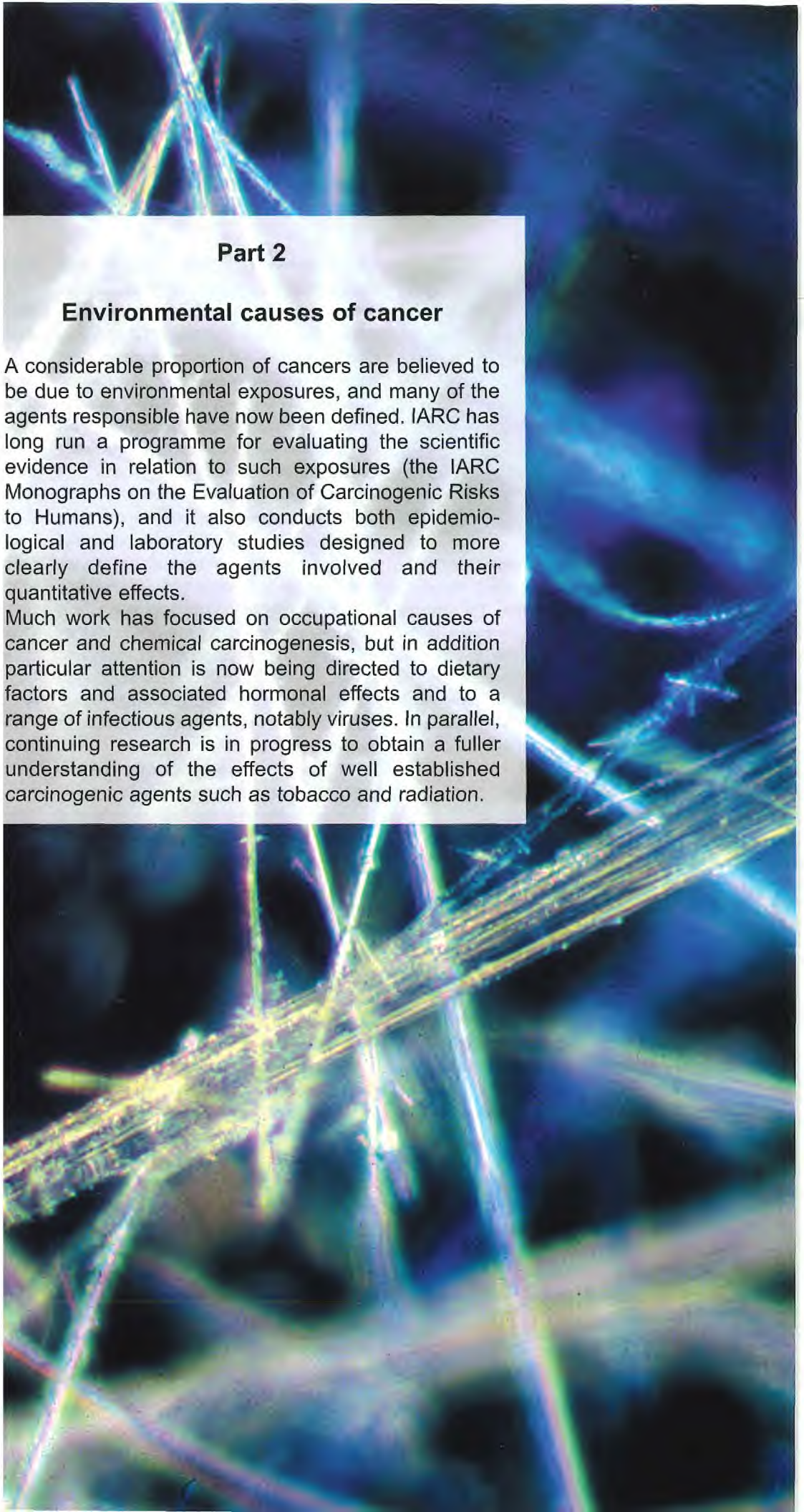
Survival data from Singapore for a 24-year period (1968–92) have been analysed [91]. The analysis involved 84 252 patients, of whom 4949 (5.8%) were lost to follow-up. The age-standardized five-

Table 1. Age-standardized five-year relative survival rates for selected cancers by sex, Singapore, 1968–92

Site	Men	Women
Nasopharynx	47	56
Oesophagus	4	8
Stomach	21	23
Colon	50	52
Rectum	44	49
Liver	3	2
Pancreas	5	8
Lung	6	7
Breast		71
Cervix		65
Ovary		62
Testis	85	
Prostate	57	
Non-Hodgkin lymphoma	36	38
Hodgkin disease	49	67
Leukaemia	14	20

year relative survival rates for selected cancer sites are given in Table 1. The overall five-year survival has increased significantly for cancer sites such as nasopharynx, stomach, colon, rectum, breast, cervix, ovary, testis and non-Hodgkin lymphoma. On average, the survival rates in Singapore are 10–15 years behind the United States SEER rates and 5–10 years behind Finland, Japan and Switzerland, but close to the rates in the United Kingdom. More in-depth analyses of survival for individual sites have been completed.

Survival data from the Mumbai cancer registry, India, have also been analysed and the results for head and neck and colorectal cancer published [541, 542].



Part 2

Environmental causes of cancer

A considerable proportion of cancers are believed to be due to environmental exposures, and many of the agents responsible have now been defined. IARC has long run a programme for evaluating the scientific evidence in relation to such exposures (the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans), and it also conducts both epidemiological and laboratory studies designed to more clearly define the agents involved and their quantitative effects.

Much work has focused on occupational causes of cancer and chemical carcinogenesis, but in addition particular attention is now being directed to dietary factors and associated hormonal effects and to a range of infectious agents, notably viruses. In parallel, continuing research is in progress to obtain a fuller understanding of the effects of well established carcinogenic agents such as tobacco and radiation.

2.1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

The *IARC Monographs* are an international consensus approach to carcinogenic hazard identification. Lists of evaluations and summaries of individual evaluations are available in searchable format through the World Wide Web, from the IARC home page at http://www.iarc.fr and at http://monographs.iarc.fr. Five working group meetings were convened during 2000–2001.

J.M. Rice, R. Baan, M. Bird, Y. Grosse, D. McGregor, N. Mironov, N. Napalkov, C. Partensky, L. Stayner, K. Straif, E. Suonio, J.D. Wilbourn. The following members of other units have contributed to the programme: P. Boffetta, P. Brennan, P. Buffler, E. Cardis, R. Corvi, S. Franceschi, M. Friesen, R. Gallagher, J. Hall-Posner, J. Hung, A. Kesminiene, V. Krutovskikh, W. Lee, C. Malaveille, M. Pearce, M. Plummer, D. Richardson, B.W. Stewart

Some industrial chemicals

(Volume 77) (15–22 February 2000)

A working group of 28 experts from 12 countries met in Lyon to evaluate or re-evaluate the evidence for carcinogenicity of sixteen industrial organic chemicals. These included some aromatic amines (*ortho*-toluidine, 4-chloro-*ortho*-toluidine and 5-chloro-*ortho*-toluidine), ethanolamines (di- and triethanolamine and *N*-nitrosodiethanolamine) and esters (di(2-ethylhexyl) phthalate (DEHP), di(2-ethylhexyl) adipate and cinnamyl anthranilate).

For *ortho*-toluidine, evidence for risk of cancer in exposed humans had increased since the previous evaluation, and this compound was upgraded to *probably carcinogenic to humans* (Group 2A). 4-Chloro-*ortho*-toluidine remained in Group 2A as before. Glycidol was evaluated for the first time and classified in Group 2A on the basis of sufficient evidence for carcinogenicity in experimental animals, supplemented by other relevant data concerning its mode of carcinogenic action.

2,2-Bis(bromomethyl)propane-1,3-diol, 2,3-dibromopropan-1-ol, ethylbenzene and nitromethane were evaluated for the first time and all classified as *possibly carcinogenic to humans* (Group 2B) on the basis of sufficient evidence for carcinogenicity in experimental animals.

5-Chloro-*ortho*-toluidine, coumarin, pyridine, diethanolamine, triethanolamine, di(2-ethylhexyl) adipate and cinnamyl anthranilate were considered *not classifiable as to carcinogenicity to humans* (Group 3). *N*-Nitrosodiethanolamine, which is readily formed from either di- or triethanolamine in the presence of inorganic nitrite, is carcinogenic in experimental animals and remained classified in Group 2B in the absence of evidence for human cancer.

DEHP belongs to a structurally diverse group of compounds that induce peroxisome proliferation in the liver in mice and rats, but not in other rodent and non-rodent species that have been tested and not in human liver tissue. DEHP causes tumours of the liver in mice and rats, but at no other site, and had previously been classified as *possibly carcinogenic to humans* (Group 2B). In the light of a large body of other relevant data, including evidence from genetically engineered mice, DEHP was deemed to meet criteria previously established for evaluation of such substances and was downgraded from Group 2B to Group 3, *not classifiable as to carcinogenicity to humans.* DEHP produces liver tumours in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation. Peroxisome proliferation and hepatocellular proliferation have been demonstrated under the conditions of the carcinogenicity studies of DEHP in mice and rats, but peroxisome proliferation has not been documented in human hepatocyte cultures exposed to DEHP nor in the livers of exposed non-human primates.

Ionizing radiation, part 2: Some internally deposited radionuclides

(Volume 78) (14–21 June 2000)

A working group of 23 experts from eight countries met in Lyon to evaluate the evidence for carcinogenicity of ionizing radiation from internally deposited radionuclides. The term 'internally deposited radionuclides' refers to those in dispersed forms (e.g., dusts, suspensions, solutions or gases) that enter the body by inhalation, ingestion, some form of injection, or, in some cases, percutaneous absorption, and undergo radioactive decay by emission of either α or β particles.

Radon and its decay products were previously evaluated in Volume 43 of the *IARC Monographs* (1988) as *carcinogenic to humans* (Group 1). Subsequently published scientific literature on occupational and residential exposures to radon was reviewed in this volume.

Six specific radionuclides (radium-224, radium-226, radium-228, thorium-232 (administered in colloidal form as thorium-232 dioxide), plutonium-239 (exposure to which also entails exposure to plutonium-240 and other isotopes of plutonium), and phosphorus-32) plus mixed radionuclides of iodine including iodine-131, were evaluated as *carcinogenic to humans* (Group 1) on the basis of sufficient evidence for increased risk of cancer in exposed individuals. Evidence for increased cancer risk in exposed humans is related to medical usage in the cases of radium-224, thorium-232 and phosphorus-32, and accidental, occupational and/or environmental exposures in the cases of plutonium-239, radium-226, radium-228 and the radioiodines.

In addition, the following global evaluations of two broad categories of internally deposited radionuclides were made on the basis of carcinogenicity in experimental animals plus other relevant data: internally deposited radionuclides that emit α particles, and internally deposited radionuclides that emit β particles are *carcinogenic to humans* (Group 1).

Some thyrotropic chemicals

(Volume 79) (10–17 October 2000)

A working group of 22 experts from eight countries met in Lyon to evaluate or re-evaluate the carcinogenicity to humans of 19 chemicals that are carcinogenic to the thyroid follicular-cell epithelium in rodents. This series of evaluations specifically included agents for which mechanisms of carcinogenesis may operate in rodents that do not operate in humans, at least under conditions of realistic human exposure. These included some so-called 'anti-thyroid' drugs (methimazole, methylthiouracil, propylthiouracil and thiouracil); some sedatives (doxylamine succinate and phenobarbital) and some other drugs including the systemic antifungal antibiotic griseofulvin, the diuretic spironolactone and the antibacterial sulfa drugs sulfamethazine and sulfamethoxazole. Other chemicals are or have been used in agriculture as pesticides (amitrole, chlordane/heptachlor, hexachlorobenzene and toxaphene), in foods and cosmetics (kojic acid), in hair dyes (2,4-diaminoanisole) or as industrial chemicals (*N,N'*-diethylthiourea, ethylenethiourea and thiourea). From available epidemiological studies, there was no indication of excess thyroid cancer risk in humans exposed to any of these agents.

For amitrole, ethylenethiourea and sulfamethazine, all with *sufficient evidence* of carcinogenicity in experimental animals, mechanistic data played an important role in making the overall evaluations. All were placed in Group 3 (*not classifiable as to carcinogenicity to humans*).

Chlordane/heptachlor, griseofulvin, hexachlorobenzene, methylthiouracil, phenobarbital, propylthiouracil, thiouracil and toxaphene were evaluated as *possibly carcinogenic to humans* (Group 2B) on the basis of *sufficient* evidence for carcinogenicity to experimental animals. 2,4-Diaminoanisole was classified as *possibly carcinogenic to humans* (Group 2B) on the basis of *sufficient evidence* of carcinogenicity in animals at multiple organ sites including thyroid, together with evidence that the compound acts by a genotoxic (DNA-reactive) mechanism. Several agents *could not be classified as to their carcinogenicity to humans* (Group 3) since the evidence of carcinogenicity in experimental animals was judged to be *limited* (*N,N'*-diethylthiourea, doxylamine succinate, kojic acid, methimazole, spironolactone, sulfamethoxazole and thiourea).

For methylthiouracil, propylthiouracil and thiouracil, there was *sufficient* evidence of carcinogenicity in experimental animals based on the production of thyroid follicular-cell tumours in mice, rats or hamsters as well as liver and/or pituitary tumours in mice. However, because the data on genotoxicity were inadequate, no consideration could be given to a possible downgrading based on mechanistic information. These agents were thus classified by default as *possibly carcinogenic to humans* (Group 2B).

Static and extremely low-frequency electric and magnetic fields

(Volume 80) (18–26 June 2001)

A working group of 21 scientific experts from 10 countries met in Lyon to evaluate possible carcinogenic hazards to human beings from exposures to static and extremely low-frequency (ELF) electric and magnetic fields. This volume is the first of two planned to deal with various kinds of non-ionizing radiation in the frequency range below that of visible light. ELF magnetic field exposures result from proximity to electric power transmission lines, household wiring and electric appliances and are in addition to the exposure due to the earth's magnetic field.

Pooled analyses of data from a number of well conducted studies show a fairly consistent statistical association between childhood leukaemia and power-frequency residential magnetic field strengths above 0.4 microtesla, with an approximately two-fold increase in risk. This association between childhood leukaemia and high residential magnetic field strengths was judged *limited evidence* for excess cancer risk in exposed humans. There is no consistent evidence that residential or occupational exposures of adults are related to excess risks of cancer at any site. Evidence for elevated risks for cancer of all other kinds, in children and in adults, as a result of exposure to ELF electric and magnetic fields was considered *inadequate*.

Numerous studies to investigate carcinogenicity of magnetic fields have been conducted in experimental animals, generally with negative or inconsistent results. Overall, evidence for carcinogenicity of ELF magnetic fields in experimental animals was judged *inadequate*. No data on carcinogenicity to animals of static magnetic fields, or of static or ELF electric fields, were available to the working group.

Many hypotheses have been put forward to explain possible carcinogenic effects of ELF electric or magnetic fields, but no scientific explanation for carcinogenicity of these fields has been established.

Overall, extremely low frequency magnetic fields were evaluated as *possibly carcinogenic to humans* (Group 2B), on the basis of the statistical association of higher level residential ELF magnetic fields with increased risk for childhood leukaemia. Static magnetic fields and static and extremely low frequency electric fields *could not be classified as to their carcinogenicity to humans* (Group 3).

Man-made vitreous fibres

(Volume 81) (9–16 October 2001)

A working group of 19 scientific experts from 11 countries met in Lyon to re-evaluate the carcinogenic hazards of airborne man-made vitreous fibres. Man-made vitreous fibres in the form of wools are widely used in thermal and acoustic insulation and in other manufactured products in Europe and North America. These products, including glass wool, rock (stone) wool and slag wool, have been in use for

decades and have been extensively studied to establish whether fibres that are released during manufacture, use or removal of these products present a risk of cancer when inhaled. More recently, much effort has gone into development of newer materials that have similar insulation properties to the older products, but which disappear from body tissues much more rapidly. The reason for this is that the high biopersistence of asbestos is known to be correlated with the strong carcinogenic potency of asbestos fibres.

Several large epidemiological studies of occupational exposures during manufacture of the older insulation wool materials have been completed since the previous IARC Monographs review of these materials in 1988. These studies provide no evidence of increased risks of lung cancer or mesothelioma (cancer of the lining of the body cavities) and inadequate evidence overall of any cancer risk. However, some populations of workers, such as individuals involved in demolition or removal of these materials from building sites, may experience higher levels of exposure to these fibres than manufacturing workers. As these workers were not included in the available epidemiological studies, the results could not be considered to provide evidence suggesting lack of carcinogenicity to humans.

The working group concluded that only the more biopersistent materials should remain classified as possible human carcinogens (Group 2B). These include refractory ceramic fibres, used industrially as insulation in high-temperature environments such as blast furnaces, and certain special-purpose glass wools that are not used as insulating materials. In contrast, the more commonly used vitreous fibre wools including insulation glass wool, rock (stone) wool and slag wool are now considered *not classifiable as to carcinogenicity to humans* (Group 3). Continuous glass filaments, which are used principally to reinforce plastics, were evaluated as *not classifiable as to carcinogenicity to humans*.

Some of the newer materials have now been tested for carcinogenicity in experimental animals, either by inhalation or by intraperitoneal injection. Many have been found to be non-carcinogenic, or to cause tumours in experimental animals only under very restricted conditions of exposure such as intraperitoneal injection of large numbers of fibres. The working group chose not to make an overall evaluation of the newly developed materials, mainly because no human data were available and it is not possible to characterize these materials as a class by composition.

2.2 Occupational 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. Also, 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 are conducted, mainly in industrialized countries, to investigate effects of either low-level exposure to known or suspected carcinogens with relatively weak potency; on the other hand, collaborative studies are 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. These studies in developing countries are based on the case–control approach, and are listed by cancer site.

Workers employed in man-made vitreous fibre production

P. Boffetta, G. Ferro; in collaboration with A. Andersen, K. Kjaerheim, Oslo, Norway; J. Chang-Claude, Heidelberg, Germany; J. Cherrie, Edinburgh, UK; K. Guldner, Würzburg, Germany; J. Olsen, J. Hansen, Copenhagen, Denmark; N. Plato, Stockholm, Sweden; F.D. Pooley, Cardiff, UK; R. Saracci, Pisa, Italy; P. Westerholm, Solna, Sweden

Occupational exposure to man-made vitreous fibres may entail a risk of lung cancer (Boffetta, 1998, in: *Current Asbestos Issues,* Lexis Publishing, Charlottesville, VA, pp. 191–218). A historical cohort study has been conducted since 1977 in 13 factories producing man-made vitreous fibres in seven European countries. A mortality follow-up to 1991 shows an increased risk of lung cancer in the rock/slagwool component of the study, which was related to technological phase, time since first employment and duration of employment. No such increase was associated with glass wool and continuous filament production.

A case–control study of lung cancer in the cohort exposed to rock/slagwool included 133 cases and 513 controls. Compared with subjects classified in the lowest quartile of cumulative fibre exposure, the odds ratios for lung cancer (with a 15-year lag) were 1.25 (95% confidence interval [CI] 0.66–2.34), 1.02 (0.54–1.93) and 0.67 (0.35–1.27) in the second to fourth quartiles of exposure. Other indicators of fibre exposure also suggested no association with lung cancer risk (Boffetta *et al.*, 2000, IARC Internal Report No. 00/004). A parallel study on lung fibre burden in cases of lung cancer is in progress.

Workers employed in the pulp and paper industry

P. Boffetta, W. Lee, D. Colin; in collaboration with A. Andersen, Oslo, Norway; A. Bergeret, Lyon, France; D. Coggon; Southampton, UK; L.A. Facchini, Pelotas, Brazil; P.K. Henneberger, Morgantown, WV, USA; P. Jäppinen, Imatra, Finland; T. Kauppinen, T. Liukkunen, Helsinki, Finland; D. Kielkowski, Johannesburg, South Africa; R. Kishi, Sapporo, Japan; E. Lynge, Copenhagen, Denmark; N. Pearce, Wellington, New Zealand; B. Persson, Linköping, Sweden; L. Settimi, Rome, Italy; J. Sunyer, M. Kogevinas, Barcelona, Spain; I. Szadkowska-Stanczyk, Lodz, Poland;

K. Teschke, A. Keefe, G. Astrakaniakis, Vancouver, Canada; H. Westberg, Örebro, Sweden

In view of a possible increased risk of cancer at certain sites (lung, gastrointestinal tract, lymphatic tissues) among workers in the pulp and paper industry —an activity employing hundreds of thousands of workers worldwide—a multicentric international cohort study is being conducted. Personnel employed in plants producing pulp, paper and paper products, and in mills involved in recycling, are included. The cohort 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. Results for the combined study population, according to department of employment, 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. An industrial hygiene study has produced time-, mill- and department-specific estimates of exposure to 27 chemicals and groups of chemicals. An analysis of exposure to sulfur dioxide (SO_2) suggested an increased risk among exposed workers (relative risk [RR] = 1.41; 95% CI 1.03–1.93) and a dose–response relationship between cumulative estimated exposure and lung cancer risk (Figure 9). Similar analyses of exposure to asbestos and other agents are under way.

Workers employed in the asphalt industry

P. Boffetta, I. Burstyn, G. Ferro; in collaboration with W. Ahrens, R. Frentzel-Beyme, Bremen, Germany; D. Heederik, H. Kromhout, Utrecht, Netherlands; B. Jarvholm, Umeå, Sweden; T. Kauppinen, P. Heikkilä, Helsinki, Finland; T. Partanen, San José, Costa Rica; S. Langard, B. Randem, Oslo, Norway; J. Shaham, Raanana, Israel; I. Stücker, Paris, France; 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). Previous epidemiological studies have suggested an increased risk of cancer of the lung and other organs, but are not adequate to disentangle the contribution of asphalt fumes from that of other agents.

A historical cohort study was initiated in 1996 in seven European countries (Denmark, Finland, France, Germany, Netherlands, Norway, Sweden) and in Israel. A detailed exposure assessment was conducted based on an extensive collection of published and unpublished data on occupational exposure of asphalt workers and on company questionnaires, which resulted in job-based estimates of exposure to bitumen fumes and other agents present in the working environment [76–78].

The results suggest a healthy-worker effect (standardized mortality ratio [SMR] for all causes = 0.92; 95% CI 0.91–0.94). Workers exposed to bitumen have increased mortality from lung cancer (SMR = 1.14; 95% CI 1.01–1.28), but no excess risk compared with workers involved in road and building construction in the same companies (RR = 1.01; 95% CI 0.82–1.24). In the analysis of the whole cohort, there was no indication of a dose–response relationship between estimated exposure to bitumen fume and the risk of any neoplasm. However, in an analysis restricted to road pavers, for whom the assessment of exposure was based on better information, a trend in lung cancer risk was suggested with increasing estimated average exposure, but not cumulative exposure, to bitumen fume (Figure 10). A nested case–control study is being planned to distinguish between the possible carcinogenic roles of bitumen fume, other occupational exposures and lifestyle factors, chiefly tobacco smoking.

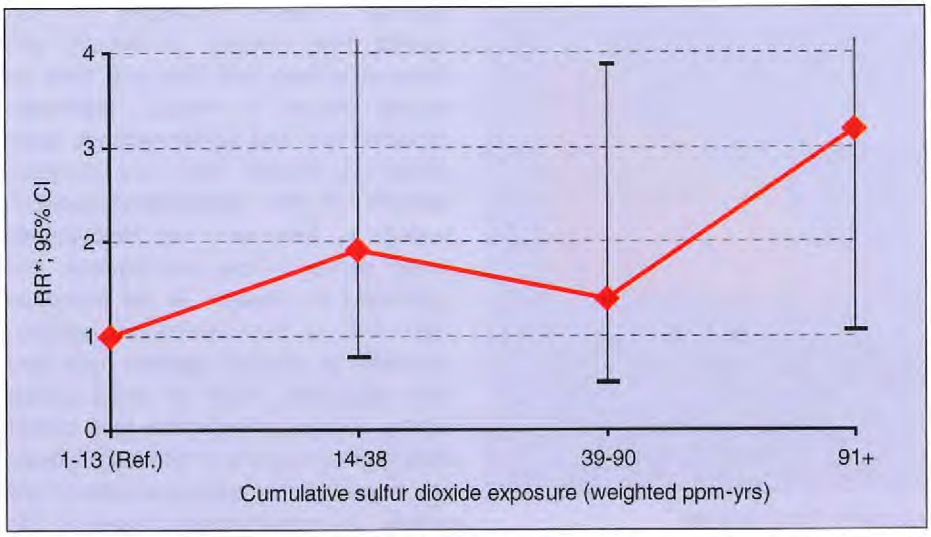


Figure 9. Relative risk of lung cancer among pulp and paper workers by cumulative exposure to sulfur dioxide

* Relative risk adjusted for country, year, age, duration of employment and exposure to other carcinogens

Workers exposed to vinyl chloride

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

A cohort study of cancer mortality and incidence among workers exposed to vinyl chloride in its production and polymerization was coordinated by IARC and conducted in Italy, Norway, Sweden and the United Kingdom during the 1980s (Simonato *et al.*, 1991, *Scand. J. Work Environ. Health*, **17**, 159–169). This revealed an increased risk of liver angiosarcoma, but the statistical power to evaluate the risk of other neoplasms

possibly linked to vinyl chloride, such as hepatocellular carcinoma and brain tumour, was limited. Data from a further 12 years of follow-up of this cohort have now been analysed. A total of 53 deaths from primary liver cancer (SMR = 2.40; 95% CI 1.80–3.14) and 18 incident liver cancers were identified, including 37 angiosarcomas, 10 hepatocellular carcinomas and 24 liver cancers of other or unknown histology. A significant exposure–response relationship was observed between estimated exposure to vinyl chloride and all liver cancers, angiosarcoma of the liver and hepatocellular carcinoma (Figure 11). The exposure–response trend estimated for liver cancer in analyses restricted to cohort members with cumulative exposures above 1500 ppm (equivalent to over 50 ppm exposure for 30 years) was identical to that for the full cohort (an increase in the log relative risk of approximately 0.7 per unit of log cumulative dose). No strong relationship was observed between cumulative vinyl chloride exposure and other cancers; elevated mortality from cirrhosis was observed at high doses [516].

Workers employed in titanium dioxide manufacture

P. Boffetta, E. Weiderpass, V. Gaborieau; in collaboration with H.-O. Adami, Stockholm, Sweden; A. Andersen, Oslo, Norway; M. Blettner, Bielefeld, Germany; J. Cherrie, B. Miller, A. Soutar, Edinburgh, UK; D. Luce, Paris, France; F. Merletti, Turin, Italy; E. Pukkala, Helsinki, Finland

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 study has been conducted. A historical cohort study of workers exposed to titanium dioxide was started in 1999 in Finland, France, Germany, Italy, Norway and the United Kingdom, including approximately 13 000 workers. Exposure to titanium dioxide and other agents present in the working environment is estimated based on past measurements and modelling. Results on mortality and cancer incidence will be available in 2002.

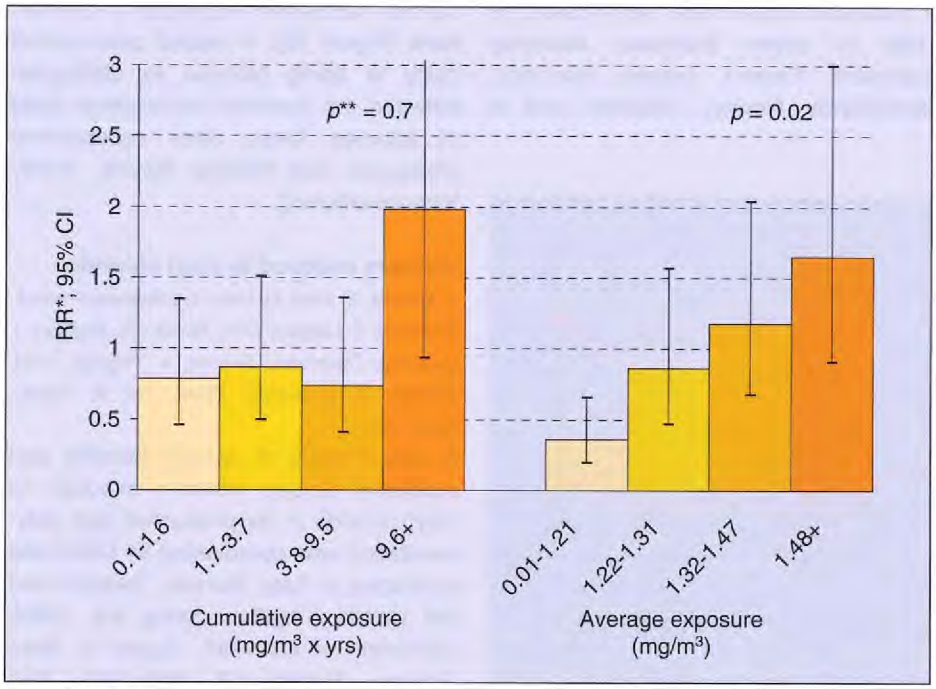


Figure 10. Relative risk of lung cancer by quantitative exposure to bitumen fume (15-year lag)

* Relative risk adjusted for country, year, age and duration of employment

** *p*-value of test for linear trend

Biology research laboratory workers

A.J. Sasco; in collaboration with A. Andersen, Oslo, Norway; S. Belli, Rome, Italy; S. Benhamou, A. Laplanche, Villejuif, France; F. Berrino, Milan, Italy; C. Chilvers, T. Brown, Nottingham, UK; T. Kauppinen, Helsinki, Finland; B. Herity, L. Daly, Dublin, Ireland; J.J. Moulin, Vandoeuvre-lès-Nancy, France; M. Tirmarche, Paris, France; F. van Leeuwen, T. van Barneveld, Amsterdam, Netherlands; D. Vecchio, Genoa, Italy; H. Wennborg, Stockholm, Sweden; supported by the Europe against Cancer, BioMed programmes of the European Union, the Ligue Nationale contre le Cancer, the Fondation Weisbrem-Benenson (Fondation de France), the Direction Générale de la Santé, France

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 employed for at least one year and one day in public research institutions was performed. This study, conducted in eight European countries (Finland, France, Ireland, Italy, Netherlands, Norway, Sweden and United Kingdom), concerns 45 163 workers contributing 650 706 person-years of observation. Results from national cohorts in Ireland, Italy, Sweden and the United Kingdom have been published. Almost all cohorts exhibit a clear healthy-worker effect, resulting in a deficit in overall as well as all-cancer mortality. Specific excesses, in part varying from country to country and between women and men, are seen for bladder cancer in Ireland, pancreatic cancer in Italy and the Netherlands, brain cancer in Ireland, Italy and Sweden, tumours of the lymphohaematopoietic system in Italy and the Netherlands, breast cancer in Italy and Sweden, and melanoma in Sweden. At the European level and in the intra-cohort analysis, excesses of common cancers have also been described, such as colon cancer among anatomopathologists, lung cancer among those working in molecular biology and breast cancer among women in cell biology. A comprehensive review on this topic has been published [364].

Additional collaborative studies of occupational cancer

P. Boffetta, P. Brennan, A. 't Mannetje, J. Hall, N. Travier, A. Pitard; in collaboration with W. Ahrens, Bremen, Germany; A. Andersen, Oslo, Norway; B. Armstrong, London, UK; A. Blair, G. Gridley, Bethesda, MD, USA; H. Checkoway, Seattle, WA, USA; J. Cherrie, G. Hughson, Edinburgh, UK; D. Coggon, Southampton, UK; M. Eglite, Riga, Latvia; E. Fabianova, Banska Bystrica, Slovakia; L. Fritschi, Melbourne, Australia; M. Garcia-Gomez, Madrid, Spain; H. Gunnarsdottir, Reykjavik, Iceland; J. Hansen, Copenhagen, Denmark; D. Heederik, Wageningen, Netherlands; V. Janout, Olomouc, Czech Republic; D. Mates, Bucharest, Romania; E. Matos, Buenos Aires, Argentina; F. Merletti, Turin, Italy; O. Nyren, Stockholm, Sweden; N. Pearce, Wellington, New Zealand; M. Rahu, Tallinn, Estonia; R. Raskeviciene, Kaunas, Lithuania; P. Rudnai, Budapest, Hungary; J. Shaham, Raanana, Israel; P. Srivatanakul, Bangkok, Thailand; L. Stayner, K. Steenland, Cincinnati, OH, USA; I. Stücker, Paris, France; N. Szeszenia-Dabrowska, Lodz, Poland; D. Zaridze, Moscow, Russian Federation

A pooled historical cohort study was initiated in 1998 of workers exposed to crystalline silica. A total of 10 cohorts have been included from different countries. The purposes of the pooled analysis are (i) to develop exposure–response data for lung cancer across a number of studies and (ii) to increase the power to detect rarer outcomes such as lymphoma and kidney disease. A common metric of exposure has been developed across studies. A linear increase in lung cancer risk with estimated cumulative exposure to crystalline silica was observed [454]; analyses of the risks of dying from other neoplasms and from silicosis are now in progress.

Exposure to diesel engine exhaust is probably carcinogenic to the lung and the bladder [45]. A study has been conducted to assess the feasibility of a historical investigation among workers exposed to diesel exhaust and employed in railway and road transport and in non-metal mining in the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, the Russian Federation and Slovakia. Companies where a full-scale study is feasible (based on quality of employment records and exposure information) have been identified. The protocol for the full-scale study is being developed and funding is being sought.

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 [38]. Previous studies, often with limited power, have considered exposure to polycyclic aromatic hydrocarbons and nitrosamines. The feasibility is being assessed of a historical cohort study of workers in the meat industry in Australia, Denmark, France, Germany, Iceland, Italy, Netherlands, New Zealand, Norway, Spain and the United Kingdom, that will additionally consider the roles of animal viruses and organic dusts. Such a study will also include a cross-sectional component to measure the prevalence of various animal viruses among meat workers. If the study proves to be feasible, a common protocol will be developed.

In Sweden, a linkage has been established between information on occupation obtained from the census and on cancer occurrence obtained from the cancer registry. This makes possible the investigation of risk of cancer among all workers employed in a given occupation at the time of the census. Analyses have been performed on workers employed in the meat industry [38], and among workers exposed to diesel exhaust [45]. Similar analyses are being conducted on workers employed as dry cleaners. In addition, it is possible to assess the risk of a specific neoplasm across various occupations: this approach is being used to study risk factors for laryngeal cancer.

A case–control study of lung cancer and occupational exposures was conducted in Buenos Aires, Argentina, in which elevated odds ratios were observed for employment in the alcoholic beverages industry, sawmills and woodmills, water transport, and chemicals/plastics manufacturing, and also for exposure to arsenic and chromium [278]. A meta-analysis of occupational risk factors for pancreatic cancer identified exposure to chlorinated solvents as a candidate for further investigation [324]. Applying an empirical Bayesian approach to study a large database on occupational cancer in the Nordic countries, we concluded that chance might account for a sizeable proportion of positive findings in studies involving multiple comparisons, even when the number of observations is large [453].

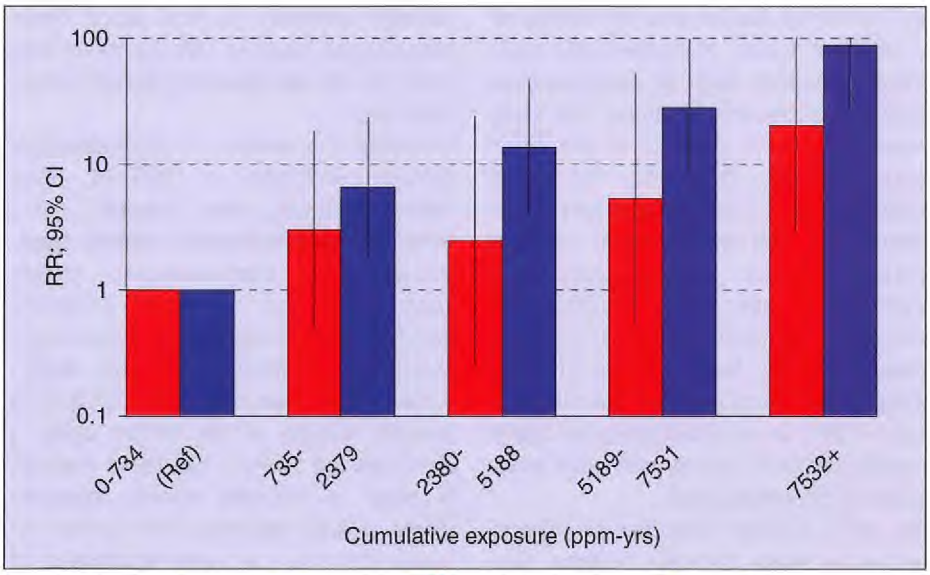


Figure 11. Relative risk of hepatocellular carcinoma ( ) and liver angiosarcoma ( ) by cumulative exposure to vinyl chloride. From Ward *et al.* [516]

Concern about a possible increase of cancer among residents of a city near to a large industrial complex in Rayong province, Thailand, has prompted an investigation on biomarkers of exposure and early biological effects following occupational and environmental exposure. During 2001, blood samples were taken from 200 workers and similar groups of neighbouring and control populations. Analyses of DNA adducts, somatic mutations and genetic polymorphism are in progress.

2.3 *Diet, nutrition, endogenous hormones and cancer*

The search for links between diet, nutritional and metabolic factors and cancer etiology is attracting increasing attention from both a scientific and a public health point of view. The public health relevance is obvious, and even a weak biological effect on the process of carcinogenesis exercised by a widely consumed food may have a large effect on the cancer burden at the population level.

The scientific bases for nutritional prevention of cancer, however, remain a subject of much discussion. Agreement reached by various international expert committees is limited to the protective role of diets rich in fruit and vegetables and to increased risks for colorectal cancer associated with high intake of red and/or processed meats, and for stomach cancer associated with high intake of salt and salt-preserved foods. There is also growing recognition of the role of obesity and lack of physical activity in increasing the risk of certain cancers (see Section 5.2).

Several recent prospective studies have lent strong support to the hypothesis formulated decades ago regarding the prominent role of endogenous hormone levels in determining risk of cancer of the breast. Variations in patterns of estrogens, androgens, insulin-like growth factors (IGFs) and their binding proteins are probably determined by both nutritional and lifestyle factors, as well as by inherited genetic characteristics.

It is thus clear that the relationship between diet and cancer is much more complex than was previously thought. The approach that has been adopted to attempt to clarify this matter is to combine laboratory investigations on human subjects with sound epidemiological projects of a prospective nature.

European Prospective Investigation into Cancer and Nutrition (EPIC)

E. Riboli, R. Kaaks, N. Slimani, C. Casagrande, B. Hémon; in collaboration with: *Denmark*: A. Tjønneland, Copenhagen; K. Overvad, Aarhus; *France*: F. Clavel, M. van Liere, C. Guibout, Villejuif; *Germany:* H. Boeing, A. Kroke, Potsdam; A.B. Miller, J. Wahrendorf, N. Becker, Heidelberg; *Greece:* A. Trichopoulou, K. Katsouyanni, Athens; *Italy:* F. Berrino, V. Krogh, Milan; P. Vineis, B. Terracini, Turin; D. Palli, E. Buiatti, Florence; R. Tumino, L. Gafà, Ragusa; S. Panico, Naples; *Netherlands:* P. Peeters, Utrecht; H.B. Bueno de Mesquita, J. Seidell, Bilthoven; *Norway:* E. Lund, Tromsø; *Spain:* C.A. González, A. Agudo, Mataró; J.R. Quíros, 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, A. Welch, Cambridge; T.J.A. Key, G. Davey, Oxford; R. Saracci, Pisa, Italy (coordinator of the EPIC-HEART component)

The EPIC project is a multi-centre prospective cohort study designed to investigate the relationships between diet, nutritional status, various lifestyle and environmental factors and the incidence of different forms of cancer and other chronic diseases such as cardiovascular diseases, stroke and diabetes. The study includes 521 273 subjects in ten European countries (Figure 12) for whom detailed data on diet, lifestyle and health factors, as well as biological samples (plasma, serum, lymphocytes and erythrocytes), have been collected. The biological samples, collected from an unprecedentedly large number of study subjects, are stored at very low temperature (–196°C in liquid nitrogen), for use in subsequent biochemical, molecular biological and genetic studies.

The study originally included 17 regional centres in seven countries (France, Germany, Greece, Italy, Netherlands, Spain, the United Kingdom). Between 1995 and 2000, the investigators in charge of five similar prospective studies joined EPIC as associated projects: the Malmö Diet and Cancer Study (Malmö) and the Västerbotten County project (based in Umeå) in Sweden; one study in two centres (Copenhagen and Aarhus) in Denmark; the ATENA study in Naples, Italy; and the Norwegian Women and Cancer Study (based on women living on the west coast of Norway and coordinated by a team in Tromsø). The extension of the study to these three Nordic countries and one additional Mediterranean region has further increased the diversity of the populations included and the total study size (Table 2).

As a rule, eligible study subjects were from the general population residing in a given geographical area, a town or a province. There were, however, a few exceptions: the French cohort was based on 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.

Following the results of methodological studies conducted in 1990–92, three dietary methods were adopted, using either a self-administered dietary questionnaire, an interview-based dietary questionnaire or a food frequency questionnaire combined with a seven-day record. In addition, a second dietary measurement was taken from an 8–10% random sample of the cohort using a computerized 24-hour diet recall method, in order to calibrate dietary measurements across countries and correct for systematic over- or under-estimation of dietary intakes. In parallel, we developed statistical methods to correct for bias in

relative risk estimates due to systematic measurement errors in the baseline questionnaire, thereby making the cohort-specific estimates more comparable between study centres (Kaaks *et al.*, 1994, *Am. J. Clin. Nutr.*, **49**, S245–S250; Kaaks & Riboli, 1997, *Int. J. Epidemiol.*, **26**, S15–S25; [206, 376]).

The fieldwork for the recruitment of study subjects, the collection of questionnaire data and anthropometric measurements, and the collection and storage of blood samples, took place from 1993 to 1998 except in Norway, where 37 231 women who had already completed diet and lifestyle questionnaires were invited to donate a blood sample; collection of blood samples was completed in 2001. The total size of the cohort will endow EPIC with unusually high power to study the various cancer risk factors of interest. Over 22 000 cases of cancer are expected to occur in the EPIC cohorts during the first ten 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.

Table 2. Subject recruitment in the EPIC study

	Subjects included with	
	Questionnaire	Blood collection
Spain	41 446	40 040
Italy	53 097	53 077
UK	88 171	43 430
Netherlands	40 110	36 357
France	69 321	24 371
Germany	53 130	50 719
Greece	27 883	28 632
Sweden	53 830	53 830
Denmark	57 054	56 800
Norway	37 231	10 000
TOTAL	521 273	397 256

Figure 12. Collaborating centres and regions covered by the EPIC study

Follow-up to identify cancer cases occurring among the EPIC cohort is based on population cancer registries in six of the participating countries (Denmark, Italy, 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). By the end of 2001, complete follow-up data had been reported to IARC for the period up to 31 December 1998 or December 1999, depending on the centre (a delay of 18–24 months in obtaining complete follow-up data is unavoidable due to the complex procedures used for the collection and verification of clinical and pathological diagnoses). As of October 2001, the total numbers of cancer cases reported with sufficient diagnostic information were 9772 in women and 3761 in men. The most common sites were breast (3878 cases) and colorectum (614) among women and lung (711) and colorectum (415) among men. 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).

Intake of specific nutrients is computed from the food consumption data obtained from dietary questionnaires, by applying food composition tables. A protocol for compiling food composition tables following a standardized procedure has

been prepared with the collaboration of Professor D. Southgate (London, United Kingdom). The subsequent work of compiling a European Nutrient Database is now in progress.

The 24-hour diet recall data collected in the subcohort designed for calibration of the dietary measurements obtained with the food questionnaire provide extremely detailed information on usual diet at the group level. The results of extensive statistical analyses on food consumption patterns have been prepared for publication in a supplement to the journal *Public Health Nutrition* (Figure 13).

We have set up analytical methods for high-performance liquid chromatography (HPLC) measurements of seven carotenoids (lutein, zeaxanthin, canthaxanthin, β-cryptoxanthin, lycopene, α-carotene and β-carotene), tocopherols (α and γ) and retinol, as well as gas chromatographic measurements of 22 fatty acids (from short-chain saturated fatty acids, C:12:0 to long-chain *n*–3 and *n*–6 fatty acids) [86]. These methods have been applied in a descriptive cross-sectional study to provide, for the first time, comparable measurements of these nutritional markers across Europe. We selected a subsample of 3100 subjects from 16 regions, with the aim of covering populations with as wide as possible a dietary range within the EPIC cohorts. Laboratory analyses on carotenoids and tocopherols and fatty acids were completed in 2000. The results indicated large variations in blood levels of some major carotenoids of interest as potential cancer-preventive agents, such as lycopene. Lycopene is mainly provided by tomato and tomato sauce. Several epidemiological studies have reported lower prostate cancer risk in subjects with high lycopene intake (Giovannucci, 1999, *JNCI*, **91**, 317–331).

Studies relevant to the hypothesis that diet and lifestyle affect the development of several cancers, particularly cancer of the breast, prostate, endometrium, ovary and colon, through modification of the endogenous hormonal milieu are described below.

Plans have been made to study genetic predisposition to cancer and possibly gene–environment interactions, by analysing DNA in stored Buffy coat from EPIC blood samples for mutations in genes conferring high cancer risk and genetic polymorphisms with metabolic implications. EPIC is not the most efficient epidemiological study for investigating genes carrying high cancer risk but with very low prevalence (such as the breast-cancer-related genes *BRCA1* and *2* and *ATM),* because, despite its large size, it remains relatively small in terms of potential carriers of rare mutations (no more than 200 *BRCA1* carriers would be expected among 400 000 subjects). However, EPIC is very appropriate for investigating the cancer risk associated with genetic polymorphisms with metabolic implications. In many instances, the stored biological samples can be used for

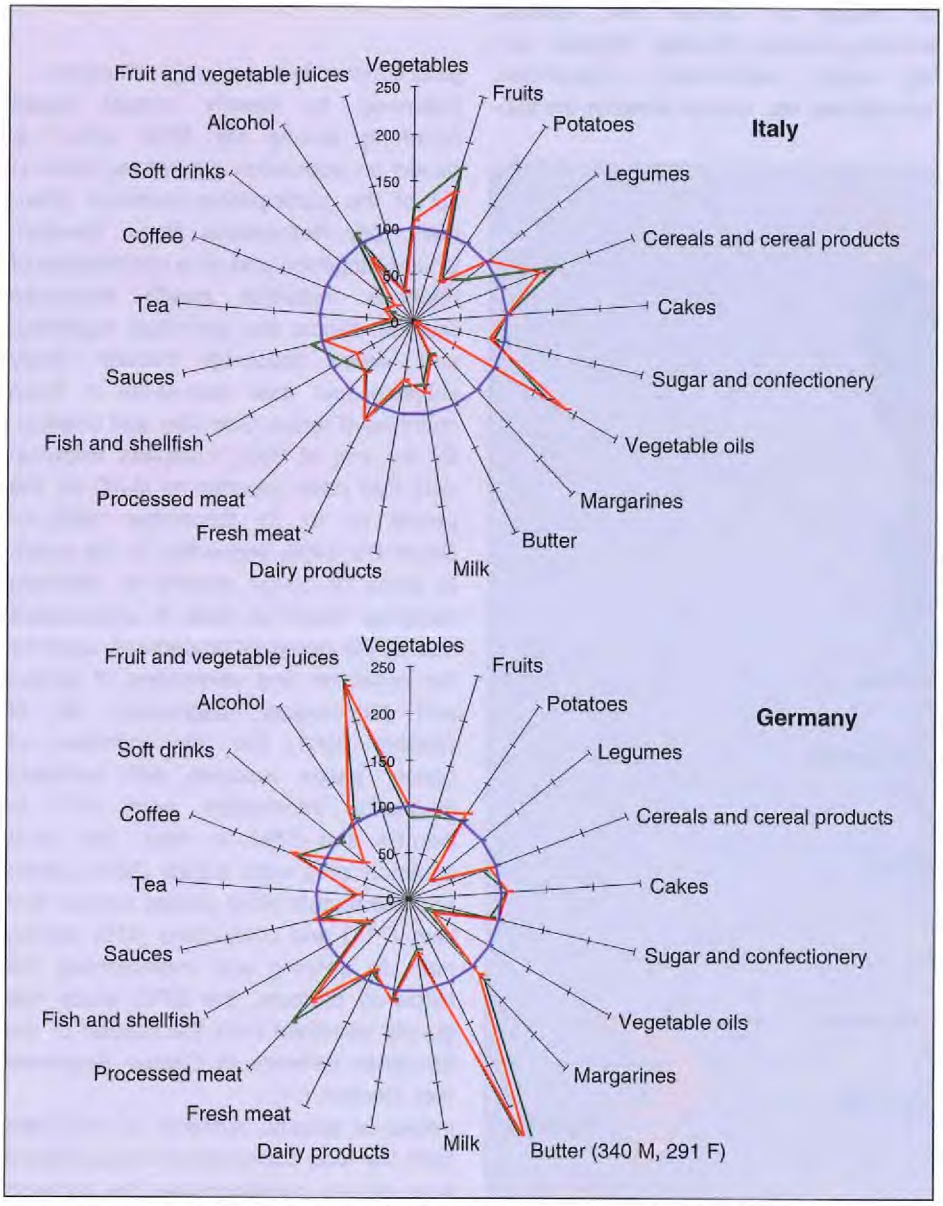


Figure 13. Consumption of different food groups in Italy and Germany among men (green) and women (red), relative to the EPIC sex-specific mean for each country (blue circle, 100%). The Italian pattern is dominated by plant foods, while Germany has much higher consumption of potatoes, animal products and processed and sweetened foods.

measuring substrate and end-products of enzymes encoded by polymorphic genes, and the dietary and lifestyle questionnaire can offer prospective information on environmental exposure. An *ad hoc* working group for these GenEPIC studies has been set up with geneticists at IARC. Collaborations are being set up with external genetic laboratories (Strangeways Research Laboratory, University of Cambridge and the Human Polymorphism Study Centre, Paris) willing to contribute either to the phase of gene sequencing for identification of polymorphisms or to genotyping.

Endogenous hormones and cancer risk

R. Kaaks, S. Rinaldi, A. Lukanova, C. Biessy, D. Achaintre, J. Bouzac, F. Canzian, C. Boillot, A. Llewellyn, E. Riboli; in collaboration with G. Berglund, Malmö, Sweden; F. Berrino, Milan, Italy; H. Dechaud, Lyon, France; G. Hallmans, Umeå, Sweden; P. Peeters, Utrecht, Netherlands; P. Toniolo, New York, USA; and the EPIC collaborators (see above)

Current theories suggest that a western lifestyle, characterized by low physical activity and a diet rich in fats, animal protein and refined carbohydrates, may increase the risk of various types of cancer through alterations in endogenous hormone metabolism. Two sets of hormonal parameters of particular interest are, on the one hand, gonadal sex steroids and sex hormone-binding globulin (SHBG) and, on the other hand, insulin, IGF-I and -II, and IGF-binding proteins (IGFBPs).

The relationships between cancer risk and plasma levels of insulin, IGF-I and IGFBPs, as well as with plasma sex steroids, are being studied in collaboration with several prospective cohort studies. These include the New York University Women's Health Study (New York University, United States), 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 separate cohorts (Risk Factor Monitoring Project and the DOM cohort) at the University of Utrecht, Netherlands. Major results from these studies were a strong increase in risk of colon cancer for subjects with elevated plasma levels of insulin [211] and elevated levels of IGF-I [328], and a significant increase in prostate cancer risk with higher levels of total plasma IGF-I and IGFBP-3 [447]. However, preliminary analyses of data from three studies on breast cancer (in Umeå, Malmö and Utrecht) showed no clear association of risk with circulating IGF-I, IGFBPs or insulin, although IGF-I was positively related to risk in subgroups. Further analyses, pooling the data from the cohorts in New York, Milan (ORDET) and Umeå, have started to examine the relationships of circulating levels of IGF-I, IGFBPs and sex steroids with risks of breast cancer in premenopausal women and of endometrial and ovarian cancer. Preliminary results from the latter studies show an increase in risk of ovarian cancer among premenopausal women who have relatively high plasma IGF-I.

The first follow-up of the EPIC study has now led to the identification of large numbers of incident cases of breast, colorectal and prostate cancer (see above). Studies are being set up to relate the risk of these three types of cancer to endogenous hormone levels, as well as to genetic polymorphisms that may co-determine endogenous hormone levels and metabolism.

One of these studies addresses the possible genetic origins of variation in circulating IGF-I levels, and of risk of breast and prostate cancers, by examining associations with polymorphisms in 15 genes related to the biosynthesis and bioactivation of IGF-I. For each gene, a systematic search for polymorphisms was made using existing public databases, and by denaturing high-performance liquid chromatography (DHPLC) and sequencing (partial or total screening of exons, including 5' and 3' untranslated regions and exon–intron junctions and promoters) of a panel of chromosomes from subjects in Europe, sub-Saharan Africa and Japan. Ninety-seven single nucleotide polymorphisms (SNPs) were described for the first time or confirmed. Seventy-eight polymorphisms were then selected on the basis of their allele frequency in the population in order to study their role as genetic determinants of blood concentrations of IGF-I and as breast or prostate cancer risk factors. A DNA microarray has been set up with the arrayed primer extension approach to perform simultaneous genotyping of all 78 polymorphisms in cases of breast and prostate cancer and controls.

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

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

While there is growing evidence that a diet rich in vegetables and fruits is associated with lower cancer risk, the biological mechanisms behind this association remain a matter of debate. Different types of study have provided contradictory results on the role of different nutrients.

Consumption of fruits and vegetables has consistently been found to be related to reduced risk of cancer of the digestive and respiratory tracts, but results have been inconsistent for breast cancer. Blood concentrations of various carotenoids (natural pigments generally found in plants) have been shown to be related to consumption of fruits and vegetables [507, 508]. The development of more sensitive methods for measurement of several different carotenoids has allowed us to examine the relationship between blood carotenoid levels and specific types of vegetable, to the way that they are cooked and to a number of nutritional and biological factors influencing carotenoid absorption and metabolism. Repeated measures of serum levels of various carotenoids were stable over one- or two-year periods, indicating that carotenoids in blood are not only sensitive but reliable markers of consumption of fruits and vegetables.

A nested case–control study within the cohort of the New York University Women's Health Study observed a two-fold higher incidence of breast cancer among women with low levels of α- and β-carotene and lutein compared with women having higher levels [485]. However, in a similar study in Umeå (northern Sweden), these effects were not confirmed [190]. We are now investigating whether different dietary sources of carotenoids, including the use of carotenoids as natural dyes in various foods, may explain these apparently contradictory results.

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

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

Ecological and migrant studies, as well as animal experiments, have suggested that high-fat diets can increase mammary tumorigenesis, and specifically that *n*–3 polyunsaturated fatty acids (PUFA) and particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish may have anti-carcinogenic effects, 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 have confirmed the protective effect of *n*–3 PUFA (especially EPA and DHA), prospective cohort studies have failed to find this effect.

In a 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 a gas chromatographic method. The results confirm the reduced cancer risk associated with higher levels of stearic acid found in our earlier study in Västerbotten, Sweden. In addition, linoleic acid (18:2 *n*–6) levels are associated with reduced breast cancer risk, whereas oleic acid (18:1 *n*–9c) and arachidonic acid (20:4 *n*–9) are associated with increased risk. It is planned to extend research on fatty acids to examine breast, colorectal and prostate cancer risk within the EPIC cohorts.

The proportion of cancers preventable by dietary changes worldwide

T. Norat-Soto, E. Riboli

As a follow-up to the World Cancer Research Fund (WCRF) report *(Food, Nutrition and the Prevention of Cancer: A Global Perspective*, WCRF, London, 1997), an extensive review of epidemiological studies conducted during the past 30 years on diet and cancer was completed with the aim of conducting a statistical meta-analysis on the association between dietary consumption of vegetables, fruit, meat and salt, and the risk of various cancers. This meta-analysis was designed to provide an overall pooled estimate of the relative risk for various cancers associated with given dietary intakes and to estimate the proportion of cancers attributable to current

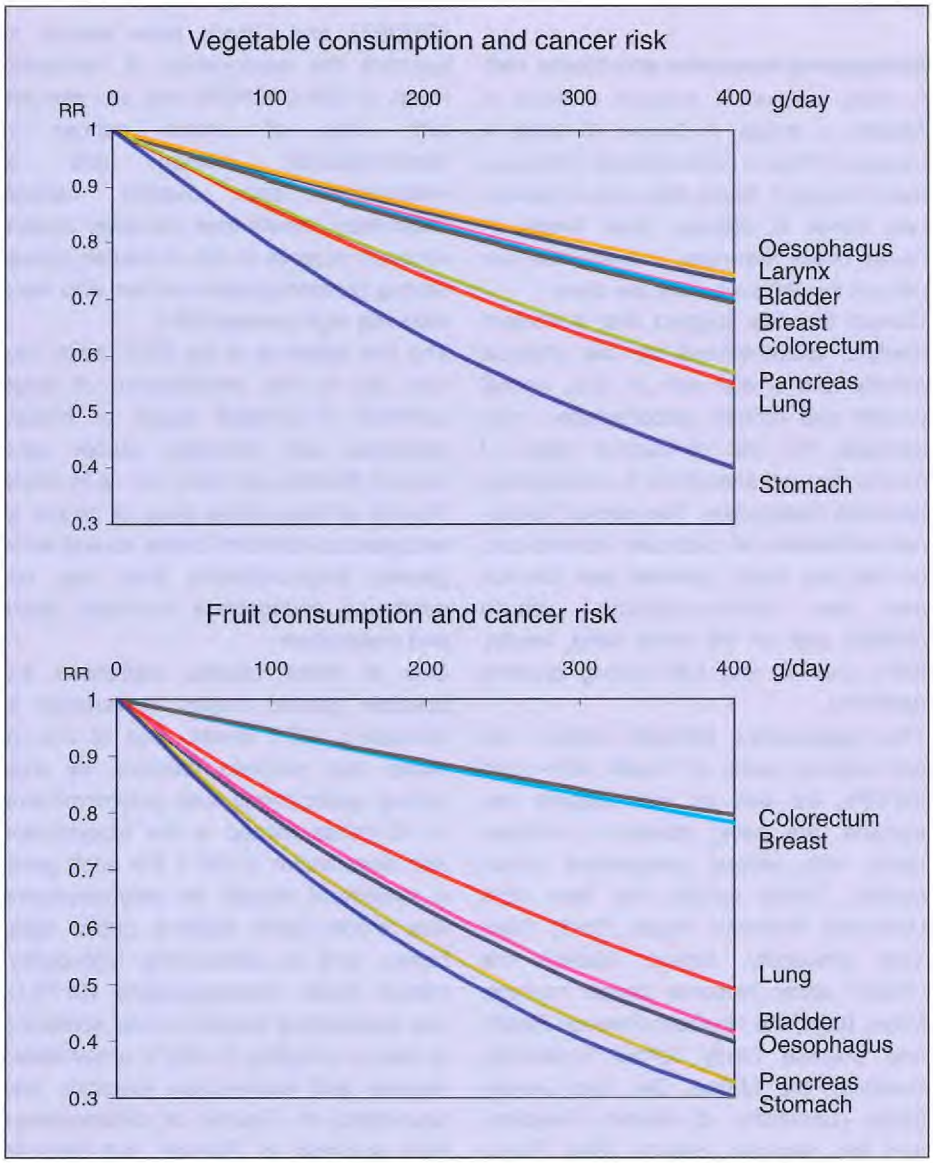


Figure 14. Dose–response relationships between risk of some cancers and consumption of vegetables (above) and fruit (below)

consumption levels and the proportion which could be prevented by hypothetical dietary changes.

For estimation of average food intake, the main difficulty is the absence of dietary surveys conducted with standardized methods in different regions of the world. The only standard data available are those published by the UN Food and Agricultural Organization (FAO) based on economic figures (production plus imports minus exports, animal feed and waste). These data, however, 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.

The results of this quantitative statistical evaluation of the epidemiological evidence agree with the main qualitative conclusions reached by the WCRF report. We found that vegetable consumption is significantly associated with reduced risk of cancers of the oral cavity, pharynx, larynx, oesophagus, stomach, colorectum and lung (Figure 14). These results are consistent for both case–control and cohort studies, although on average the former found a stronger protective effect. Fruit consumption shows very similar associations, but breast cancer is only weakly reduced in relation to fruit and vegetable consumption.

In the study on meats, we confirmed the overall association between red meat consumption (beef, pork and lamb) and colorectal cancer risk, as indicated in the WCRF report. However, when we analysed separately studies where fresh red meat was grouped together with processed meat (e.g., sausages, ham, bacon, *charcuterie*) and studies where fresh red meat was considered separately from processed meat, the risk was higher for the fresh plus processed meat group. We also found that the risk increase was much stronger for processed meat than for any other subcategory of meat (Figure 15) [312, 313]. Further studies are in progress within the EPIC study to analyse in detail the relationship between colorectal cancer risk and specific meat product consumption. No association with total consumption of fresh meat (including poultry) was detected. A strong association was found between gastric cancer and salt intake. Statistical analyses on attributable risk have also been conducted.

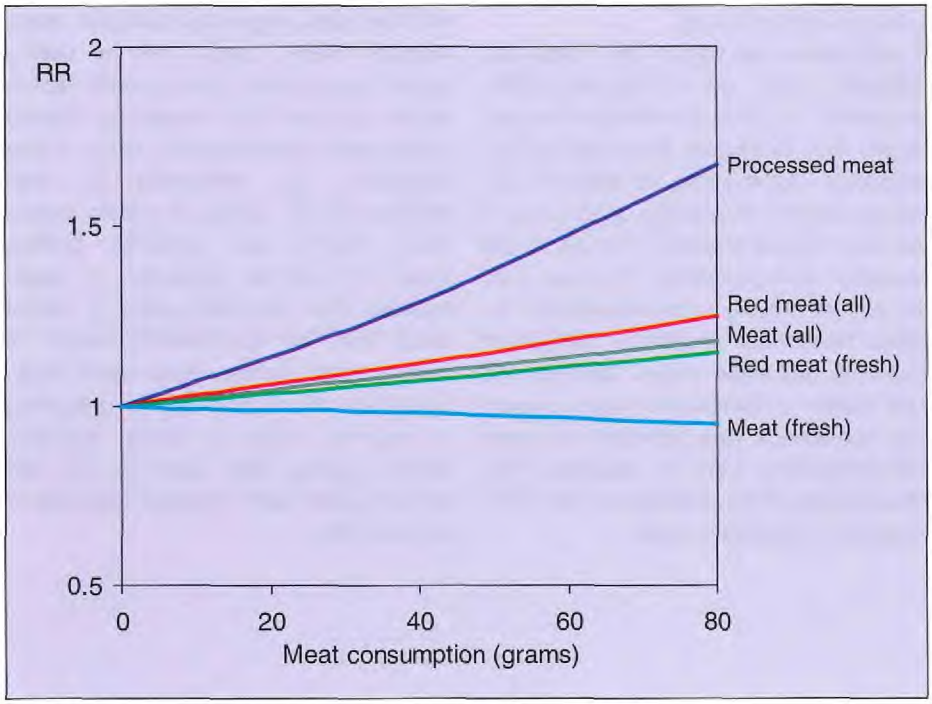


Figure 15. Dose–response relationship between risk of colorectal cancer and meat consumption

Consumption of dairy products and cancer risk

T. Norat-Soto, N. Slimani, P. Ferrari, E. Riboli; in collaboration with P. Bougnoux, V. Chajès, Tours, *France*

The relationship between consumption of dairy products and cancer risk has attracted considerable attention because of opposite and contrasting hypotheses about how milk products, or some of their major components, could either increase or decrease cancer risk. It has been hypothesized that calcium may prevent colorectal cancer, mainly through intraluminal effects, but also that that high calcium intake may increase prostate cancer risk, via down-regulation of vitamin D synthesis mediated through a feedback involving parathyroid hormones.

Fats present 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 not only cardiovascular risk but possibly also cancer risk.

Milk, and particularly aged cheese, contains conjugated linoleic acid (CLA), an isomer of linoleic acid, which is formed by the microflora of the rumen. CLA has been found to prevent mammary carcinogenesis in rodents following treatment with various chemical carcinogens, particularly DMBA.

We have carried out a review of published epidemiological studies for cancers of the breast, colorectum, prostate, kidney, upper aerodigestive tract, stomach, pancreas, bladder and ovary in relation to consumption of milk. For most of the cancer sites considered, this did not reveal that dairy products play a major role in carcinogenesis. The data are generally inconsistent or insufficient to establish whether milk or its derivatives

have a protective or promoting effect on cancers of the breast, mouth and larynx, oesophagus, bladder and ovary. For cancers of the kidney, colon and prostate, the data suggest that an association does exist [441]. The results of published case–control and cohort studies on dairy products and colorectal cancer have been summarized in a meta-analysis. Cohort studies consistently found a protective effect for total dairy products and milk intake, but this finding is not supported by case–control studies. No relationship was found with cheese or yoghurt intake. As the number of cohort studies is limited, these results need to be confirmed by further prospective studies.

In a case–control study on breast cancer, the fatty acid composition of breast adipose tissue has been measured by gas capillary chromatography in samples from breast cancer patients and controls with benign lesions. CLA concentrations were also measured by HPLC–mass spectrometry. Preliminary results indicate no relationship between CLA concentrations and breast cancer risk.

Nutrition, hormones, genetic predisposition and cancer of the prostate

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

The incidence of prostate cancer varies very widely between different populations. It is highest in black Americans, intermediate in white Americans and western Europeans, and lowest in Asians. It is now hypothesized that these differences, as much as 20-fold between the highest and lowest incidence rates, are probably due to a combination of genetic susceptibility and lifestyle factors, including western diet and obesity.

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

We are conducting a case–control study in Havana, Cuba, in which questionnaire data were collected on current diet, lifestyle and reproductive and sexual history. Anthropometric measurements were taken using standardized methods and data on past height and weight were sought. In addition, blood samples and tumour and normal prostate tissue from both cases and controls were collected and stored. The fieldwork has been completed, for a total of 274 cases and 253 controls. Questionnaire data and blood samples have been transferred to IARC. Statistical analyses on diet and lifestyle and laboratory analyses on genetic polymorphisms and biomarkers of diet are in progress.

European Conference on Nutrition and Cancer, Lyon, June 2001

E. Riboli, R. Lambert, R. Alloin

A conference was held at the Palais des Congrès, Lyon, on 21–24 June 2001, sponsored by the Directorate-General, Health and Consumer Protection of the European Commission, to present and discuss current knowledge on the role of diet and related metabolic factors in the causation and prevention of cancer, with the aim of making recommendations for public health and research. Thirty-eight scientists presented invited lectures and 128 poster presentations were shown. The conference was attended by some 390 participants from 31 countries. The proceedings will be published in the IARC Scientific Publications series.

Estrogens and diet during pregnancy and breast cancer risk

E. Weiderpass; in collaboration with H.-O. Adami, Stockholm, Sweden; L. Hilakivi-Clarke, B. Trock, T. Skaar, Washington, DC, USA

During pregnancy, estrogen levels are elevated 50–100-fold and inter-individual variability in estrogen levels is 4–6-fold. Women with the highest estrogen levels in pregnancy are thought to be at increased risk of developing breast cancer, perhaps due to estrogen-induced promotion of existing transformed cells. Diet, particularly dietary fat, may affect estrogen levels in pregnancy and later breast cancer risk. In animal studies, high fat intake significantly increases pregnancy estrogen levels and pregnancy-promoted mammary tumour incidence. Polymorphism in genes that metabolize estrogens and have been linked to increased breast cancer risk may also affect pregnancy estrogen levels.

We have initiated a study (*a*) to determine whether dietary fat intake affects pregnancy estrogen levels in women, possibly by interacting with polymorphism in the CYP17 and catechol *O*-methyltransferase (COMT) enzymes, and (*b*) to examine whether high pregnancy estrogen levels increase breast cancer risk by raising growth factor levels. Such growth factors could originate from mutated or already transformed mammary cells, which during pregnancy are stimulated by high estrogen levels. Levels of growth factors (EGF, TGFα and IGF-I/IGF binding protein 3) will be measured in nipple aspirate fluid obtained using a breast pump from the non-lactating breast 12 months after women have given birth. Enrolment of pregnant women attending a maternity clinic in Solna, Sweden, started during 2001 and so far 124 women have been enrolled, towards a target of 200.

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 cancer and head and neck cancers addressing various aspects of the carcinogenic effect of tobacco smoke are reported in Sections 3.7 and 3.8.

Population studies of tobacco use in Europe

A.J. Sasco, L. Laforest; in collaboration with P. Delormas, Grenoble; G. Freyer, Lyon, France; J. Talmud, Cambo, France; J. Vulliet, Annecy, France

Analyses of studies conducted since 1985 to evaluate risk factors for smoking and other substance-abuse behaviour among young children [415] show that smoking is mostly influenced by peer and family habits and attitudes. Other factors such as the practice of sport also play a role in determining smoking habits [462]. Recent studies among pregnant women in the Rhône-Alpes region of France have provided data that will contribute to public health efforts to discourage risky behaviours by parents [416] and more generally by women who already exhibit a heavy burden of mortality and morbidity [402].

Participation in national and international expert groups has led to the production of reports on passive smoking [114, 413] and on risk reduction for tobacco use.

During 2001, a large study of more than 16 000 subjects to evaluate the association between acne and smoking has been initiated with the French Federation of Dermatology-Venereology.

Anti-smoking strategies

A.J. Sasco, D. d'Harcourt, S. Michard; in collaboration with P. Mélihan-Cheinin, P. Mourouga, Paris, France; R. Roemer, Los Angeles, USA; supported in part by the Europe Against Cancer programme of the European Union

Evaluation of anti-smoking strategies is being carried out at the European, national and local levels. A recently conducted evaluation on the efficacy of a health promotion programme conducted among more than 6000 children aged 10–12 years following a randomized design at the school level and over a three-year period failed to show any substantial results on smoking initiation. In contrast, positive effects are seen among children belonging to non-smoking clubs such as those existing in France. Further analyses are in progress. A large database on smoking and other related behaviours has been set up for subsequent studies.

The EuroLego project involves an exhaustive compilation, review and critical analysis of all legislative texts in the field of tobacco and tobacco control, passed up to 2001, in the 15 Member States of the European Union. These texts deal with 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. Nearly 500 texts have been collected, translated and analysed. Trends over time 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 [411]. The full report is being prepared for publication in book and possibly electronic forms. Recently, the study has been extended to countries not currently members of the European Union [414] for the issue of passive smoking [284] and therefore regulation of smoking in public and workplaces.

Tobacco use in Africa

A.J. Sasco, H. Besson, L. Laforest; in collaboration with M. Bartal, Casablanca, Morocco; F. Ben Ayed, W. Ben Ayoub, Tunis, Tunisia; M. Hamdi-Cherif, Setif, Algeria; H.R. Wabinga, Kampala, Uganda; P. Wangai, Nairobi, Kenya

Tobacco use is at last receding, albeit slowly, in several western countries, at least among men. In contrast, the developing world and in particular Africa, represents an ever-expanding market for cigarettes, including high-tar and unfiltered products. Baseline data on tobacco use among adult and young populations have been collected, using a standardized questionnaire developed at IARC, in the general population of the wilaya of Setif in Algeria, and of Uganda and Kenya [515], as well as among schoolchildren in Guinea, Senegal and Tunisia [127]. For the time being, the tobacco epidemic remains limited essentially to men in Africa, but women seem likely to follow in the near future.

The health consequences of tobacco use are already visible on the African continent, and are bound to increase. An international case-control study of lung cancer is being conducted in three countries of the Maghreb, Algeria, Morocco and Tunisia. Data collection is in progress in Tunisia and Algeria, whereas preliminary results are already available for Morocco. They indicate high risks for active tobacco smoking, along with a slightly elevated risk for passive smoking. Other risk factors of interest include selected occupational exposures and cannabis use. A review of the literature on cannabis and cancer has revealed evidence of the carcinogenicity of smoked cannabis [83]. Plans have been made for a large international multicentric case–control study of lung and upper aerodigestive tract cancers in young

people to evaluate the potential carcinogenic effect of cannabis.

Cohort study of tobacco use and mortality in India

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

Two cohort studies are being conducted in India to address the effects of non-cigarette use of tobacco, that is widely prevalent in developing countries (such as *bidi* smoking and various forms of smokeless tobacco use). In the first phase (1991–94) of the cohort study in Mumbai, initiated in 1991, individuals aged at least 35 years were recruited, and this group of 99 600 was later supplemented by a further 60 000 men aged 45 or more, since it was found that prevalence of tobacco smoking in women was very low (less than 1%). The individuals recruited in the first phase were actively followed up during the period 1997–2000 and 86% were successfully traced, the remainder having emigrated. There were a total of some 546 000 person-years of observation and some 7500 deaths had occurred. Among men, the overall relative risk (RR) for smoking was 1.70 (59 183 person-years). The age-adjusted RRs were 1.39 for cigarette smoking and 1.92 for *bidi* smoking. The predominant habit among women was pan tobacco chewing, which was associated with a relative risk of 1.41 for mortality (based on 96 231 person-years). The results indicate that *bidi* smoking is no less hazardous than cigarette smoking and that smokeless tobacco use may also result in high all-cause mortality. Preliminary results by cause of death suggest a risk of 5.8 for respiratory neoplasms in male smokers. In 2001, linkage of the study cohort with the files of the Mumbai Cancer Registry was carried out.

The cohort study in Trivandrum district in India, initiated in 1996, has recruited around 196 200 adults aged 35 years and over and has accrued around 430 000 person years. Active follow-up of the cohort has been initiated. Mortality data are actively collected. Verbal autopsies to establish the cause of death are routinely carried out. Efforts are being made to collect biological samples from a sample of the cohort.

Figure 16. Participants receiving information about the cohort study on tobacco use in Mumbai, India, before enrolment

Dietary phenolics as chemopreventive substances for bladder cancer in smokers

C. Malaveille, A. Hautefeuille; in collaboration with G. Talaska, Cincinnati, USA; P. Vineis, Turin, Italy

We have previously reported that consumption of fruit and vegetables may protect against bladder cancer by inhibiting DNA adduction with aromatic and heterocyclic amines and we proposed that the protective effect of fruit and vegetables may be attributable to their content in catechol flavonoids. These notions are being assessed in a randomized trial in which diets with different level of phenolics have been administered to smoking volunteers, the statistical analysis will be completed during 2002.

Polymorphisms in xeno(endo)biotic metabolism and DNA repair and urinary bladder cancer risk

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

In a molecular epidemiological study with 162 cases and 104 controls, we previously assessed the relevance of various genetic polymorphisms of metabolic enzymes as urinary bladder cancer risk factors in smokers. Among the polymorphisms investigated, only that of *N*-acetyltransferase-2 (NAT-2) was found to be associated with a low level of cancer risk; the level of DNA adduction in white blood cells was strongly associated with the slow-acetylator NAT-2 genotype. Since interindividual variation in DNA repair capacity has been shown to be due to polymorphisms of various genes, we have analysed polymorphisms of three DNA repair proteins, including XRCC3, in relation to cancer risk. Results obtained with 124 cases and 85 controls show that only XRCC3 polymorphism affects the risk of bladder cancer. In keeping with our previous data, this polymorphism inter-

acts with the NAT-2 genotype, its effect being limited to the slow-acetylator NAT-2 genotype (OR = 3.4, 95% CI 1.5–7.9), suggesting that XRCC3 may be involved in a common pathway for repair of bulky DNA adducts. In addition, the risk of having DNA adduct levels above the median was higher in NAT-2 slow acetylators who were homozygotes for the XRCC3 variant allele (OR = 14.6, 95% CI 1.5–138). However, any conclusions should be considered preliminary because of the small numbers involved. Our results suggest that bladder-cancer risk can be genetically modulated by XRCC3, which may repair DNA cross-link lesions produced by aromatic amines and other environmental chemicals [279].

Exposure to tobacco-derived 4-aminobiphenyl (4-ABP) is an important cause of urinary bladder cancer in humans. To study whether smoking, NAT-2 polymorphism, diet and tumour grade are determinants of 4-ABP–DNA adduct levels, we analysed these adducts by gas chromatography coupled to mass spectrometry in 75 bladder cancer biopsies. Detectable adduct levels were found in half of the samples and detection was strongly associated with tumour grade. In patients with detectable 4-ABP–DNA adducts, the odds ratios for having a tumour of grade 2 or 3 were 4.3 (95% CI 0.8–21.9) and 6 (1.3–27.5), respectively, compared with grade 1. A non-statistically significant association was found between the adduct level and the slow-acetylator NAT-2 genotype for tumour grades 2 and 3. Higher intake of fruit and vegetables was linked to a lower frequency of detectable adducts, though the association was not statistically significant. Detectable 4-ABP–DNA adducts were clearly associated with current smoking in higher tumour grades. A possible interpretation of these findings is that malignant clones undergo selection in such a way that cells carrying higher levels of DNA adducts are characteristic of more invasive (higher-grade) tumours. Such clonal selection would be facilitated by high levels of aromatic adduct-forming carcinogens derived from tobacco smoke and modulated by intake of fruit and vegetables.

We have also examined whether the pattern and/or frequency of *TP53* mutations in 45 bladder cancers are associated with various polymorphic metabolic traits. No specific pattern was evident for *TP53* mutations. Eight out of ten mutations occurred in grade 3 tumours. All *TP53* mutations occurred in subjects with the mutated alleles of catechol *O*-methyl transferase (*COMT*) ($p = 0.03$). The prevalence of cases with *TP53* mutations was 3.5-fold higher in subjects with wild type than in those with variant alleles of glutathione *S*-transferase (GST) P1 ($p = 0.03$). The other polymorphisms investigated were not associated with *TP53* mutations [271].

2.5 Radiation and cancer

Studies in this area are addressing 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 conducted. The motivation for this work is twofold: to strengthen the scientific basis of radiation protection and to improve our understanding of biological mechanisms of carcinogenesis.

International collaborative study of cancer risk among radiation workers

E. Cardis, E. Amoros, E. Combalot, A. Monnet, M. Pearce, D. Richardson, H. Tardy, I. Thierry-Chef; in collaboration with: *Australia*, R. Habib, C. Hacker, Menai; J. Kaldor, Sydney; *Belgium*, P. Deboodt, H. Engels, Mol; *Canada*, P. Ashmore, Ottawa; L.M. Green, Toronto; G. Cowper, B. Heinmiller, Chalk River; *Finland*, A. Auvinen, H. Hyvonen, Helsinki; M. Hakama, Tampere; *France*, F. Berman, Paris; A. Biau, Le Vésinet; C. Hill, Villejuif; *Germany*, M. Blettner, Bielefeld; G. Seitz, Cologne; *Hungary*, A. Kerekes, I. Turai, Budapest; *Japan*, T. Iwasaki, M. Murata, S. Ohshima, Tokyo; T. Yoshimura, Kitakyushu; *Slovak Republic*, G. Gulis, O. Fitz, Trnava; K. Holan, Bratislava; *Spain*, J. Bernard Solano, A. Diez Sacristán, Madrid; *Sweden*, M. Eklöf, Osthammar; H. Malker, Sundsvall; G. Engholm, Stockholm; *Switzerland*, M. Moser, Bern; M. Usel, Geneva; *UK*, M. Marshall, C. Muirhead, Chilton; *USA*, J. Fix, Richland; E. Gilbert, Rockville; G. Howe, B. Murray, D. Richardson, R. Rinsky, M. Schubaeur-Berigan, D.Utterback, Cincinnati; G. Howe, New York

This retrospective cohort study of over 600 000 nuclear industry workers in seventeen countries (Table 3) is designed 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. Data from all countries have been received during 2001. Validations were carried out and corrections were completed by the end of 2001.

In the study of biases and random errors in the radiation dose estimates, the major sources of systematic and random errors have been identified by facility, time period, dose level and, where relevant, activity. The errors related to exposure conditions and dosimetry technology have been quantified, and their uncertainty estimated, by facility and time period. Work on errors in doses related to dosimetric and recording practices is nearly complete.

Methodological developments have focused on methods to take into account the results of the study of errors in dose estimates in the risk analyses and on fitting random effects models using a Cox proportional hazards model and an excess relative risk model.

Analysis of data from the individual cohorts is in progress. Preliminary combined analyses have started. The first results of the study will be available in 2002.

Health consequences of the Chernobyl accident

Chernobyl accident recovery workers

E. Cardis, A. Kesminiene, E. Maceika, V. Tenet; in collaboration with: *Belarus*, A. Mirkhaidarov, Gomel; N.N. Piliptsevitch, I. Malakhova, S. Poliakov, E.P. Demidchik, E. Ivanov, V. Gapanovitch, Minsk; *France*, P. Hubert, Paris; *Russian Federation*, V.K. Ivanov, A.P. Konogorov, E.P. Rastopchin, V.A. Pitkevitch, Obninsk; I. Golovanov, Yu. Gavrilin, V. Krjuchkov, M. Savkin, A. Tukov, Moscow; I. Shantyr, St Petersburg; *Ukraine*, E. Bakhanova, V. Chumak, Kiev; V. Andreev, V. Glebov, S. Illychov, A. Tsykalo, Chernobyl; *USA*, A. Bouville, Bethesda, MD; L. Anspaugh, Salt Lake City, UT

Two case–control studies are being carried out 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, Estonia, Latvia, Lithuania or the Russian Federation, and, in particular, to study the effect of exposure rate.

The study population consists of the approximately 20 000 Baltic country, 40 000 Belarusian and 51 000 Russian liquidators (residing in five regions of the Russian Federation) who worked in the 30 km zone in the period 26 April 1986 to 31 December 1987, and who have been included in the state Chernobyl registry of these countries. The study includes cases diagnosed in 1993–99 and four controls for each case. Information on all study subjects was obtained through face-to-face interview using a standard questionnaire. Information was collected on demographic factors, on variables related to radiation dose and on exposure to potential confounding factors. A blood sample was obtained from prospective cases (before treatment) and relevant controls for the purpose of future biological dosimetry.

Data collection is complete. Interviewing of cases and controls is almost complete and data validation and correction are in progress. Overall, over 50 cases of leukaemia and lymphoma and 55 cases of thyroid cancer as well as their respective controls have been interviewed. All diagnoses are to be reviewed by a panel of pathologists.

A method for analytical dose reconstruction (and estimation of associated uncertainties) using information collected by questionnaire together with dosimetric and environmental measurements has been developed, validated extensively and applied to the estimation of doses and related uncertainties for all the subjects in the study. Preliminary analyses have started and the first results are expected in 2002.

Thyroid cancer in young people

E. Cardis, A. Kesminiene, E. Maceika, V. Tenet; in collaboration with: *Belarus*, N.N. Piliptsevitch, I. Malakhova, S. Poliakov, N. Shebeka, E.P. Demidchik, L.N. Astakhova, E. Cherstvoy, Yu. Sidorov, V. Ostapenko, V Shevchhuk, Minsk; V. Drozdovitch, V. Masyakin, Gomel; T. Krupnik, Mogilev; *Germany*, G. Goulko, Munich; *Italy*, A. Pinchera, F. Pacini, R. Elisei, Pisa; *Japan*, S. Yamashita, Y. Shibata, M. Ito, Nagasaki; M. Hoshi, Hiroshima; *Russian Federation*, V.K. Ivanov, M. Maksyoutov, E.P. Parshkov, E. Parshin, Shakhtarin, V.A. Stepanenko, V.A. Pitkevitch, O. Vlassov, Obninsk, V. Khrouch, Moscow; M. Balonov, A. Bratilova, I. Zvonova, St Petersburg; *UK*, D. Williams, G. Thomas, Cambridge; *USA*, A. Bouville, Bethesda, MD

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 was noted after the Chernobyl accident. There is strong circumstantial evidence that this increase was due to radioactive fall-out from the accident, but host and environmental factors may modify the risk of radiation-induced cancer (Cardis *et al.*, 1996, in: *The Radiological Consequences of the Chernobyl Accident*, Brussels, European Commission, pp. 835–850). Because of the rarity of this disease, this situation provides a unique opportunity to identify such factors and quantify their effect.

Table 3. Countries, facilities and approximate numbers of workers included in the International Collaborative Study.

Countries	Facilities	Workers
Australia	All	4500
Belgium	SCK, Belgo Process, Belgo Nucléaire	4859
	Doel, Tihange	3000
Canada	All	50 000
Finland	All	13 000
France	CEA-COGEMA, civil	15 000–17 000
	CEA-COGEMA, others	10 000–15 000
	Electricité de France	21 000
	Contracting companies	10 000
Germany	All	6000–8000
Hungary	All	3500
Japan	All	115 000
Korea	All	30 000
Lithuania	Ignalina	7000
Russia	Institute of Physics and Power Engineering	40 000
Slovakia	All	2804
Spain	All	3846
Sweden	All	22 500
Switzerland	All	2025
United Kingdom	All	125 000
United States	Oak Ridge National Laboratory	8318
	Hanford	36 235
	Portsmouth	10 000
	Idaho National Engineering Laboratory	50 000
	15 utilities	50 000

CEA, Commissariat à l'Energie Nucléaire; COGEMA, Compagnie Générale des Matières Nucléaires; SCK, Studiecentrum voor Kernenergie

A case–control study to assess the roles of genetic predisposition, iodine status and very short-lived isotopes of iodine in radiation-induced thyroid cancer has therefore been carried out 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 Chernobyl accident. The cases are all patients with a thyroid carcinoma occurring in the study population in 1990–98 and operated in Belarus or Russia. All cases have been independently verified by an international panel of pathologists. For each case, four controls have been selected.

Information was obtained by questionnaire administered by a trained interviewer. This includes questions about the behaviour of the subject at the time of the accident and shortly after; about stable iodine prophylaxis and thyroid hormone administration; and about familial history of cancer, thyroid disorders and other conditions possibly associated with thyroid cancer in familial syndromes. In addition, information was compiled from medical and school records, results of geographical surveys of iodine deficiency, surveys of countermeasures and analysis of biological samples and ultrasound evaluation of thyroid volume.

Methods for estimating individual thyroid doses of iodine-131 and short-lived isotopes (and associated uncertainties) have been developed and validated. Dose estimates have been derived for all subjects and estimation of related uncertainties is in progress.

Information on iodine deficiency at the time of the accident and subsequently has been collected and reviewed critically for analysis of a possible modifying role of iodine deficiency on the risk of radiation-induced cancer. Information on stable iodine content in soil and on iodine prophylaxis and supplementation is also being collected.

Data collection, now complete, has been carried out jointly (using a common questionnaire) with investigators of a collaborative Belarus/Russian/Japanese study with complementary objectives and overlapping study populations. Interviews and examination of about 300 cases and 1700 controls have been carried out. Preliminary analyses of the dose–response relationship are under way, with first results expected in early 2002. Analysis of a wide range of modifying factors has recently begun. At a later stage, it is hoped to analyse blood samples from study subjects for mutations in relevant genes (see Section 4.2) and thus evaluate the risk of radiation-induced thyroid cancer associated with possible genetic predisposition.

The European Childhood Leukaemia/ Lymphoma Incidence Study (ECLIS)

D.M. Parkin, E. Masuyer; in collaboration with: *Austria,* B.G. Bennett, J. Langgaßner, Vienna; *Belarus,* E. Ivanov, Minsk; *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; S. Schraub, Besançon; *Germany,* A. Loos, J. Michaelis, Mainz; *Hungary,* E. Apjok, Budapest; *Italy,* P. Crosignani, Milan; C. Magnani, B. Terraccini, Turin; *Latvia,* A. Stengrevics, Riga; *Lithuania,* R. Kriauciunas, Vilnius; *Netherlands,* J.W.W. Coebergh, Eindhoven; *Norway,* F. Langmark, Oslo; *Poland,* W. Zatonski, Warsaw; *Romania,* R. Tulbure, Bucharest; *Russian Federation,* A. Boukhny, Moscow, 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; J. Torhorst, Basel; *Ukraine,* G. Moroz, Kiev; *UK,* D. Brewster, Edinburgh; 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 Chernobyl in 1986. The study followed the recommendations of an expert committee established by the European Commission to review possible health effects of the accident in European populations.

The study began in 1988. Thirty-six cancer registries in 24 European countries provided 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. Estimates of the excess radiation doses received as a result of the accident were provided by UNSCEAR. Data collection finished in 2000, by which time almost all participants had provided case listings to the end of 1997.

Analyses of data from the first five years of follow-up showed no evidence of an association between radiation doses received due to the accident and risk of childhood leukaemia in the populations studied. However, an analysis of the data-set at seven years suggested a small increase in incidence in infants (less than one year) born soon after the accident; this 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.

This analysis will be repeated with the full data-set (with 10 years' follow-up after the accident), after a careful verification exercise 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 for 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 a listing of thyroid cancer cases in the age group 0–19 years, and this information was supplemented with data submitted within the framework of the ACCIS project (Section 1.3). Although there were geographical differences in incidence and temporal changes in risk, no evidence was found that the relatively low exposure to radioactive iodine had played any role.

Effects of static and time-varying electric and magnetic fields

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, CA, USA; A. Swerdlow, London, UK; P. Vecchia, 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 in the frequency range 0–300 GHz (divided into static (0 Hz), extremely low-frequency (ELF; > 0–300 Hz) and radiofrequency (RF; 300 Hz–300 GHz) fields).

Resources of relevant international and national agencies and other scientific institutions are being pooled. 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 aims of IARC's involvement are to evaluate the carcinogenic risk associated with exposure to electric and magnetic fields and to identify gaps in scientific knowledge and recommend research protocols. IARC has participated in critical reviews of the literature on ELF and RF radiation.

Cancer in relation to mobile telephone use

E. Cardis, M. Kilkenny, L. Richardson, N. Encrenaz, L. Ardoino, L. Montestrucq; in collaboration with: *Australia*: B. Armstrong, J. Brown, Kings Cross; M. Kilkenny, Carlton South; *Canada*: D. Krewski, Ottawa; J. Siemiatycki, L. Richardson, Laval-des-Rapides; M. McBride, Vancouver; *Denmark*: C. Johansen, H. Collatz, Copenhagen; *Finland*: A. Auvinen, T. Salminen, Tampere; *France*: J. Wiart, Issy-Les-Moulineaux; M. Hours, Lyon; *Germany*: M. Blettner, G. Berg, Bielefeld; J. Michaelis, J. Schuez, Mainz; K. Schlaefer, B. Schlehofer, Heidelberg; *Israel*: S. Sadetzki, Tel-Hashomer; *Italy*: S. Lagorio, P. Vecchia, Rome; *Japan*: M. Taki, T. Takebayashi, N. Yamagouchi, Tokyo; *New Zealand*: A. Cook, N. Pearce, A. Woodward, Wellington South; *Norway*: T. Tynes, L. Klaeboe, Oslo; *Sweden*: A. Ahlbom, M. Feychting, S. Lönn, Stockholm; *UK*: P. McKinney, J. Doughty, R. Parslow, Leeds; A. Swerdlow, M. Schoemaker, Sutton; S. Mann, Oxford; M. Van Tongeren, Birmingham; *USA*: S. Preston-Martin, Los Angeles, CA; F. Davis, Chicago, IL; J. Bowman, Cincinnati, OH; Q. Balzano, Fort Lauderdale, FL

In view of the recommendations of several recent expert groups, and following a detailed feasibility study, a series of multicentric case–control studies has been set up to determine whether mobile telephone use increases the risk of cancer and, specifically, whether the RF radiation emitted by mobile telephones is carcinogenic. Participating countries are Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the United Kingdom. The study may also be extended to the United States.

Separate studies are being carried out on acoustic neurinoma, gliomas and meningiomas and tumours of the parotid gland, the tumours that would be most likely to be related to mobile telephone use. A study of leukaemia risk is also planned, conditional on funding. The studies use a common core protocol. The main focus is on tumours in people aged 30–59 years, who had the highest prevalence of mobile phone use 5–10 years ago, and on regions within the participating countries with longest and highest use of mobile phones (mainly the major urban areas).

The aim is to enrol about 6000 cases of glioma or meningioma, 1000 of acoustic neurinoma and 600 of parotid gland tumours. The numbers of controls per case are one for brain tumours; two for acoustic neurinoma and three for parotid gland tumours. Controls are either individually or frequency-matched on age (within five-year categories), sex and study region. Control selection is generally population-based. In some countries, controls are drawn from hospitals, but from the same population base as the cases.

The primary source of information is a computer-assisted interview conducted by a trained interviewer. Retrospective and prospective validation studies are examining the accuracy of self-reported use of mobile phones. A group of experts in exposure assessment is developing and testing an exposure index based on information from the questionnaire, as well as technical information on the characteristics of the network and of the telephones used and the time period. In some countries, samples of blood or buccal cells are being collected for possible future analyses of gene–environment interactions, in collaboration with the United States National Cancer Institute.

A workshop to train interviewer trainers from most of the participating countries was held in June 2000. The questionnaire has been translated into all languages of the study. Interviews started between September 2000 and October 2001, depending on the country. Recruitment will extend over a period of two to three years, depending on the study and region.

Table 4. Studies of cancer in relation to mobile telephone use: distribution of expected numbers of cases by tumour type and country

Country	Glioma and meningioma	Acoustic neurinoma	Parotid gland
Australia	566	150	75
Canada	180	53	84
Denmark	750	–	100
Finland	422	50	–
France	400	130	–
Germany	349	24	–
Israel	450	10	40
Italy	320	40	125
Japan	450	50	
New Zealand	209	37	10
Norway	218	38	14
Sweden	570	104	132
UK, London	926	56	
UK, North	482	73	
Total	6292	815	580

2.6 Viruses and cancer

The expected epidemic of human immunodeficiency virus (HIV)-related cancers in sub-Saharan Africa is being monitored in the populations which have been continuously served by a cancer registry since the infection began to spread. Hypotheses on interactions between the infection and other characteristics of the population are formulated and are tested 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) and the Gambia Hepatitis Intervention Study (Section 5.1) is examining the effect of vaccination against the hepatitis B virus in preventing liver cancer.

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

D.M. Parkin; in collaboration with V. Beral, R. Newton, R. Weiss, Oxford, UK; K. deCock, London, UK; H. Jaffe, Atlanta, USA; E. Katangole Mbidde, H. Wabinga, Kampala, Uganda; J.-P. Magaud, J. Fabry, C Trepo, Lyon, France; M. Raphaël, Paris, France; J.O. Thomas, Y. Aken'ova, G. Falade, Ibadan, Nigeria

The analysis of the study of the association between HIV infection and non-Hodgkin lymphomas in children and adults in Uganda was completed [339]. In children, the great majority of non-Hodgkin lymphomas were Burkitt lymphomas; practically all cases were positive for Epstein–Barr virus DNA, and there was no association with HIV infection. In adults, Burkitt lymphomas 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 two-fold).

A study of non-Hodgkin lymphomas in Ibadan, Nigeria, supported by a grant from the Association pour la Recherche sur le Cancer (France), was delayed during review of ethical considerations. Subject recruitment began in July 2001. The main interest is the role of viral infections.

Association of human papillomaviruses and other viruses with conjunctival lesions

E. Weiderpass, S. Franceschi; in collaboration with H.-O. Adami, Stockholm, Sweden; A. Agaba, E. Mbidde, F. Wabwire-Mangen, Kampala, Uganda

Conjunctival squamous-cell carcinoma, a hitherto rare tumour, has increased in incidence many-fold since the advent of HIV and acquired immunodeficiency syndrome (AIDS). Its etiology is unknown, but there is evidence that ultraviolet light has an important role. HPV has also been suspected to be involved, but data are scanty.

A hospital-based case–control study of approximately 200 cases and 200 controls, frequency-matched by five-year age groups and sex, in three hospitals in Uganda is being set up. The objectives are (*a*) to establish the presence of DNA of HPV and other viruses (such as human herpesvirus 8 and herpes simples viruses 1 and 2) in neoplastic and dysplastic lesions of the conjunctiva and (*b*) to identify the HPV subtypes in these lesions to establish whether certain subtypes are significantly associated with conjunctival cancer. Cases are patients with histologically proven squamous-cell carcinoma or precancerous lesions of the conjunctiva. Controls are patients, selected from the same clinics, with histologically proven pterygium, pingueculae and other eye conditions which require surgery. All subjects will have excision biopsies taken for histological examination and HPV detection and typing and a blood sample taken for HIV serology and CD4 counts. A pilot study is in progress and personnel are being trained to perform the fieldwork, which will start in early 2002. Results are expected in 2004.

Cancer excess in individuals with HIV infection or AIDS

S. Franceschi; in collaboration with L. Dal Maso, Aviano, Italy; G. Rezza, D. Serraino, Rome, Italy; R. Zanetti, Turin, Italy; and the Italian Association of Tumour Registries

HIV-infected individuals show greatly increased risk of Kaposi's sarcoma (RR > 1000) and non-Hodgkin lymphoma (NHL; RR > 100) [198]. Increased RRs for Hodgkin disease, cervical cancer, non-melanomatous skin cancer and cancers of the conjunctiva, lung and brain have also been reported, but the possible associations require further study.

Figure 17. Young women participating in a study of papillomavirus infection at Naguru Clinic, Kampala, Uganda

We have been estimating cancer excess among people with HIV infection or AIDS by means of (*a*) record linkage studies between AIDS registries and cancer registries in Italy, and (*b*) follow-up studies of selected cohorts of intravenous-drug users with or without HIV infection in southern Europe [107, 197, 236, 425]. These studies contribute to the estimation of cancer excess attributable to HIV or AIDS, particularly with respect to NHL [109, 479] and cancers of the genital tract [110, 111, 144].

In Italian cancer registries (covering some 15% of the total Italian population), 11.6% of male cases of NHL and 4.1% of female cases presented with AIDS between 1985 and 1994. Among individuals with AIDS, the RR ranged between 105 for low-grade NHL to 383 for high-grade NHL. Two-year survival of AIDS-related NHL cases was only 10% and did not differ according to histological type [109]. A significant six-fold excess of lung cancer was seen among HIV-positive intravenous drug addicts in France and Italy. A similarly increased risk was found, however, also among HIV-negative addicts, suggesting that heavy smoking, rather than immune impairment, is responsible for our findings [425].

Genetic epidemiology of nasopharyngeal carcinoma

D.E. Goldgar, M. Corbex , A.J. Sasco; in collaboration with F. Ben Ayed, Tunis, Tunisia; G. Lenoir, Paris, France

Nasopharyngeal carcinoma (NPC) is an interesting model for genetic epidemiology studies of a complex cancer phenotype, as it has a highly variable incidence pattern worldwide. It is relatively uncommon in most areas of the world, but has very high incidence rates in south-east Asia and north Africa, where it is a major public health problem. NPC is an EBV-associated tumour with strong environmental factors, which may be population-specific, but there is also strong evidence for genetic susceptibility. There is also a clear association, found in many populations, between NPC and the major histocompatibility complex (HLA). One report also found significant genetic linkage to HLA from analysis of 36 affected sib pairs in Singapore and in Nanning and Hong Kong, China. The tumours frequently show loss of heterozygosity on chromosome 3p. We have initiated a collaborative international study in order to obtain a sufficient number of families to detect linkage to an NPC susceptibility locus and a large number of matched cases and controls to investigate low- to moderate-risk polymorphisms. Collaborators in Algeria, China (Guangzhou, Hong Kong), Malaysia, Morocco, Sweden and Tunisia have been contacted or already enrolled in the project. We have completed the common core questionnaire and study protocol.

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.

Combined analysis of cancer registry data on second malignancies

P. Brennan, D. Colin, P. Boffetta; in collaboration with A. Andersen, Oslo, Norway; B. Armstrong, Sydney, Australia; R.J. Black, Edinburgh, UK; H. Botha, Sheffield, UK; J. Jonasson, Reykjavik, Iceland; E. Kliewer, Winnipeg, Canada; H.P. Lee, Singapore; M. McBride, Vancouver, Canada; J. Olsen, Copenhagen, Denmark; V. Pompe-Kirn, Ljubljana, Slovenia; D. Robson, Regina, Canada; J. Smith, Winchester, UK

Previous studies of multiple primary cancers have helped to identify cancer sites which are likely to share a common etiology and to identify treatment strategies which influence the risk of subsequent cancers. To extend this work, data on second cancers for a pooled analysis have been obtained from 12 large cancer registers which have at least 20 years of follow-up, yielding a data-set of over 4 000 000 primary cancers. Preliminary analyses have been conducted on risk of second primaries following non-Hodgkin lymphoma in New South Wales, Australia [73]. The analysis of the combined data is in progress and has sufficient power to reveal relationships between both rare and common tumours. The analysis is conducted for each cancer site as a primary tumour and also for each cancer site as a secondary tumour.

Cancer risk following non-neoplastic diseases

P. Boffetta; in collaboration with H.-O. Adami, O. Nyren, Stockholm, Sweden; R.J. Black, Edinburgh, UK; G. Gridley, Bethesda, MD, USA; J. Olsen, Copenhagen, Denmark; L. Simonato, Padua, Italy

The risk of cancer has been reported to be increased (or decreased) among patients suffering from several non-neoplastic conditions. These associations, if real, might be due to: (i) common risk factors; (ii) a carcinogenic action of the non-neoplastic disease (e.g., through chronic inflammation); or (iii) a carcinogenic effect of therapy. In any of these cases, the study of cancer risk following non-neoplastic diseases can provide useful information on the etiology and pathogenesis of cancer. However, the study of cancer risk following non-neoplastic conditions suffers from potential biases, including reporting bias, surveillance bias and reverse causality, as well as from lack of statistical power because of the rarity of most neoplastic and non-neoplastic diseases. Large, population-based prospective studies represent a powerful tool to investigate these associations.

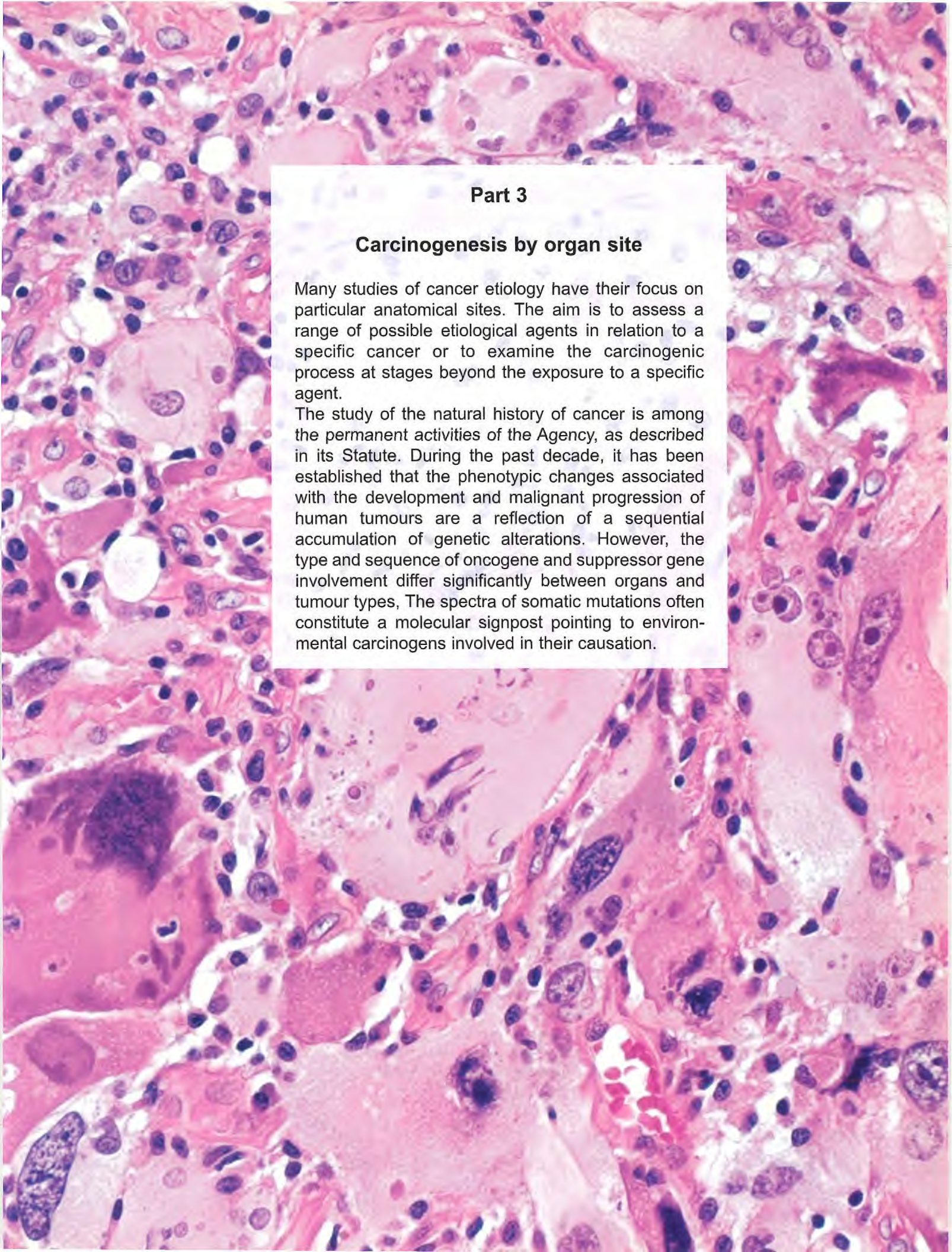
Population-based registries of out-patients and in-patients are available for several large populations, and can be linked to cancer registries. This approach has been applied in Sweden to study the risk of melanoma and other neoplasms in patients hospitalized for psoriasis [39], the risk of head and neck cancer among alcoholics [48], and the risk of lung cancer and oesophageal adenocarcinoma in asthma patients [49, 540]. Other analyses of data on patients hospitalized in the Veterans Administration hospitals in the United States are being conducted. A pooled analysis of data from Denmark, Italy, Scotland and Sweden is planned.

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

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

The carcinogenicity of tamoxifen for the uterus is now well established, but more data are needed in relation to other cancer sites and in the context of use of tamoxifen in chemoprevention among healthy women.

Case–control studies of cancer of the endometrium and ovarian cancer following breast cancer have been conducted in France and Switzerland, using data from 12 population-based cancer registries. Preliminary analyses have been conducted on 127 cases of endometrial cancer and 86 cases of ovarian cancer, with 508 and 334 controls, respectively, matched for age and period of diagnosis and for duration of period at risk. These have confirmed the role of tamoxifen in the occurrence of endometrial cancer, but the relationship appears less clear for ovarian cancer, a cancer less directly linked to hormones [407, 408] than endometrial cancer.



Part 3

Carcinogenesis by organ site

Many studies of cancer etiology have their focus on particular anatomical sites. The aim is to assess a range of possible etiological agents in relation to a specific cancer or to examine the carcinogenic process at stages beyond the exposure to a specific agent.

The study of the natural history of cancer is among the permanent activities of the Agency, as described in its Statute. During the past decade, it has been established that the phenotypic changes associated with the development and malignant progression of human tumours are a reflection of a sequential accumulation of genetic alterations. However, the type and sequence of oncogene and suppressor gene involvement differ significantly between organs and tumour types, The spectra of somatic mutations often constitute a molecular signpost pointing to environmental carcinogens involved in their causation.

3.1 Oesophageal cancer

Squamous cell carcinoma (SCC) of the oesophagus occurs at very high frequencies in several regions of central and eastern Asia, Africa and South America. In contrast, adenocarcinoma (ADC) of the oesophagus is mostly a tumour of industrialized countries, where it is the most rapidly increasing type of cancer. Both types of tumour are difficult to detect at an early stage and have a very poor cure rate. There is evidence that exogenous factors of risk are involved in their pathogenesis. The *TP53* tumour-suppressor gene is often mutated in both types and mutation patterns vary from one region to the other, suggesting that they may reflect differences in the exogenous factors involved.

Cellular and molecular alterations in oesophageal cancer

P. Hainaut, G. Martel-Planche, D. Guimaraes, P. Tanière, A. Sepehr; in collaboration with C. Gallo, Rio de Janeiro, Brazil; F. Saidi, Teheran, Iran; Hsu Chin Lu, Beijing, China; A. Chanvitan, Songkhla, Thailand; J. Jankowsky, Birmingham, UK; J.-Y. Scoazec, Lyon, France

We are establishing a world map of *TP53* mutations in oesophageal cancers that should provide clues to the mutagenic mechanisms involved in their etiology. We have already completed studies on tumours from high-incidence areas in southern Thailand (Songkhla Province), central China (Linxian, Henan Province) and northern Iran, as well as from low-incidence areas of western Europe (Figure 18).

The incidence of SCC in northern Iran is the highest reported for any cancer anywhere in the world. After a break of over 20 years, IARC has resumed studies on the causes of SCC in this region, building upon information from epidemiological studies carried out in the 1970s. We have found that SCC in northern Iran has an unusual pattern of *TP53* mutations, reflecting a possible role of nitric oxide in mediating the formation of specific mutations (C to T transitions at dipyrimidine dinucleotides). However, the mutation patterns are significantly different between men and women, suggesting a role of gender-specific mechanisms or differences in cultural and lifestyle factors between the sexes. Studies are in progress to better characterize such factors.

Comparative studies on SCC and ADC have revealed that *P63*, a gene encoding a close homologue of p53, is often amplified and over-expressed in SCC, but never in ADC. Moreover, the P63 protein is constitutively expressed in the basal layers of normal squamous epithelium of the oesophagus, but is absent in the glandular cells of Barrett's metaplasia. These observations suggest that P63 acts as a 'switch' in the differentiation of mucosal cells into either squamous or glandular cells. We are now exploring the role of deregulation of P63 expression in the pathogenesis of Barrett's oesophagus.

We have also performed comparative studies on subtypes of adenocarcinoma arising within the gastric cardia, at the oesophago-gastric junction. We have found different patterns of genetic alterations and of cytokeratin expression between tumours of the cardia and ADC of the lower oesophagus or of the upper stomach. These findings support the hypothesis that these cancers correspond to a pathological entity different from either oesophageal or gastric adenocarcinomas.

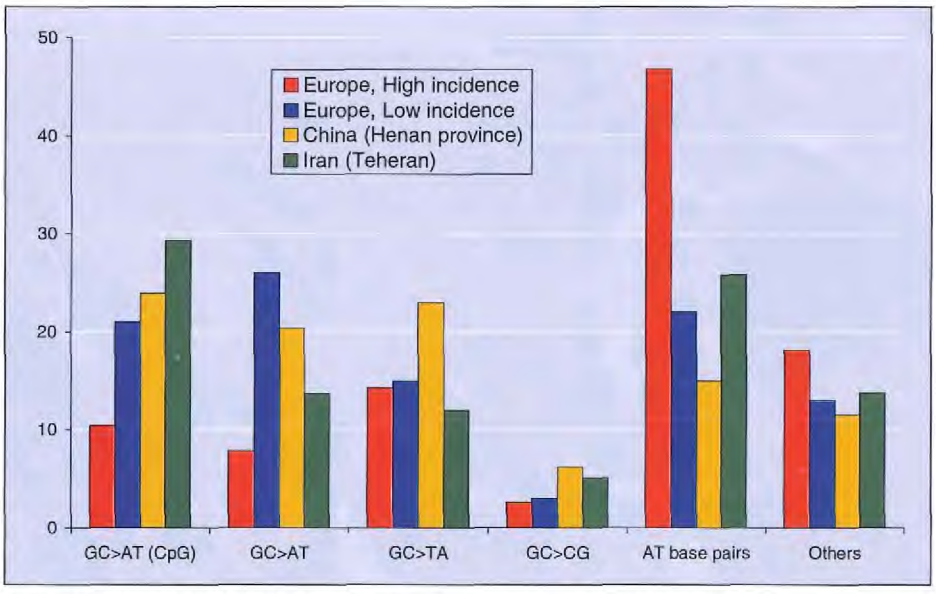


Figure 18. Patterns of *TP53* mutations in squamous cell carcinomas from different geographic areas.
Note the high prevalence of GC>AT CpG transitions in Iran and the high prevalence of mutations at AT base pairs in high-incidence areas of western Europe (Normandy, France; northern Italy). This latter type may reflect a mutagenic effect of metabolites of alcohol such as acetaldehyde.

3.2 Cancer of the stomach

Cancer of the stomach is the second most common cancer in men in developing countries, despite a steady decline observed everywhere. The highest incidence rates are observed in eastern Asia, particularly China and Japan. In contrast, low rates are reported in southern Asia: India, Thailand and Viet Nam. Among the risk factors identified to date, infection with the bacterium *Helicobacter pylori* is believed to account for a large number of cases due to its high prevalence, particularly in less affluent countries. Several hypotheses have been proposed to explain the lack of association at the geographical level between the infection and the risk of stomach cancer. These include the possibility of variants of bacterial strains with different carcinogenic potential.

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

P. Pisani, D.M. Parkin; in collaboration with H. Mitchell, Australia; Pham Hoang Anh, Hanoi, Viet Nam; S. Sriamporn, Khon Kaen, Thailand

Two case–control studies are being conducted, in the low-risk population of Khon Kaen, Thailand, and in Hanoi, Viet Nam, where gastric cancer incidence is twice that in Thailand. Data collection has been completed in Khon Kaen, where 131 incident cases and twice as many hospital controls have been interviewed and donated a blood sample. Information was collected on sociodemographic factors, living hygienic conditions and home crowding at present and in childhood, sources of water supply, history of tobacco smoking and betel-nut chewing and alcohol drinking. Usual dietary habits were assessed using a questionnaire of the dietary history type. Only high intakes of salted and fermented food items were associated with significantly increased risk (OR = 1.76; 95% CI 1.05–2.97 and 1.90; 95% CI 1.10–3.30, respectively). Preference for spicy food (chilli) was not associated with risk (OR = 1.01). None of the other factors investigated was statistically associated with the risk of gastric cancer.

Anti-*H. pylori* immunoglobulins were determined by an ELISA test. As in other case–control studies, more controls than cases were found positive, suggesting an apparent protective effect of the infection. Lower levels of serum antibodies to *H. pylori* in the presence of extensive areas of atrophic gastritis could explain this inverse association. To investigate this hypothesis, the levels of pepsinogens I and II are being assessed in the sera of cases and controls as a modifier of the association between *H. pylori* and gastric cancer. In addition, anti-*H. pylori* antibodies will be re-tested using antigens derived from bacterial strains endemic in eastern Asia in order to improve the accuracy of the test.

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

Case–control study of stomach cancer in Tachira, Venezuela

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

Gastric cancer is the leading cause of death from cancer in Venezuela. The mortality rate is particularly high in the state of Tachira (cumulative mortality to age 74 years 4.1% in males and 2.2% in females). In a case–control study to identify causes of gastric cancer in this high-risk population, 292 histologically confirmed cases and 485 neighbourhood controls were recruited between January 1991 and August 1997.

Serum antibodies to *H. pylori* were analysed in three different laboratories using four different antigens in order to investigate the claim that assays based on local strains of *H. pylori* are more accurate. The first assay used antigens derived from Dutch strains of *H. pylori*. Two further assays conducted in the same laboratory used antigens derived from French strains and Venezuelan strains. In addition, a commercial kit was used. Estimates of *H. pylori* prevalence using these assays were in the range 72–92%. According to the assay using French strains, the prevalence was lower in cases than controls. No relationship was observed with the other assays. The negative relationship became evident for all assays when the data were analysed by antibody titre instead of classifying subjects as 'positive' or 'negative'. The lower antibody levels found in cases may be due to loss of *H. pylori* from the gastric lumen in the precancerous stages of the disease or to reduced immune response in cases [359].

Antibodies to cagA were also investigated. This is a marker for the presence of a 40 kb pathogenicity island encoding a specialized secretion mechanism unique to *H. pylori* strains with enhanced virulence. 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.

There was a strong inverse association between stomach cancer incidence and social class, as measured by education and by indicators of poverty. The results of the dietary analysis suggest that a diet high in starch and low in fish, meat and fresh vegetables increases the risk of gastric cancer. A protective effect was observed for frequent consumption of allium vegetables. Inverse associations were found with height, which may reflect nutritional status in childhood, and with availability of a refrigerator in the first two decades of life. Alcohol drinkers were at higher risk than non-drinkers and there was a small excess risk for current smokers compared with never-smokers. There was limited evidence of familial aggregation of gastric cancer [300].

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

E. Weiderpass, S. Franceschi, H. Ohshima, C. Lavé, N. Muñoz; in collaboration with B. Appelmelk, Amsterdam, Netherlands; L.E. Bravo, Cali, Colombia; A. Covacci, Siena, Italy; R. Herrero, M. Matamoros, San José, Costa Rica; E. Kasamatsu, Asunción, Paraguay; H. Posso, Bogotá, Colombia; D. Queiroz, Belo Horizonte, Brazil; E. Salazar, Cuernavaca, Mexico; C. Saul, Porto Alegre, Brazil

H. pylori Infection is extremely common in many populations, and the reported prevalence of serological markers of infection does not seem to explain the wide geographical variations in incidence of peptic ulcer disease and stomach cancer that are observed. Although infection is almost ubiquitous, particularly in developing countries, 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 having higher pathogenic potential, such as those carrying the cagA pathogenicity island (see above) might explain the geographical differences. Other possible cofactors include use of selected drugs, diet, food preparation practices, salt ingestion, smoking and individual inflammatory responses.

We are conducting an international survey of *H. pylori* infection in subjects attending gastroscopy clinics with a histological diagnosis of peptic ulcer disease, gastritis, gastric cancer precursors and invasive cancer, in areas of five countries in Latin America with high, intermediate or low incidence of stomach cancer. In each centre, about 400 subjects are enrolled, including a pre-defined number in each diagnostic category and age group. 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 biomarkers. Genes such as *vacA* and *cagA* are evaluated using a PCR-based reverse hybridization method, to look for geographical patterns. Some biopsies are cultured for *H. pylori* at central laboratories, to genetically characterize the strains in the different lesions. In addition, various markers of activation of inflammatory cells, oxidative stress, enzymatic antioxidant defence and cytokine induction in human gastric mucosa are being investigated in relation to *H. pylori* strains and individual susceptibility. A blood sample is also collected to investigate serological markers of *H. pylori* infection, auto-immune responses to *H. pylori* and pepsinogen levels, which can be markers of chronic atrophic gastritis.

The numbers of patients recruited up to July 2001 were: Brazil, 100; Colombia, 276; Costa Rica, 115; Mexico, 423; Paraguay, 73.

Effect of *N*-methylnitrosourea in p53 knock-out mice

H. Ohgaki, M. Fukuda, Y. Tohma, H. Huang; in collaboration with L.A. Donehower, Houston, TX, USA; C. Furihata, Kanagawa, Japan; H. Sakai, N. Shirai, M. Tatematsu, T. Tsukamoto, M. Yamamoto, K. Yoshida, Nagoya, Japan; G. Stoica, College Station, TX, USA

Nullizygous p53 knock-out ($p53^{-/-}$) mice are highly susceptible to spontaneous tumorigenesis, particularly malignant lymphomas at an early age. Heterozygous p53 knock-out ($p53^{+/-}$) mice develop spontaneous tumours less frequently but may show increased susceptibility to chemical carcinogens. In this study, $p53^{-/-}$, $p53^{+/-}$ and wild-type ($p53^{+/+}$) mice were treated with *N*-methylnitrosourea (MNU) by gastric intubation. This treatment significantly enhanced spontaneous development of malignant lymphomas and sarcomas, in terms of both incidence and latency, in $p53^{-/-}$ and $p53^{+/-}$ mice. The overall incidence of tumorous changes in the stomachs of $p53^{+/-}$ (7/12, 58%) and $p53^{+/+}$ mice (9/31, 29%) was not significantly different ($p = 0.090$), but adenocarcinomas invading to submucosa were observed only in $p53^{+/-}$ mice, suggesting a slightly higher susceptibility to MNU-induced gastric carcinogenesis in $p53^{+/-}$ mice [318].

p53 knock-out mice were also treated with MNU in the drinking water. After five weeks, the numbers of pepsinogen-altered pyloric glands, putative preneoplastic lesions, were much higher in $p53^{-/-}$ mice than in $p53^{+/+}$ or $p53^{+/-}$ mice. After longer treatment with MNU, adenomas were found 60% of the $p53^{-/-}$ mice. One well differentiated adenocarcinoma was observed in a $p53^{-/-}$ mouse. After 40 weeks' treatment with 120 or 30 p.p.m. MNU, there was no significant difference in the incidence of gastric tumours between $p53^{+/+}$ and $p53^{+/-}$ mice. However, mortality from carcinogen-induced lymphomas, leukaemias and sarcomas was greater in the latter group [537].

3.3 Cancer of the liver

A number of risk factors for liver cancer have been identified, such as infection with hepatitis viruses and exposure to aflatoxins. Epidemiological studies are being pursued to better define the causes in particular populations. In parallel, molecular studies are examining the gene mutations found in association with liver cancer.

Cohort study of HBsAg carriers in Thailand

M. Plummer, E. Weiderpass, S. Franceschi, C. Lavé, N. Muñoz; in collaboration with P. Coursaget, Tours, France; P. Srivatanakul, S. Purbahat, Bangkok, Thailand; C.P. Wild, Leeds, UK

A cohort of 1745 male carriers of hepatitis B surface antigen (HBsAg) over the age of 30 years has been recruited in Bangkok, Thailand. 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 hepatocellular carcinoma (HCC) has been conducted. Forty-one cases have been diagnosed and two age-matched controls have been selected for each case. No association of HCC was found with diet, alcohol, smoking and socio-economic status, nor with genetic polymorphisms or aflatoxin exposure. Assays for markers of infection with hepatitis B or C virus (HBV, HCV) (HBeAg, HBV DNA, HBsAg titre, anti-HCV) and prognostic factors (e.g., α-fetoprotein) have been conducted. At the five-year follow-up, 55 subjects had either developed liver cirrhosis or HCC or had died from cancer-related causes (disease-free survival = 95.8 ± 0.6%). The level of α-fetoprotein at study entry was the strongest prognostic factor, with a decrease of liver disease-free survival among subjects with levels above 4.5 μg/mL compared with those below 4.5 μg/mL.

Hepatitis C virus and hepatocellular carcinoma and non-Hodgkin lymphoma in Italy

S. Franceschi; in collaboration with M. Crovato, Pordenone, Italy; C. La Vecchia, Milan, Italy; M. Montella, Naples, Italy; R. Talamini, L. Dal Maso, Aviano, Italy

Hepatocellular carcinoma (HCC) has higher incidence in Italy than in most European countries, being the fifth cause of cancer death in Italian males (5% of total cancer deaths in 1994), following a three-fold increase in mortality rate since 1955 [239]. HBV and HCV [153] are major causes of chronic liver disease, such as chronic hepatitis and cirrhosis, as well as HCC. HCV infection has also been associated with certain extrahepatic manifestations, and it has been hypothesized that it may be involved in the etiology of B-cell non-Hodgkin lymphomas.

We are conducting a hospital-based case–control study in north-eastern (Pordenone, Aviano) and southern Italy (Naples) to determine the role of lifestyle risk factors (e.g., alcohol drinking, tobacco smoking and diet) and viral risk factors, with particular emphasis on HCV RNA and HCV genotype in anti-HCV-positive subjects. Cases are males and females (age <79 years) with consecutive new diagnoses (not previously treated) of HCC and non-Hodgkin lymphoma. Controls are subjects admitted, as in-patients or out-patients, to hospitals with the same catchment areas as those of cases, for acute conditions (orthopaedic, acute surgical conditions, eye and skin disorders) unrelated to alcohol and tobacco consumption. All patients are invited to provide a 20-mL blood sample for virological and genetic (HLA and selected polymorphisms) investigations and a tumour biopsy is taken when possible. Up to September 2001, 259 cases of HCC, 299 of non-Hodgkin lymphoma and 441 control subjects had been recruited.

Cohort study of liver and other cancers

P. Pisani, D.M. Parkin; in collaboration with V. Vatanasapt, 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 1993–97 reported by the Khon Kaen Cancer Registry were 96.9 in men and 35.3 in women. Cholangiocarcinoma represents 90% of all liver cancers occurring in this population, while hepatocellular carcinoma is the predominant type everywhere else in the world.

Over 24 000 individuals had been enrolled by June 2001 (16 000 women and 8000 men). Interview data are complemented with samples of blood and faeces. Procedures to link the cohort with the database of the provincial population-based cancer registry have been developed. A nested case–control study confirmed a strong association between infection with the parasite *Opisthorchis viverrini* and the risk of developing cholangiocarcinoma.

The cohort size, initially set at 9000 to study cholangiocarcinoma, was more than doubled between October 1997 and June 2001. This increase will allow examination of the following associations: (*a*) all-cause and cardiovascular disease mortality and life-expectancy in relation to a variety of lifestyle factors, with particular emphasis on tobacco and alcohol consumption; (*b*) cervical cancer and infection with various types of human papillomavirus (see Section 3.4); and (*c*) lung, colorectal and breast cancer in relation to genetic factors and environmental exposures. Metabolic phenotypes such as GSTM1 and CYP1A1, which may predispose to cancer at various sites, have shown race-specific polymorphisms, but previous studies of Caucasians and Asians have given inconsistent results. Cross-sectional studies to validate the questionnaire and define the characteristics of the cohort are in progress.

Cohort study of liver cancer in Qidong, China

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

In a project established in Qidong county, China, in 1989, about 45 000 men were screened for HBsAg. About 20% proved to be positive. Blood specimens from 6000 HBsAg-positive subjects, and 10 000 HBsAg-negative have been stored since that time.

Within this cohort, a nested case–control study is being conducted to assess: (*a*) the role of exposure to dietary aflatoxins in the etiology of liver cancer, based on serial estimates of aflatoxin–albumin adducts in cases and controls; (*b*) whether liver cancers bearing the specific mutation (G:C to T:A transversion) at codon 249 of the *TP53* gene are more frequent in individuals who had measurably higher exposure to aflatoxin in the past; (*c*) the role of genetic polymorphisms in susceptibility to aflatoxins; and (*d*) the magnitude of the combined effects of aflatoxin and hepatitis viruses.

The study began in 1999, with completion of the computer file of cohort members who were HBsAg-negative at enrolment, followed by matching of the cohort members with the records of liver cancer cases and deaths in the Qidong County cancer registry and the death register. 130 subjects who developed liver cancer and one control for each case (without liver cancer at the time of the case-subject's diagnosis) were identified. Specimens of tumour tissue were available for 21 case subjects. The specimens were checked for markers of infection with hepatitis viruses (HBsAg, anti-HCV) in Qidong and for albumin–aftatoxin adducts and genetic polymorphisms (*GSTM1*, *GSTT1*, epoxide hydrolase) in Leeds, United Kingdom.

TP53 mutations are being analysed in Lyon. ^{249}Ser mutations have so far been found in 13 out of 17 confirmed analyses. In three out of seven cases (43%) for which peri-tumoral, cirrhotic tissue was available, the ^{249}Ser mutation was also detected. These results confirm earlier findings of an extremely high prevalence (around 75%) of ^{249}Ser mutations in liver cancer from high-incidence regions of China. We have also extracted DNA from serum specimens of all individuals in the case–control study. In 38 serum samples collected less than two years before cancer diagnosis, no mutations at codon 249 of the *TP53* gene were detected using RFLP. The analysis is being repeated using a new approach based on mass spectrometry (short oligonucleotide mass analysis, SOMA). The laboratory analyses were completed at the end of 2001.

Etiopathogenesis of hepatocellular carcinoma in the Gambia

E. Gormally, K. Szymanska, S. Michel, M. Friesen, D.M. Parkin, F. Lesi, P. Hainaut; in collaboration with G. Kirk, Bethesda, MD, USA; H. Whittle, Fajara, Gambia; O. Sam, Banjul, The Gambia; C.P. Wild, Leeds, UK; I. Chemin, J.-Y. Scoazec, Lyon, France

In regions of high incidence in sub-Saharan Africa and south-eastern Asia, HCC shows a very high prevalence of a characteristic mutation in codon 249 of the *TP53* tumour-suppressor gene. There is evidence that this mutation (AGG to AGT, arginine to serine) occurs as a result of the concerted action of the two main risk factors for HCC in these regions, chronic infection with hepatitis B virus and dietary ingestion of aflatoxin B_1, a potent hepatocarcinogen. Pilot studies have shown that this mutation is often detectable in DNA fragments isolated from plasma of HCC patients in the Gambia. We have extended these studies by analysing plasma DNA for the presence of mutations in large series of specimens collected in eastern China (Qidong) (see above) and in the Gambia.

Studies in the Gambia (Figure 19) are part of a case–control study funded by the United States National Cancer Institute, with over 900 cases and controls. HCC and liver cirrhosis patients were identified at three hospitals and extensive information on biological, clinical and epidemiological parameters was collected. Laboratory studies include determination of HBV and HCV infection status (at the laboratories of the United Kingdom Medical Research Council, Fajara, The Gambia), analysis of several common genetic polymorphisms in candidate susceptibility genes (at the University of Leeds, United Kingdom) and detection of *TP53* mutations in plasma DNA. All components of these studies are now complete. This is the largest molecular study of liver cancer ever performed in Africa. Preliminary results confirm the very strong association of the *TP53* codon 249 mutant in plasma DNA with both HBV- and HCV-positive HCC. Furthermore, this mutant is also detectable in a proportion of patients with liver cirrhosis (up to 20%) as well as in a subgroup of control individuals who are chronic carriers of HBV or HCV (3–5%), suggesting that detection of mutant *TP53* in plasma DNA may be useful for early detection of individuals at high risk of HCC.

Figure 19. Drs Funmi Lesi and Greg Kirk, working on the results of a case–control study in the IARC office of the Gambia Hepatitis Intervention Study (GHIS) at the Medical Research Council laboratories in Fajara, The Gambia

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 several less prevalent types (e.g., 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, to provide essential background information for planning preventive strategies using HPV vaccines already under development (Section 5.1).

Pooled analyses for the multicentre case–control study of cervical cancer

S. Franceschi, N. Muñoz, J. Smith, M. Plummer, A. Arslan; in collaboration with M. Almonte, E. Caceres, Lima, Peru; R. Ashley, Seattle, WA, USA; F.X. Bosch, X. Castellsagué, V. Moreno, Barcelona, Spain; C. Bosetti, Milan, Italy; N. Chaouki, Rabat, Morocco; S. Chichareon, Hat-Yai, Thailand; P. Coursaget, Tours, France; J. Eluf-Neto, São Paulo, Brazil; D. Hammouda, Alger, Algeria; R. Herrero, San José, Costa Rica; C. Ngelangel, Manila, Philippines; R. Peeling, Winnipeg, Canada; T. Rajkumar, Chennai, India; P.A. Rolón, Asunción, Paraguay; M. Santamaria, Pamplona, Spain; P. Snijders, Amsterdam, Netherlands

Case–control studies to investigate the role of specific HPV types and its cofactors in the etiology of cervical cancer have been completed in Algeria, Brazil, India, Mali, Morocco, Paraguay [382], Peru [397], Philippines and Thailand, in addition to the studies in Spain and Colombia [442]. These allow estimation of the prevalence of 33 HPV types in more than 2000 cases of cervical carcinoma, which is essential information in order to prioritize the HPV types to be targeted by future vaccines (Figure 20).

In order to obtain more precise risk estimates for various HPV types and possible cofactors, we pooled the data from eight case–control studies of histologically confirmed squamous-cell invasive cervical carcinoma and two studies of carcinoma *in situ*. Most of the analyses were restricted to a total of 1676 cases (1465 invasive and 211 *in situ*) and 255 controls who were HPV DNA-positive, corresponding to 94% of the invasive carcinoma cases, 72% of the cases of carcinoma *in situ* and 11% of the controls combined. This has permitted evaluation of the role of factors possibly contributing to cervical cancer development exclusively among 'at-risk' women (i.e., those who were HPV carriers).

Use of oral contraceptives (OCs) for less than five years was not associated with increased cancer risk [297]. Odds ratios (ORs) of 2.8 and 4.0 were associated with use of OCs for 5–9 years and for 10+ years, respectively (Figure 21). The increased risk among long-term OC users did not vary according to time since first or last use. OC use was not associated with HPV DNA-positivity among control women. These findings need to be confirmed in populations where long-term OC use is more frequent than in our study, but it seems clear that long-term users of OCs deserve special attention in cervical screening programmes [297].

A direct association between number of full-term pregnancies and squamous-cell cancer risk was also found: the OR for seven or more full-term pregnancies was 3.8 relative to nulliparous women and 2.2 to women with one or two full-term pregnancies. For adeno- or adenosquamous invasive cervical carcinoma, parous women had a non-significant three-fold increased risk compared with nulliparae, but no trend in risk with number of pregnancies was found. Hence, the secular decline in parity may partly explain the reduction in cervical cancer seen in countries where effective screening programmes have not been implemented.

Among control participants, the prevalence of serum antibodies against herpes simplex virus 2 (HSV-2) (detected by western blot) ranged from 9.2% in the Philippines to 56.9% in Colombia [249, 443]. Among HPV DNA-positive cases

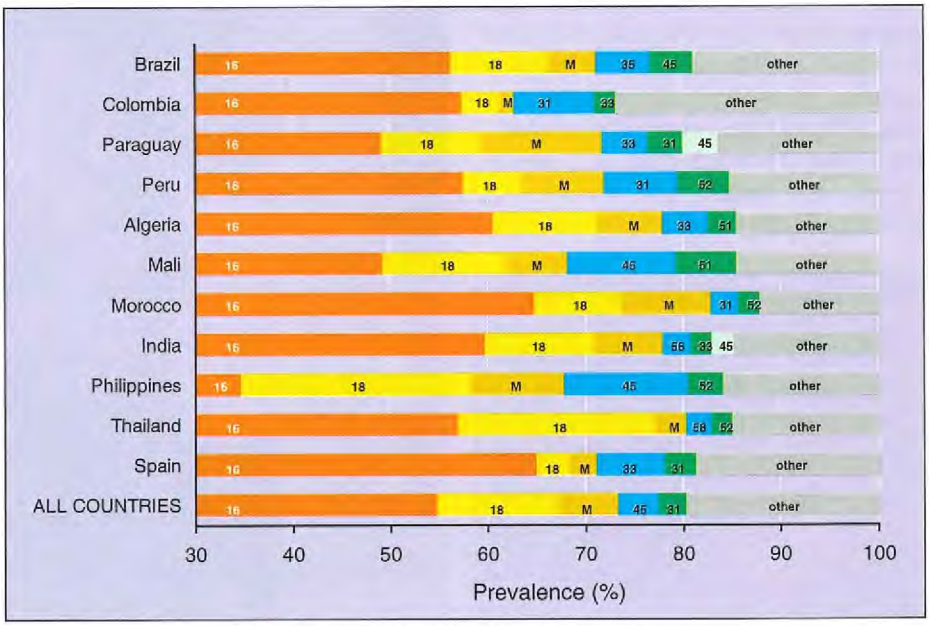


Figure 20. The most common HPV types in cervical carcinoma biopsies by country
M = multiple infections with 16 and/or 18

and controls, HSV-2 seropositivity was associated with increased risk of squamous-cell cervical carcinoma (OR = 1.7; 95% CI 1.1–2.6), after controlling for various confounding variables. Presence of HSV-2 antibodies was also associated with an increased risk of adenocarcinoma/adenosquamous carcinoma (OR = 2.4). In countries where HSV-2 seroprevalence was low among control participants (Spain and Philippines), HSV-2 seropositivity was more clearly associated with invasive cancer than in those where the majority of the women were seropositive (Colombia and Brazil).

Chlamydia trachomatis seropositivity (evaluated by means of a micro-immunofluorescence assay) was higher among invasive cervical cancer cases (52.1%) than among controls (30.8%). In the pooled analysis of women positive for HPV DNA, the risk of squamous-cell cervical carcinoma was moderately elevated among women who were *C. trachomatis*-seropositive (OR = 1.6; 95% CI 1.1–2.4), after adjustment for potential confounders [444]. There was also an indication of increasing cancer risk with increasing *C. trachomatis* antibody titre.

Overall, past infection with HSV-2 and *C. trachomatis* seems to be associated with invasive cervical carcinoma among women positive for cervical HPV DNA. Any effect of HSV-2 and *C. trachomatis* infection, however, appeared to be modest compared with the strong effect of HPV [444].

There was an excess risk for cervical cancer associated with ever having smoked among HPV-positive women (OR = 2.2; 95% CI 1.5–3.2). When results were analysed by histological type, an excess risk was observed for squamous-cell carcinoma among current smokers and ex-smokers. There were too few adenocarcinomas for separate analysis.

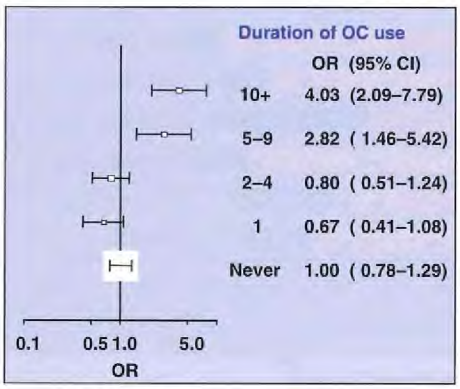


Figure 21. Odds ratio of squamous-cell carcinoma of the cervix by duration of oral contraceptive use

Cohort study on HPV, hormonal contraception and cervical neoplasia

N. Muñoz, S. Franceschi, E. Weiderpass, M. Plummer, A. Arslan; in collaboration with H. Posso, C. Camargo, C. Molina, O. Orozco, Bogotá, Colombia; K. Shah, Baltimore, MD, USA; A. van den Brule, M. Molano, Amsterdam, Netherlands

This cohort study was initiated in 1993 in Bogotá, Colombia (Figure 22), 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.

A total of 2139 eligible women were contacted, of whom 2011 had samples tested for HPV DNA and 1859 had normal cervical cytology. 1845 answered a questionnaire interview regarding sexual, reproductive and lifestyle characteristics. We tested for HPV using a polymerase chain reaction (PCR)-based assay, identifying 37 HPV types. We defined as high-risk (HR) types HPV 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and Iso 39 and as low-risk (LR) types HPV 6, 11, 40, 42, 43, 44, 54, 55, 57, 61, 70, 72, MM4, MM7, MM8, CP8061, CP6108 and CP8304.

Thirty-two different HPV types were detected, HPV 16, 58, 56, CP8304 and 18 being the most common. The overall HPV DNA prevalence was 16.4%. Among women with normal cytology (i.e., 95% of study women), 14.8% were infected with HPV: 9% with HR types, 3.1% with LR types, 2.3% with both types and 0.4% with uncharacterized types (HPV X). 29.7% of HPV-positive women had multiple infections. The age-specific HPV prevalence was 26.1% among women younger than 20 years, 2.3% in women aged 45–54 years and 13.2% in women aged 55 or more years.

Thus, in our study population, cervical HPV infection is frequent. The prevalence of HPV infection was particularly high among teenagers and postmenopausal women. High educational level and use of hormonal contraception were associated directly with risk of HPV infections. Among those

Figure 22. Collaborators at the National Cancer Institute, Bogotá, Colombia

infected, it was common that at least two HPV types were present in the cervix.

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

S. Franceschi, J. Smith, A. Arslan, S. Vaccarella, N. Muñoz; *in collaboration with* P.T.H. Ahn, Hanoi, Viet Nam; R. Ashley, Seattle, WA, USA; P. Coursaget, Tours, France; R.C. Ferreccio, Washington DC, USA; R. Herrero, San José, Costa Rica; N.T. Hieu, Ho Chi Minh City, Viet Nam; E. Lazcano, Cuernavaca, Mexico; E. Matos, G. Amestoy, Buenos Aires, Argentina; H. Posso, Bogotá, Colombia; G. Ronco, Turin, Italy; S. de Sanjosé, Barcelona, Spain; K.V. Shah, Baltimore, MD, USA; H.R. Shin, Pusan, Republic of Korea; P. Snijders, C. Meijer, Amsterdam, Netherlands; S. Sukvirach, Bangkok, Thailand; J.O. Thomas, Ibadan, Nigeria

HPV is now considered the central cause of cervical neoplasia [54, 142, 151, 298]. Given the strength of the association, with risk estimates often in the hundreds, and the marked regional variations in the incidence of cervical cancer, it has been postulated that the prevalence of HPV infection in certain segments of the population may be the most important correlate of the incidence of cervical cancer in a specific country or region.

To investigate the age-specific prevalence of HPV infection and its immunological correlates in different geographical regions, we are carrying out a series of surveys in age-stratified random samples of the female population in areas with different incidence rates of cervical cancer. The population-based nature of the studies will allow investigation of the prevalence of a series of life-style factors (e.g., sexual and reproductive behaviour, contraceptive use, smoking, alcohol, cervical cytological screening habits) as well as the prevalence of markers of past or current exposure to other sexually transmitted diseases. 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. Antibodies against HSV-1 and -2 and *C. trachomatis* in blood samples are also assessed. The study has been completed in Hanoi and Ho Chi Minh City, Viet Nam; Lampang and Songkhla, Thailand; Pusan, Republic of Korea; Concordia, Argentina [277]; Morelos State, Mexico [246, 249, 250]; Barcelona, Spain; and Ibadan, Nigeria. Fieldwork is still in progress in Santiago, Chile and Turin, Italy. In Thailand, study women were re-examined in 2001 and will be followed up for at least one more year. The baseline data from our cohort study in Bogotá, Colombia will also represent a prevalence survey to add to this series.

HPV testing is being conducted at the laboratory of Professor Meijer and Dr Snijders, by means of PCR-based assays using GP5+/6+ primers, and determination of antibodies against L1 HPV virus-like particles (VLPs) of HPV types 16, 18 and 31 is being carried out at Dr Coursaget's laboratory. The evaluation of antibodies against HSV-1 and -2 and *C. trachomatis* is performed in the laboratory of Dr Ashley.

Cervical cancer incidence in participating areas ranges from about 9 per 100 000 women in Spain (age-standardized incidence rate) to 45 per 100 000 women in Mexico and overall prevalence of cervical HPV infection correlates with cervical cancer incidence. Different age patterns are observed: in some areas, such as Lampang, Thailand and Argentina, prevalence of HPV detection declines consistently after age 20–25 years, while in others, including Colombia, Costa Rica and Mexico, some increase in HPV detection is observed after menopause. High-risk HPV types are the most commonly detected in all areas, but the relative prevalence of low-risk types tends to increase with age. These different age patterns may in part be cohort effects associated with changes in sexual behaviour. They also suggest a possibility of reactivation or increased detectability of HPV infections after menopause.

In Thailand, it has been possible to compare HPV prevalence in two areas with different age-standardized incidence rates of cervical cancer. The prevalence of abnormal cytology was 5% in Lampang, and 2.3% in Songkhla. Among cytologically normal women, a higher prevalence of HPV DNA was found among women in Lampang (5.7%) than in Songkhla (3.3%). In Lampang, HPV DNA prevalence decreased from 10.7% among women aged < 25 years to 1.7% among women over 65 years of age. In Songkhla, HPV prevalence peaked at ages 25–34 years (6.4%), declined thereafter, but increased again above 65 years (6.3%). Overall, of 79 HPV-positive women, 60 had single type infections. HPV types most commonly found as single infections were HPV 72, 16, 70 and CP 8304. HPV DNA prevalence was significantly higher among women who were HSV-2-seropositive, reported a history of sexually transmitted diseases, had a history of condom use or reported that their husband had other sexual partners or contact with prostitutes.

Genital papillomavirus infection in men

S. Franceschi, J. Smith, N. Muñoz; *in collaboration with* X. Castellsagué, F.X. Bosch, Barcelona, Spain; L. Dal Maso, Aviano, Italy; R. Herrero, San José, Costa Rica; E. Lazcano, Cuernavaca, Mexico; K.V. Shah, Baltimore, MD, USA; P. Snijders, C. Meijer, Amsterdam, Netherlands

The importance of the 'male factor' in the etiology of cervical carcinoma in women was suggested years before sexual transmission of HPV was identified as the central cause of this tumour. Close correlations have been reported between the frequency of cervical cancer and penile cancer in either populations or individual couples. However, progress in defining the prevalence and natural history of HPV infection in men has been slow. The collection of penile specimens by brushing the penile surface and urethra is not well accepted by men and often yields few exfoliated cells. Other sampling methods (e.g., search for HPV in urine samples and sperm) have not been found satisfactory [249].

We analysed data from 1921 couples enrolled in five case–control studies of

invasive cervical cancer and two of cervical carcinoma *in situ*, carried out in Brazil, Colombia, Philippines, Spain and Thailand. Exfoliated cells from the woman's cervix and the man's glans and distal urethra were collected for HPV DNA detection using PCR-based systems.

'Current partner' (referred to as husband in the following) was defined as a man having had sexual intercourse with the index case of cervical carcinoma or control women for at least six months. The prevalence of penile HPV infection was 13.1% among the husbands of control women, 17.5% among those of invasive carcinoma cases and 21.2% among those of cases of carcinoma *in situ*. The agreement between husbands and wives in HPV infection of any type or of the commonest specific types (i.e., HPV 16 and 18) was no better than expected by chance.

The prevalence of penile HPV varied by country from 5% in the Philippines to 39% in Brazil but moderately according to the number of lifetime sexual partners (OR for ≥ 51 versus 1 sexual partner = 2.3). Age, smoking habits and age at first sexual intercourse were unrelated to penile HPV infection. Male circumcision conferred a 63% reduction in the risk of penile HPV infection. The protective effect was particularly strong in men reporting 'high-risk' sexual behavior. As a protective effect has been noted among circumcised men for other sexually transmitted infections (notably HIV), circumcision may deserve evaluation as a simple, inexpensive intervention against sexually transmitted diseases and related complications.

3.5 Brain tumours

Glioblastoma (WHO grade IV) may develop *de novo* (primary glioblastomas) or by progression from low-grade or anaplastic astrocytoma (secondary glioblastomas). These glioblastoma subtypes constitute distinct disease entities that evolve through different genetic pathways (Figure 23), affect patients at different ages and are likely to differ in prognosis and response to therapy [221, 320]. The Unit of Molecular Pathology has also carried out genetic profiling of rare glioblastoma variants, gliosarcomas and giant cell glioblastomas [220].

Low-grade diffuse astrocytoma (WHO grade II) is a well differentiated, slowly growing tumour, but has an inherent tendency to progress to anaplastic astrocytoma (WHO grade III) and glioblastoma. Little is known about its molecular basis except that mutations of the *TP53* tumour-suppressor gene are found in > 60% of cases. The factors determining the kinetics of malignant progression of low-grade diffuse astrocytomas are still poorly understood [320]. The Unit has started to search for additional genetic alterations in low-grade astrocytomas using cDNA arrays.

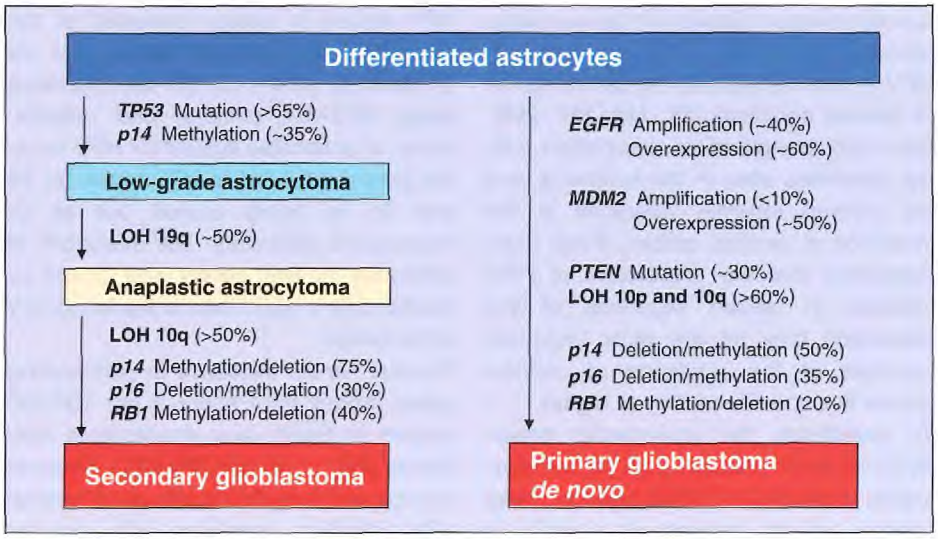


Figure 23. Genetic pathways leading to primary (*de novo*) and secondary glioblastomas

Genetic alterations in human astrocytic brain tumours

Loss of heterozygosity in primary and secondary glioblastomas

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We have examined primary and secondary glioblastomas for deletions on chromosomes 10, 19, 13 and 1 using PCR-based microsatellite analysis. Loss of heterozygosity (LOH) at chromosome 10 was seen at similar frequency in primary (47%) and secondary glioblastomas (54%); in primary glioblastomas this appeared to correspond to loss of the entire chromosome 10, while in secondary glioblastomas there was partial or complete loss of chromosome 10q but no loss of 10p [158]. LOH on chromosome 19q was frequent in secondary glioblastomas (54%), with a common 19q13.3 deletion, but rare in primary glioblastomas (6%), suggesting that tumour-suppressor gene(s) located on chromosome 19q are frequently involved in the progression from low-grade astrocytoma to secondary glioblastoma, but do not play a major role in the evolution of primary glioblastomas. LOH on chromosome 1p was detected in 12% of primary and 15% of secondary glioblastomas. LOH on 13q was detected in 12% of primary and in 38% of secondary glioblastomas and typically included the *RB1* locus. Except for one case, LOH 13q and 19q were mutually exclusive [304].

Promoter hypermethylation of the RB1, p14^{ARF} *and* p16^{INK4a} *genes in primary and secondary glioblastomas*

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Loss of expression of the retinoblastoma gene (*RB1*) has been shown to occur in up to 25% of glioblastomas. To elucidate the mechanism underlying this process, we assessed *RB1* promoter hypermethylation using methylation-specific PCR and *RB1* expression by immunohistochemistry in primary and secondary glioblastomas. Promoter hypermethylation was significantly more frequent in secondary (43%) than in primary glioblastomas (14%). There was a clear correlation between loss of *RB1* expression and promoter hypermethylation. In the majority of glioblastomas lacking *RB1* expression, there was promoter hypermethylation (85%), while 93% of tumours with *RB1* expression had normal *RB1* gene status. In three glioblastomas, areas with and without *RB1* expression were microdissected; promoter hypermethylation was detected only in areas lacking *RB1* expression (Figure 24). In patients with multiple biopsies, methylation of the *RB1* promoter was not detectable in the less malignant precursor lesions, i.e., low-grade diffuse and anaplastic astrocytoma. These results indicate that promoter hypermethylation is a late event during astrocytoma progression and is the major mechanism underlying loss of *RB1* expression in glioblastomas [305].

The *CDKN2A* locus on chromosome 9p21 contains the *p14^{ARF}* and *p16^{INK4a}* genes and is frequently deleted in human neoplasms, including brain tumours. We assessed homozygous deletion, promoter hypermethylation and loss of expression of these genes in primary and secondary glioblastomas. A total of 29 glioblastomas (58%) had a *p14^{ARF}* homozygous deletion or methylation, and 17 (34%) showed *p16^{INK4a}* homozygous deletion or methylation. Loss of *p14^{ARF}* expression in the majority of glioblastomas (76%), assessed by immunohistochemistry, was correlated with the gene status, i.e., homozygous deletion or promoter hypermethylation. There was no significant difference in the overall frequency of *p14^{ARF}* and *p16^{INK4a}* alterations between primary and secondary glioblastomas. Analysis of multiple biopsies from the same patients revealed hypermethylation of *p14^{ARF}* (5/15 cases) and *p16^{INK4a}* (1/15 cases) even in low-grade diffuse astrocytomas but an absence of homozygous deletions [302].

Promoter methylation of the DNA repair gene MGMT *and* TP53 *gene mutations in astrocytomas*

M. Nakamura, T. Watanabe, P. Kleihues, H. Ohgaki; in collaboration with Y. Yonekawa, Zürich, Switzerland

O^6-Methylguanine-DNA methyltransferase (MGMT) is a repair protein that specifically removes promutagenic alkyl groups from the O^6 position of guanine in DNA. Repair of O^6-alkylguanine adducts by tumour cells has been implicated in drug resistance, since it reduces the cytotoxicity of alkylating chemotherapeutic agents. We detected methylation of the *MGMT* gene promoter, assessed by methylation-specific PCR, in 26 of 54 (48%) low-grade diffuse astrocytomas and in 12 of 16 (75%) of secondary glioblastomas. The frequency was significantly lower in primary *(de novo)* glioblastomas (36%). The majority of low-grade astrocytomas with *MGMT* methylation (92%) contained a *TP53* mutation, whereas only 39% of cases without *MGMT* methylation carried a *TP53* mutation. Furthermore, G:C→A:T transition mutations at CpG sites were significantly more frequent in low-grade astrocytomas with *MGMT* methylation (58%) than in those without (11%). These results suggest that loss of *MGMT* expression due to promoter methylation frequently occurs at an early stage in the pathway leading to secondary glioblastomas and appears to be associated with increased frequency of *TP53* mutations, in particular G:C→A:T transitions [303].

Genetic profile of the gliosarcoma

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Gliosarcoma is a rare glioblastoma variant characterized by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation. Analysis of

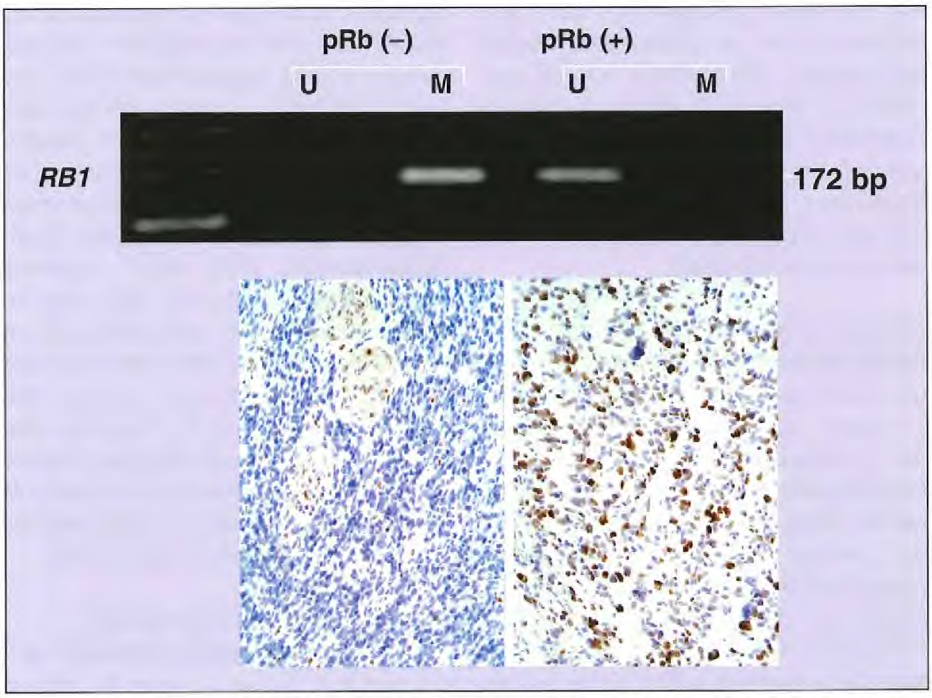

Figure 24. Methylation-specific PCR of CpG islands of the *RB1* promoter in a glioblastoma. Note that *RB1* methylation (M) is restricted to areas lacking pRB immunoreactivity.

19 gliosarcomas revealed a genetic profile similar to that of primary glioblastomas, except for the absence of *EGFR* amplification or overexpression. Identical genetic alterations (*PTEN* and *TP53* 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 [369].

Second primary glioblastoma

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Although characterized by a highly variable phenotype and multiple genetic alterations, glioblastomas are considered monoclonal in origin. We have analysed tumours from a 64-year-old patient who developed a second glioblastoma in the left frontal lobe 10 years after surgical resection of a glioblastoma of the right frontal lobe. The first tumour contained two *TP53* mutations, one missense *PTEN* mutation and a silent *PTEN* mutation. The second glioblastoma also contained multiple but different *TP53* and *PTEN* mutations. The discordant pattern of mutations indicates that the second glioblastoma was not a recurrence but an independent second glioblastoma. The presence in these neoplasms of multiple mutations in tumour-suppressor genes suggests the involvement of a novel disease mechanism, but there was no indication of a DNA mismatch repair deficiency or an inherited tumour syndrome [368].

Mutations of hBUB1, hBUBR1 and hBUB3 genes in glioblastomas

R.M. Reis, M. Nakamura, J. Masuoka, T. Watanabe, S. Colella, P. Kleihues, H. Ohgaki; in collaboration with Y. Yonekawa, Zürich, Switzerland

Glioblastomas, the most malignant human brain tumours, are characterized by marked aneuploidy, suggesting chromosomal instability which may be caused by a defective mitotic spindle checkpoint. We screened 22 glioblastomas for mutations in the mitotic spindle checkpoint genes *hBUB1*, *hBUBR1* and *hBUB3*. DNA sequencing revealed silent mutations of *hBUB1* and *hBUBR1* in several glioblastomas. We also observed polymorphisms in *hBUBR1* and *hBUB3* with frequency similar to those in healthy Caucasians. Screening of *hBUB1* in 18 cases of giant cell glioblastoma, a variant characterized by a predominance of bizarre, multinucleated giant cells, revealed no changes except for a silent mutation at codon 144 in two cases. These results suggest that mutations in these mitotic spindle checkpoint genes do not play a significant role in the causation of chromosomal instability in glioblastomas [370].

Mutations and expression of protein phosphatase 2A subunits in human gliomas

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Protein phosphatase 2A (PP2A) consists of three subunits, the catalytic subunit, C, and two regulatory subunits, A and B. The A and C subunits both exist as two isoforms (α and β) and the B subunit as multiple forms subdivided into three families, B, B' and B''. It has been reported that the genes encoding the Aα and Aβ subunits are mutated in various human cancers, suggesting that they may function as tumour suppressors. We have used SSCP analysis and DNA sequencing to look for Aα and Aβ mutations in 58 brain tumours, including glioblastomas, oligodendrogliomas and anaplastic oligodendrogliomas. Only silent mutations were detected in the Aα gene and no mutations in the Aβ gene. However, in 43% of the tumours, the level of Aα was reduced at least 10-fold, although the levels of the Bα and Cα subunits were mostly normal. These analyses indicate that the tumours contain very low levels of core and holoenzyme and high amounts of unregulated catalytic C subunit [96].

Invasiveness in vitro *and biological markers in human primary glioblastomas*

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Invasion of spheroids from 20 human primary glioblastomas into recultured fetal rat brain tissue in culture has been studied and quantified. From 30 to 98% of the normal brain tissue was destroyed by invading glioma cells within four days. The degree of invasion did not correlate with patient survival. Slightly higher invasiveness and shorter survival were seen for tumours with *EGFR* overexpression, and the opposite pattern for tumours with a *TP53* mutation. The degree of invasiveness *in vitro* was far higher than would be expected from the dynamics of clinically observed tumour spread. This suggests that mechanisms suppressing invasion may be operative in the normal brain; alternatively the differences may be due to a higher permissiveness of the fetal brain tissue for invasion *in vitro* [241].

Genetic evidence of the neoplastic nature of gemistocytes in astrocytomas

R.M. Reis, A. Hara, P. Kleihues, H. Ohgaki

Gemistocytic astrocytoma is characterized by a predominance of large astrocytes with plump processes and massive accumulation of glial fibrillary acidic protein (GFAP) (gemistocytes). This histological variant of low-grade diffuse astrocytoma (WHO grade II) is prone to more rapid progression to anaplastic astrocytoma and glioblastoma than the ordinary fibrillary astrocytoma. The biological basis of this unfavourable prognosis is unclear, since gemistocytes have low proliferative activity, even if present in anaplastic astrocytomas or glioblastomas. This raised the question of whether gemistocytes are neoplastic cells or dysplastic reactive astrocytes. In this study, gemistocytes and non-gemistocytic neoplastic cells were separated by laser-assisted microdissection from six gemistocytic astrocytomas carrying *TP53* mutations. In all cases, identical *TP53* mutations were identified in both cell types, indicating that gemistocytes are indeed neoplastic cells. Their lack of proliferative activity may indicate terminal differentiation [367].

Gene expression profiling of low-grade diffuse astrocytomas by cDNA arrays

H. Huang, S. Colella, P. Kleihues, H. Ohgaki; in collaboration with M. Kurrer, Y. Yonekawa, Zürich, Switzerland

We have examined profiles of gene expression in 11 diffuse astrocytomas using cDNA expression arrays. Expression of six genes (TIMP-3, c-myc, EGFR, DR-nm23, nm23-H4 and GDNPF) was detected in 64–100% of diffuse astrocytomas, but not in non-tumorous brain tissue. Seven genes (AAD14, SPARC, LRP, PDGFR-α, 60S ribosomal protein L5, PTN and hBAP) were up-regulated more than two-fold in 20–60% of cases, while 11 genes (IFI 9-27, protein kinase CLK, TDGF1, BIN1, GAB1, TYRO3, LDH-A, adducin 3, GUK1, CDC10 and KRT8) were down-regulated to less than 50% of normal levels in 64–100% of cases (Figure 25). Semi-quantitative conventional RT-PCR was performed for 11 genes, of which nine showed an expression profile similar to that obtained with cDNA expression arrays. Immunohistochemical staining for SPARC showed cytoplasmic immunoreactivity of neoplastic cells in all diffuse astrocytomas analysed. These results indicate significant changes in gene expression in diffuse astrocytomas, but it remains to be shown which of these are causally related to the transformation of glial cells [188].

Genetic alterations in non-astrocytic brain tumours

Promoter hypermethylation and homozygous deletion of the $p14^{ARF}$ *and* $p16^{INK4a}$ *genes in oligodendrogliomas*

T. Watanabe, M. Nakamura, P. Kleihues, H. Ohgaki; in collaboration with Y. Yonekawa, Zürich, Switzerland

The *INK4a/ARF* locus containing $p14^{ARF}$ and $p16^{INK4a}$ genes on chromosome 9p21 is deleted in up to 25% of oligodendrogliomas and 50% of anaplastic oligodendrogliomas, but little is known on the frequency of gene silencing by DNA methylation. We found hypermethylation of the $p14^{ARF}$ gene promoter in 6/29 (21%) oligodendrogliomas (WHO grade II) and in 3/20 (15%) anaplastic oligodendrogliomas (WHO grade III). None of the oligodendrogliomas and only one out of 20 anaplastic oligodendrogliomas showed hypermethylation of $p16^{INK4a}$. Homozygous deletion was not detected in any of the WHO grade II oligodendrogliomas but was present in 25% of anaplastic

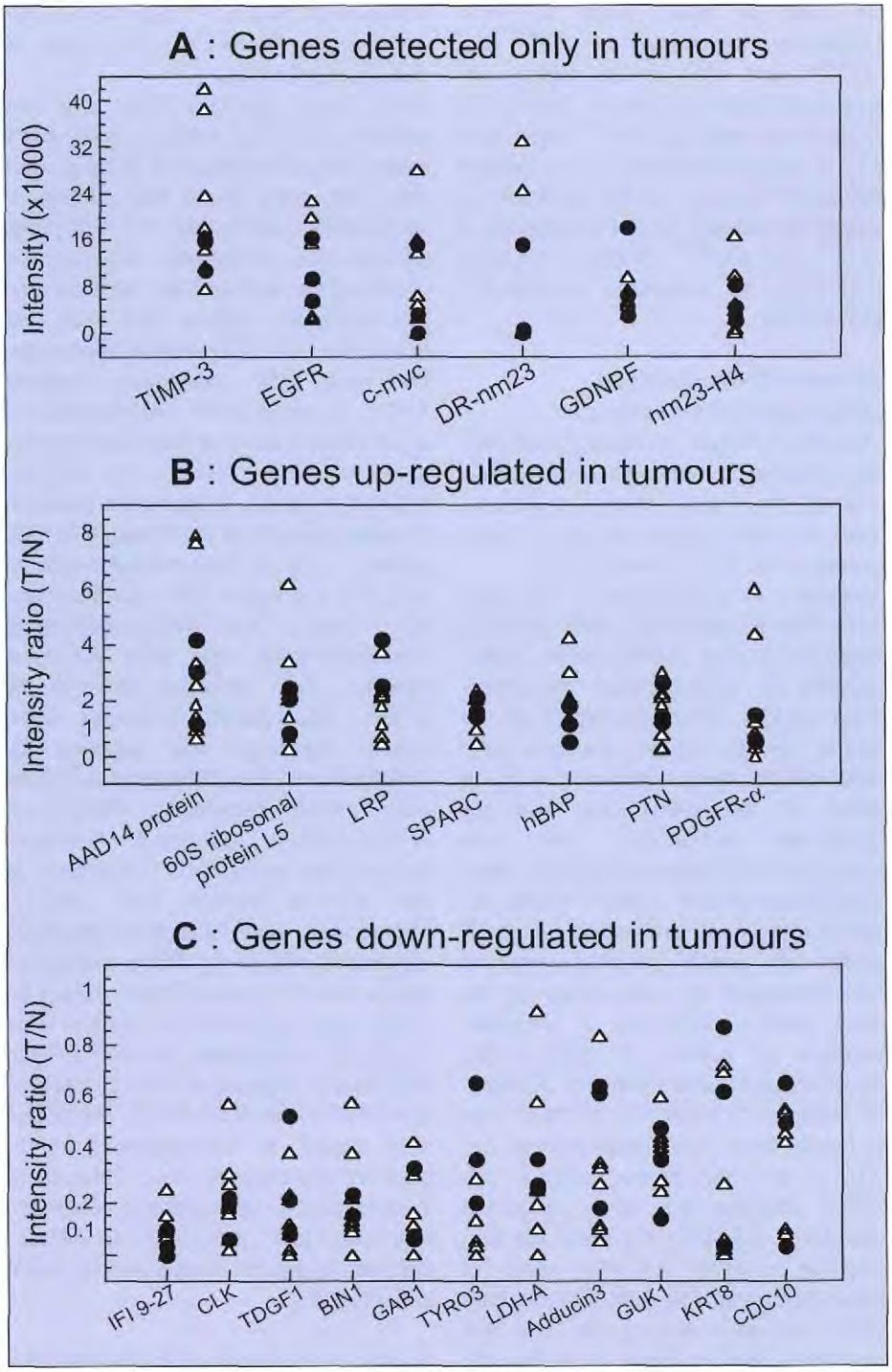

Figure 25. Expression array data presented as net intensity in tumours (A), or as intensity ratio T/N of tumour (T) to non-tumorous tissue (N) (B and C). Each spot represents data obtained from one tumour. Filled circles, tumours with wild-type p53; triangles, tumours with mutant p53. Note the heterogeneity of gene expression among low-grade astrocytomas and the absence of significant differences between tumours with and without *TP53* mutation.

oligodendrogliomas and always affected both genes. In one tumour containing distinct areas with and without anaplasia, $p14^{ARF}$ hypermethylation was detected in the area of WHO grade II, while homozygous co-deletion of $p14^{ARF}$ and $p16^{INK4a}$ was seen in the region with anaplastic features (grade III). These data suggest that aberrant $p14^{ARF}$ expression due to hypermethylation is the earliest *INK4a/ARF* change in the evolution of oligodendrogliomas, while the presence of $p14^{ARF}$ and $p16^{INK4a}$ deletions indicates progression to anaplastic oligodendroglioma [518].

Germline SDHD *mutation in paraganglioma of the spinal cord*

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Hereditary paraganglioma of the head and neck is associated with germline mutations in the *SDHD* gene, which encodes a mitochondrial respiratory chain protein. Paragangliomas of the central nervous system are very rare, occur almost exclusively in the cauda equina of the spinal cord and are considered non-familial. We have screened 22 apparently sporadic paragangliomas of the cauda equina for *SDHD* mutations. One spinal paraganglioma and similar cerebellar tumours that developed 22 years later in the same patient contained a missense mutation at codon 12 (GGT→AGT, Gly→Ser) and a silent mutation at codon 68 (AGC→AGT, Ser→Ser). There was no family history of paragangliomas, but DNA from white blood cells of this patient showed the same sequence alterations, indicating the presence of a germline mutation. All other cases of spinal paraganglioma had the wild-type *SDHD* sequence, except one case with the same silent mutation at codon 68. This is the first observation indicating that inherited *SDHD* mutations can cause the development of paragangliomas in the central nervous system [275].

Mechanisms of apoptosis in human brain tumours

APO2L/TRAIL expression in human brain tumours

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APO2 ligand (APO2L)/TRAIL is a new member of the TNF cytokine family and a potent inducer of apoptosis in tumour cell lines. We have found that APO2L is consistently expressed in low-grade astrocytomas, anaplastic astrocytomas, glioblastomas and derived cell lines, and that malignant glioma cell lines are susceptible to APO2L-induced apoptosis. We have now investigated whether APO2L is expressed in medulloblastoma or neuroblastoma cell lines and whether these cells are sensitive to APO2L-induced apoptosis. Immunoblot analyses revealed expression of full-length APO2L protein in one of three medulloblastoma cell lines but not in two neuroblastoma cell lines. The APO2L-expressing medulloblastoma cells were the most sensitive and apoptosis induced by APO2L was greatly enhanced when protein synthesis was inhibited by cycloheximide. Neuroblastoma cell lines were almost completely resistant to APO2L-induced apoptosis. Immunohistochemical analysis of 115 tumours of the nervous system with different histogenesis and biological behaviour revealed a pattern of APO2L expression largely similar to that of GFAP, except for choroid plexus tumours and three of eight anaplastic meningiomas, in which APO2L was focally expressed without concomitant GFAP expression. APO2L expression was absent in meningiomas, neurocytomas and schwannomas. Thus, there is considerable heterogeneity of APO2L expression and susceptibility to APO2L-induced apoptosis among human brain tumours [301].

Soluble decoy receptor 3 is expressed by malignant gliomas and suppresses CD95 ligand-induced apoptosis and chemotaxis

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Decoy receptor (DcR3) is a newly identified soluble protein that binds to CD95 ligand (CD95L) and inhibits its proapoptotic activity. The presence of DcR3 correlates with the grade of malignancy: 15 of 18 (83%) glioblastomas but none of 11 low-grade diffuse astrocytomas exhibited DcR3 immunoreactivity. We found that human malignant glioma cells engineered to release high amounts of DcR3 into the cell culture supernatant are protected from CD95L-induced apoptotic cell death. In contrast, DcR3 does not confer protection from the death ligand APO2 ligand (TRAIL). Ectopic expression of DcR3 in a rat gliosarcoma model caused substantially altered immune cell infiltration, with greatly decreased infiltration of $CD4^+$ and $CD8^+$ T cells as well as microglia/macrophages into glioma in DcR3-producing tumours compared with control tumours. Chemotaxis assays revealed that DcR3 counteracts the chemotactic activity of CD95L against microglial cells *in vitro*. These findings suggest that DcR3 may be involved in the progression and immune evasion of malignant gliomas [383].

Environmental and hereditary factors

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

H. Ohgaki, H. Huang, H. Vainio, P. Kleihues; in collaboration with M. Haltia, Helsinki, Finland

We have analysed 13 glioblastomas, 10 ependymomas and 7 choroid plexus papillomas from patients in Finland, a country where polio vaccine contaminated with simian virus 40 (SV40) was not used. Using a highly specific and sensitive PCR-hybridization method established in our laboratory, we failed to detect SV40 sequences in any brain tumour from Finland, while 25–56% of brain tumours from Switzerland contained SV40 sequences. This strongly suggests that SV40 in human brain tumours originates from SV40-contaminated polio vaccine, and that SV40 is able to spread vertically in human populations, so that it is now commonly present even 40 years after cessation of the use of SV40-contaminated polio vaccine.

Because of the large number of people involved, the etiological role of SV40 in human cancers needs to be carefully investigated. However, no increase in the incidence of brain tumours has been reported in populations that received SV40-contaminated polio vaccine, and incidence rates for brain tumours are similar in countries that did (Switzerland, United States) or did not (Finland) use SV40-contaminated vaccine. Thus, the evidence speaks against a causative role of SV40 in the development of human brain tumours. Instead, its presence probably reflects a bystander infection due to an intra-tumoural microenvironment that favours viral replication in humans with latent SV40 infection [319].

TP53 germline mutations and Li–Fraumeni syndrome

H. Ohgaki, P. Hainaut, P. Kleihues

Analysis of 805 tumours in 143 families with a *TP53* germline mutation reported from 1990 to 1998 shows that breast cancers are most frequent (20.7%), followed by sarcomas (18.6%) and brain tumours (13.5%). 69 kindreds (48.3%) had at least one family member with a brain tumour. Several of the families showed a remarkable clustering of brain tumours. Of the 109 brain tumours recorded, 61 (59%) had been classified histologically, and of these, 39 (64%) were of astrocytic origin, including low-grade astrocytomas, anaplastic astrocytomas, glioblastomas, oligoastrocytomas and gliosarcomas.

Intracranial and spinal tumours in patients with Down syndrome

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Brain tumours in patients with Down syndrome are rarely reported and their behaviour is not well known. In a male patient aged 19 years with Down syndrome, a diffuse astrocytoma (WHO grade II) recurred twice despite treatment, leading to a glioblastoma and, finally, to death in just over two years. A review of literature on brain tumours in Down syndrome patients revealed only 36 patients with brain neoplasms and two spinal tumours. The distribution of histological tumour types, with overrepresentation of germ-cell and mesenchymal tumours and a lack of embryonal tumours, was unusual, but consistent with the known tumour profile of Down syndrome patients. Cerebral tumours in patients with Down syndrome have a specific distribution and may behave differently compared with those in the general population. These features may be related to the gene dosage effect of oncogenes, anti-oncogenes and genes involved in cerebral development due to the supernumerary chromosome 21 [419].

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 the detailed aspects of the carcinogenic effect of tobacco smoking and the modification of risk due to polymorphism of metabolic enzymes.

Environmental risk factors and genetic susceptibility to bladder cancer in Italy

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

500 cases of bladder cancer and matched controls have been recruited at two hospitals in Brescia, to assess the interaction between environmental and occupational exposure to bladder carcinogens and polymorphisms of metabolic enzymes. Data collection was completed in 2000 and laboratory analyses were completed in 2001; the statistical analysis will be completed in 2002.

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

P. Boffetta, P. Brennan, A. 't Mannetje; in collaboration with U. Bolm-Audorff, Wiesbaden, Germany; J. Chang-Claude, J. Wahrendorf, Heidelberg, Germany; S. Cordier, Rennes, France; F. Donato, Brescia, Italy; E. Greiser, W. Schill, Bremen, Germany; M. Hours, Lyon, France, K.-H. Jöckel, Essen, Germany; M. Kogevinas, C. Serra, Barcelona, Spain; G. Lopez-Abente, Madrid, Spain; A. Tzonou, Athens, Greece; 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 has been established and analyses have been conducted on aspects of tobacco carcinogenesis that cannot be properly addressed in individual studies. Bladder cancer risk increased up to consumption of 20 cigarettes per day, while above that level there was no apparent further increase [512]. The carcinogenic effect of tobacco smoking in women was similar to that observed in men [70, 71]. The risk among cigar and pipe smokers was increased, albeit to a smaller degree than that among cigarette smokers; this result can be attributed to lower overall tobacco consumption in the former group (Figure 26) [358].

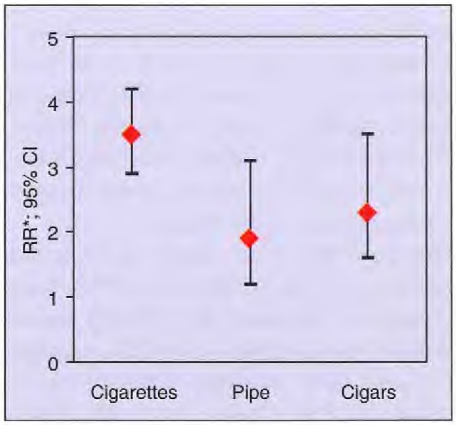

Figure 26. Relative risk of bladder cancer among smokers of one type of tobacco product

* Relative risk adjusted for study, age, and exposure to occupational agents

Multicentre case–control study of kidney cancer in central and eastern Europe

P. Brennan, P. Boffetta, A. 't Mannetje, N. Travier; in collaboration with V. Bencko, Prague, Czech Republic; W.-H. Chow, Washington, DC, USA; J. Fevotte, Lyon, France; A. Fletcher, London, UK; L. Foretova, Brno, Czech Republic; V. Janout, Olomouc, Czech Republic; D. Mates, Bucharest, Romania; N. Szeszenia-Dabrowska, Lodz, Poland; J. Youngson, Liverpool, UK; D.G. Zaridze, Moscow, Russian Federation

Countries of central Europe experience the highest incidence of kidney cancer worldwide. In parallel with a project on lung cancer (see Section 3.7), a case–control study of kidney cancer has been initiated in the Czech Republic, Poland, Romania and the Russian Federation to assess the relative contributions of established risk factors (tobacco smoking, obesity, hypertension) as well as occupational exposures and genetic factors. A total of 1000 cases are being enrolled. The control group partially overlaps with that of the lung cancer project; enrolment of subjects will be completed in 2002.

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.

Lung cancer among non-smokers

P. Boffetta, P. Brennan, S. Lewis, P. Buffler, C. Cohet, J. Hall, M.D. Friesen, G. Ferro; in collaboration with W. Ahrens, Bremen, Germany; A. Andersen, Oslo, Norway; H. Batura-Gabryel, Poznan; S. Benhamou, Villejuif, France; I. Brüske-Hohlfeld, Munich, Germany; V. Constantinescu, Bucharest, Romania; E. Fontham, New Orleans, LA, USA; C. Fortes, Rome, Italy; K. Husgafvel-Pursiainen, Helsinki, Finland; N. Malats, Barcelona, Spain; A. Menezes, Pelotas, Brazil; G. Pershagen, F. Nyberg, Stockholm, Sweden; R. Peto, Oxford, UK; L. Simonato, Padua, Italy; D.G. Zaridze, Moscow, Russian Federation

Results from two large case–control studies, one coordinated by IARC, have shown an increased risk of lung cancer among non-smokers following exposure to involuntary smoking (Boffetta *et al.*, 1998, *J. Natl Cancer Inst.*, **90**, 1440–1450; Fontham *et al.*, 1994, *JAMA*, **271**, 1752–1759). Although these studies each included a large number of subjects, they could not address some detailed aspects of the carcinogenicity of involuntary smoking because of the low risks involved. The data from the two studies were therefore combined in 2001, for a pooled analysis to be complete in 2002.

The data collected within the framework of the IARC study of lung cancer in non-smokers were analysed with respect to low intake of fruit and vegetables [74] and to the interaction between this factor and exposure to environmental tobacco smoke, suggesting independent effects of the two exposures [72]. Furthermore, a detailed review of cancer risk from childhood exposure to environmental tobacco smoke suggested a possible risk of childhood cancer following paternal exposure [46].

In a separate study, blood samples and detailed questionnaire information have been collected from about 250 non-smoking lung cancer cases, 200 smoking lung cancer cases and 250 non-smoking control subjects from Brazil, France, Germany, Italy, Poland, Romania, the Russian Federation and Sweden. Polymorphism of the *GSTM1* gene was associated with a 50% increased risk of lung cancer; this effect was independent from the carcinogenic effect of exposure to environmental tobacco smoke [268]. Analyses of nitrated and oxidized proteins as biomarkers of oxidative stress and chronic inflammation and of genetic polymorphisms in samples from this study are described in Section 4.3. Analysis of *TP53* mutations in groups of smoking and non-smoking cases suggested a higher proportion of cases with mutations among smokers than among non-smokers. In the latter group, however, the proportion was non-significantly higher among subjects exposed to environmental tobacco smoke than among other subjects (Table 5) [191]. Analyses of polymorphisms of genes involved in DNA repair are also in progress.

The Janus biological bank in Norway includes serum samples from over 200 000 blood donors and other healthy individuals, who have provided information on lifestyle factors at the time of enrolment and have been followed up for cancer incidence since the mid-1970s. During 2001, cases of lung cancer were selected and their serum samples will be analysed for cotinine. The results will be compared with self-reported consumption of tobacco and—for non-smokers—with exposure to environmental tobacco smoke.

Table 5. Association between active smoking, involuntary smoking and *TP53* mutations in a case-only study of lung cancer [191]

	TP53 mutation	
	Absent (ref.)	Present
Active smoking		
No	71	9
Yes	34	16
OR (95% CI)	1.0	2.7 (1.1–6.8)
Involuntary smoking[a]		
No	37	3
Yes	36	6
OR (95% CI)	1.0	1.6 (0.3–7.6)

[a] Among non-smokers

OR, odds ratio adjusted for age, gender and centre; CI, confidence interval; ref., reference category

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

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

Data on cases of lung cancer and controls enrolled in 10 western European centres have been combined; the heterogeneity of the effect of tobacco smoking among European countries has been explored [434], as has the risk among women [1]. Analyses are under way to determine which components of tobacco consumption most influence the risk of lung cancer.

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

P. Brennan, P. Boffetta, F. Gemignani, A. 't Mannetje, N. Travier; in collaboration with V. Bencko, Prague, Czech Republic; E. Fabianova, Banska Bystrica, Slovakia; J. Fevotte, Lyon, France; A. Fletcher, London, UK; L. Foretova, Brno, Czech Republic; V. Janout, Olomouc, Czech Republic; D. Mates, Bucharest, Romania; P. Rudnai, Budapest, Hungary; N. Szeszenia-Dabrowska, Lodz, Poland; J. Youngson, Liverpool, UK; D.G. Zaridze, Moscow, Russian Federation; W. Zatonski, J. Lissowska, Warsaw, Poland

Countries of central and eastern Europe experience the highest lung cancer incidence and mortality ever recorded. Air pollution is often blamed as the main contributor to the excess, but the evidence for its role is limited. A study has been initiated in nine areas of the Czech Republic, Hungary, Poland, Romania, the Russian Federation and Slovakia, as well as in Liverpool, United Kingdom, to assess the relative contributions of tobacco smoking, occupational exposures and outdoor air pollution in lung carcinogenesis. More than 3000 cases and a similar number of controls were enrolled during 1998–2001; special efforts are being made to assess past occupational exposures through evaluation of detailed employment histories by panels of local experts. Blood samples have also been collected, for investigation of polymorphisms of metabolic enzymes (see Section 6.1). Tumour samples from cases are collected whenever available, to study genetic alterations following exposure to specific agents.

Multicentre case–control study of lung cancer in India and Pakistan

P. Boffetta, P. Brennan; in collaboration with Y. Bhurgri, Karachi, Pakistan; C.K. Gajalakshmi, Chennai, India; D.H. Jetly, Ahmedabad, India; A. Matthew, Trivandrum, India; U. Sen, Calcutta, India

Although the incidence of lung cancer is increasing in southern Asia, limited information is available on risk factors in these countries, in particular on the role of local tobacco products and other environmental and genetic factors. Following the completion of pilot studies in Karachi, Pakistan, and in Mumbai, Trivandrum and Chennai, India, a case–control study of lung and laryngeal cancer (see Section 3.8) was started in 2000 in Karachi, Pakistan, and in Chennai, Calcutta and Ahmedabad, India, with a main objective of assessing interactions between genetic and environmental factors. Data collection will be completed in 2002, with a total of 1000 lung cancer cases and 1000 controls.

3.8 Head and neck cancer

Tobacco, alcohol and a diet poor in certain micronutrients have been 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 HPV with cervical cancer and other anogenital malignancies suggests that some HPV types could be involved in the etiology of other epithelial tumours. Some studies have indicated a possible role of HPV in the etiology of cancer of the oral cavity and pharynx, particularly for certain tumour sites, notably the tonsils.

Genetic studies of head and neck cancers are described in Section 4.2 and a study of screening for oral cancer is covered in Section 5.3.

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

P. Boffetta, P. Brennan, A. 't Mannetje, N. Travier, E. Weiderpass, S. Franceschi; in collaboration with M.P. Curado, Goiânia, Brazil; A. Daudt, Porto Alegre, Brazil; L. Fernandez, Havana, Cuba; M. Kogevinas, Barcelona, Spain; S. Koifman, Rio de Janeiro, Brazil; E. Matos, Buenos Aires, Argentina; A. Menezes, Pelotas, Brazil; V. Wunsch, J. Eluf-Neto, E. Levi, São Paulo, Brazil

Argentina and southern Brazil experience high incidence rates of laryngeal cancer, which do not seem to be explained only by exposure to known carcinogens such as tobacco smoking and alcohol drinking. A multicentric study of oral and laryngeal cancer is being conducted in five areas of Brazil (Rio de Janeiro, São Paulo, Pelotas, Porto Alegre and Goiânia) and in Buenos Aires, Argentina, in collaboration with an investigation of the role of HPV infection in oral cancer (see below). The study aims to identify occupational risk factors for 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 was completed in 2001.

Multicentre case–control study of oral and laryngeal cancer in central and eastern Europe

P. Brennan, P. Boffetta, A. 't Mannetje, N. Travier; in collaboration with V. Bencko, Prague, Czech Republic; E. Fabianova, Banska Bystrica, Slovakia; J. Fevotte, Lyon, France; A. Fletcher, London, UK; L. Foretova, Brno, Czech Republic; V. Janout, Olomouc, Czech Republic; D. Mates, Bucharest, Romania; P. Rudnai, Budapest, Hungary; P. Snijders, Amsterdam, Nether-

lands; N. Szeszenia-Dabrowska, Lodz, Poland; D.G. Zaridze, Moscow, Russian Federation; W. Zatonski, J. Lissowska, Warsaw, Poland

In parallel with a project on lung cancer (see Section 3.7), a case–control study of oral, laryngeal and pharyngeal cancer has been initiated in the Czech Republic, Hungary, Poland, Romania, the Russian Federation and Slovakia, in collaboration with an investigation of the role of HPV infection in oral cancer (see below), to assess the relative contributions of tobacco smoking, occupational exposures, diet and HPV infection. A total of 600 cases of each neoplasm are being enrolled. The control group and the timetable are the same as for the lung cancer project.

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

P. Brennan, P. Boffetta; in collaboration with M.E. Ardanaz Aicua, Pamplona, Spain; C. Bouchardy, Geneva, Switzerland; P. Crosignani, Milan, Italy; T. Cuchi, Zaragoza, Spain; G. Launoy, Caen, France; F. Merletti, Turin, Italy

During the 1980s, IARC conducted a multicentre 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 France, Italy, Spain and Switzerland. The series of cases is now being re-examined with respect to the association between risk factors and occurrence of and survival from second primary tumours. The occurrence of second primaries in the cancer cases is being analysed with respect to exposure to risk factors. In parallel, occurrence of cancer will be studied in the series of population controls. The follow-up is expected to be completed in 2002.

Multicentre case–control study of laryngeal cancer in India and Pakistan

P. Boffetta, P. Brennan; in collaboration with Y. Bhurgri, Karachi, Pakistan; R. Dikshit, Bhopal, India; C.K. Gajalakshmi, Chennai, India; D.H. Jetly, Ahmedabad, India; A. Matthew, Trivandrum, India; U. Sen, Calcutta, India

India is the country with the largest estimated number of cases of laryngeal cancer worldwide, and the incidence of this neoplasm is also relatively high in other countries of that region. However, little information is available on the risk factors of laryngeal cancer in southern Asia, in particular on the role of chewing and smoking local tobacco products, as well as exposure to other environmental and genetic factors. In parallel with a study on lung cancer (see Section 3.7), a case–control study of laryngeal cancer was started in 2000 in Karachi, Pakistan, and Chennai, Calcutta and Ahmedabad, India, with a main objective of assessing the interaction between genetic and environmental factors. Data collection will be completed in 2002, with a total of 1000 lung cancer cases and 1000 controls.

Molecular epidemiology of cancer of the oral cavity and oropharynx

S. Franceschi, S. Vaccarella, E. Weiderpass, A. Arslan, N. Muñoz, R. Sankaranarayanan; in collaboration with P. Balaram, Trivandrum, India; F. Barbone, Udine, Italy; X. Castellsagué, Barcelona, Spain; S. Diehl, Bethesda, MD, USA; L. Fernandez, Havana, Cuba; R. Herrero, San José, Costa Rica; A. Idris, Khartoum, Sudan; F. Kee, Belfast, UK; J. Lissowska, Warsaw, Poland; C. Martinez, Granada, Spain; A. Nieto, Sevilla, Spain; M. Pawlita, U. Nair, Heidelberg, Germany; J. Pintos, E. Franco, Montreal, Canada; T. Rajkumar, Chennai, India; B. Rose, Sydney, Australia; K.V. Shah, R. Viscidi, Baltimore, MD, USA; P. Snijders, C. Meijer, Amsterdam, Netherlands; H. Sridhar, Bangalore, India; S.R. Talamini, Aviano, Italy; A. Tavani, C. La Vecchia, Milan, Italy; P. Zambon, L. Simonato, Padua, Italy

We have completed a hospital-based case–control study of incident cancers of the oral cavity and pharynx in 14 areas (Sydney, Australia; Montreal, Canada; Havana, Cuba; Trivandrum, Bangalore and Chennai, India; Aviano and Milan, Italy; Warsaw, Poland; Barcelona, Seville, Granada, Spain; Khartoum, Sudan; and Belfast, United Kingdom). A total of 1759 cases and 1733 controls were interviewed and a valid cancer biopsy was available from 933 cases. HPV DNA was found five times more frequently in oropharyngeal cancer (14.4%) than in oral cancer (3.9%). The prevalence of HPV DNA in exfoliated cells of the mouth was similar in cases (32/611, 5.2%) and controls (42/613, 6.9%). The PCR signals detected in exfoliated cells were, however, weak and not indicative of clonal expansion. The percentage of HPV-DNA-positive biopsies did not vary according to the presence of histologically confirmed malignant tissue in the examined biopsy and the agreement between HPV in biopsy and exfoliated cells in each individual case was poor, suggesting that, unlike cervical carcinomas, oral carcinomas do not shed HPV-infected cells.

Analyses of antibodies against L1 VLPs of HPV types 16, 18, 31, 33, 45 and 11, and against the E6 and E7 proteins of HPV 16, which have been linked to invasive HPV-related disease, and of polymorphisms of the *ADH2*, *ADH3*, *GSTMu*, *GSTTan*, *TGFA* and *EGFR* genes is planned or in progress.

The heavy smoking of cigarettes and cigars and some dietary deficiencies among the Cuban population have been examined in relation to oral cancer risk. Smoking more than 30 cigarettes per day showed an OR of 20.8, similar to the OR of 20.5 associated with smoking more than four cigars daily. Intake in the highest tertile was directly associated with oral cancer risk for maize, meat and ham and salami, whereas high fruit intake decreased risk significantly. ORs of 2.7 and 2.6 were seen for a high number of missing teeth and poor general oral condition at oral inspection, respectively. In agreement with the findings of the study in Italy [461], the number of sexual partners, marriages or contacts with prostitutes, practice of oral sex and history of various sexually transmitted diseases, including genital warts, were not directly associated with oral cancer risk. Thus, 82% of oral cancer cases in Cuba were attributable to tobacco smoking and 19% were accounted for by smoking cigars or pipe only. Smaller fractions were attributable to alcohol drinking (7%) and low fruit intake (11%) [133].

The case–control study in three areas of southern India (Bangalore, Chennai and Trivandrum), including 591 incident cases

of cancer of the oral cavity (282 women) and 582 hospital controls (290 women), revealed a higher OR for pan-chewing among women (OR = 42; 95% CI 24–76) than among men (OR = 5.1; 95% CI 3.4–7.8). A similar OR was found among chewers of pan with (ORs = 6.1 in men and 46 in women) or without tobacco (ORs = 4.2 in men and 16.4 in women). Among men, 35% of oral cancer in southern India is attributable to the combination of smoking and alcohol drinking and 49% to pan-tobacco chewing. Among women, chewing and poor oral hygiene explained 95% of oral cancer.

In collaboration with the multi-site case–control studies described above, additional centres have started data collection in Argentina (Buenos Aires); Brazil (Rio de Janeiro, São Paulo, Goiania, Porto Alegre and Pelotas); Hungary (Budapest); Poland (Lodz); Romania (Bucharest); the Russian Federation (Moscow) and Slovakia (Banka Bystrica).

A series of large questionnaire-based case–control studies on upper aerodigestive tract cancer in Italy (598 cases of cancer of the oral cavity and pharynx and 1501 controls; 304 cases of oesophageal cancer and 743 controls) [55, 56, 58–60, 88, 108, 146, 147, 149, 154, 155, 159, 160, 258, 307, 435, 445, 461, 471, 543] has elucidated some new aspects of the relationship between smoking, alcohol drinking, dietary habits and anthropometric measures, including an adverse effect of high intake of animal fat and different risk patterns for smoking and drinking between oral and pharyngeal cancer [85, 146].

3.9 *Soft-tissue tumours and lymphomas*

The incidence of non-Hodgkin lymphoma is increasing in many parts of the world; the reasons are not clear but probably reflect changes in immunocompetence linked to exposure to infectious or environmental agents. In addition, the distribution of sub-types of lymphomas, a very diverse family of neoplasms which only recently has been classified according to molecular and genetic criteria, varies greatly between geographic regions, so that international studies are of particular value.

Multicentre case–control study of lymphomas in Europe and Mediterranean countries

P. Boffetta, P. Brennan, A. 't Mannetje; in collaboration with N. Becker, Heidelberg, Germany; M. Boyiadzis, A. Odysseos, Nicosia, Cyprus; P.L. Cocco, Cagliari, Italy; L. Foretova, Brno, Czech Republic; M. Hsairi, Tunis, Tunisia; J. Iscovich, Raanana, Israel; M. Maynadié, Dijon, France; C. Meijer, Amsterdam, Netherlands; M.B. Qasem Al-Hijawi, S. Al-Kayed, Amman, Jordan; S. de Sanjosé, Barcelona, Spain; A. Soliman, Fakkous, Egypt; A. Staines, Dublin, Ireland; M. Vornanen, Kotka, Finland

A case–control study is being conducted in five European countries in order to test several hypotheses relating to the increase in incidence of lymphomas. Over 1500 cases of lymphoid neoplasms and a group of comparable controls are being recruited. All participants complete a questionnaire including information on sources of ultraviolet radiation, use of hair dyes, 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 biological bank of serum samples will be used to test hypotheses regarding some 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 2002. It is planned to extend the project to countries of the Mediterranean basin, where lymphoma incidence is high and T-cell lymphomas predominate.

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, E. Démaret; in collaboration with Nguyen Chan Hung, Cung Tuyet Anh, Ho Chi Minh City, Viet Nam; Hoang Dinh Cau, Viet Anh, Vu Ngoc Phan, Hanoi, Viet Nam; S. Cordier, Rennes, France; M. Kogevinas, Barcelona, Spain; M. Raphaël, Paris, France; J.M. Rivera-Pomar, Vizcaya, Spain; S. Stellman, New York, USA; Jui-Chun Hung, Los Angeles, CA, USA. Supported by the French Ministry of the Environment, the Ligue Contre le Cancer (France), the Association de Recherche sur le Cancer (France), National Institute of Environmental Health Sciences (USA) and the Italo-Vietnamese Committee (Lombardy, Italy)

This study is investigating whether any excess risk for soft-tissue sarcomas and non-Hodgkin lymphomas in Vietnamese residents can be linked to environmental exposure to herbicides sprayed during the Second Indochina War onto the territory of South Viet Nam. Most frequent among the herbicides was Agent Orange, contaminated with the human carcinogen 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

For the study, 152 cases of soft-tissue sarcoma (STS) and 147 cases of non-Hodgkin lymphoma (NHL) were recruited. Two controls were matched with each case by sex, age and residence (one control with a cancer and one hospital control with non-malignant condition or healthy). Each subject completed a questionnaire and provided a sample of blood and adipose tissue. Due to the relatively long biological half-life of dioxin, it is still possible to detect its presence in human fat tissues 30 years after exposure.

Individual exposure assessment was based on self-reporting of exposure and on records of residential history, linked with records of the US Air Force (HERBS tape) containing the dates, location, type and quantity of herbicide sprayed. To ensure reliability of exposure assessment, coding of places of residence was validated in a special exercise and methods of calculation of the exposure index were compared.

The potential exposure level was calculated for each place of residence and each subject and the association between the estimated doses and disease was evaluated using conditional logistic regression.
No association was found between self-reported exposure to sprays and STS or NHL. In the matched analyses, a significant association was seen for the STS patients compared with non-cancer controls (OR = 3.0; 95% CI 1.1–8.3) for spraying within a radius of 5 km from the place of residence. A small increase in risk was also seen for development of NHL compared with the cancer controls (OR = 1.8; 95% CI 1.2–2.7). Although some professional exposure to herbicides used in agriculture was associated with elevated risk for STS or NHL, it was a less important contributor than exposure to Agent Orange.

Adipose tissue samples from 25 male subjects were analysed at the Midwest Research Institute, Kansas City, United States, in a pilot study of the association between the calculated exposure index and the measured level of dioxin content in the tissues. The correlation coefficient between the two measures was insignificant. Further analyses of the remaining tissue samples are planned.

3.10 Breast cancer

Breast cancer is the most common cancer in women worldwide. In addition to the affluent countries of northern America, Europe, Australia and New Zealand, high incidence is observed in developing countries such as Argentina and Uruguay and the incidence is increasing in many low-risk countries such as China, India and Japan. In developed countries, improvements in disease prognosis occurred in the 1980s with the introduction of adjuvant chemotherapy combined with surgery and radiotherapy. Screening by mammography has been implemented in many high-risk countries, either as organized programmes or as sporadic activities available to the whole population. In the 1990s, tamoxifen became a standard treatment, further reducing the fatality rate of the disease. In the many parts of the world where there are no organized screening programmes, Stage II disease is more common than Stage I disease and overall survival is therefore poorer.
Despite many years of research, questions remain unsolved regarding the etiology of breast cancer, including the role of the environment [404], the interaction between genetics and other factors and the role of diet.

Breast cancer prognosis

A.J. Sasco; in collaboration with J. André, J.Y. Bobin, F. Descotes, S. Saez, Lyon, France

Clinical epidemiological studies are focusing on identification and evaluation of markers which could have prognostic value after breast cancer diagnosis, adding to the information provided by classical factors such as tumour size, nodal involvement and histology. We are conducting studies, based on a series of hospitalized cases in the Rhône-Alpes region of France, of biochemical tissue markers such as urokinase plasminogen activator (UPA), inhibitor of plasminogen type 1 (PAI 1) and type 2 (PAI 2), thymidine kinase (TK) and others. Preliminary analysis of 380 cases suggests that TK and PAI 1 are the most promising markers. The full study is planned to include more than 1000 cases.

Polymorphism in xeno(endo)biotic metabolism and DNA repair, 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 are conducting a molecular epidemiological study to assess the role of various metabolic and DNA repair polymorphisms as risk factors that may affect the response to environmental exposures and influence endogenous processes. So far, 278 cases recruited at the Centre Régional de Lutte contre le Cancer, Montpellier (France) have been analysed. Recruitment and data collection were completed at the end of 2001. This study is designed to allow assessment of interactions between environmental exposures, dietary habits and genetic polymorphisms and of the roles played by these factors in breast cancer risk.

Worldwide patterns of treatment for early breast cancer

P. Pisani, D.M. Parkin; in collaboration with R. Peto, C. Davies, Oxford, UK; A. Laudico, Manila; S.Surapon, Khon Kaen, Thailand; M. Sanchez, San José, Costa Rica

Both in developed and in developing countries, appropriate management of early breast cancer is of particular importance, as there are widely available and practicable medical treatments that, after surgery, can substantially affect 10-year survival. Various hormonal treatments, particularly use of tamoxifen and ovarian ablation, are of substantial value if, as is generally the case, a surgically removed tumour is hormone-sensitive (that is, estrogen-receptor-positive; ER+). Moreover, hormonal treatments are likely to be affordable wherever surgery is affordable.
The extent to which various treatments are used in different populations needs to be monitored, as do the trends in the use of such treatments, to identify practical opportunities for the control of the disease. The aims of this study are (*a*) to monitor trends in the frequency of early breast cancer; (*b*) to describe and compare patterns of treatment in early breast cancer worldwide; and (*c*) to relate early diagnosis and treatment trends to trends in cause-specific mortality following breast cancer. In collaboration with cancer registries, data collection has been initiated in two populations of eastern Asia. Collaborations with cancer registries of Latin America and other regions are being established.

Part 4

Mechanisms of carcinogenesis

Elucidation of the mechanisms underlying the development of tumours provides powerful supporting information on the causal nature of associations with risk factors. It can also indicate possibilities for cancer-preventive interventions and therapeutic treatments and point to populations who are at unusually high risk for certain cancers. The identification by laboratory research of the sequence of steps leading to cancer allows definition of biomarkers that can be measured in biological samples collected in epidemiological studies of human cancer. There is thus increasingly a two-way exchange of data between field studies and laboratory research.

More fundamental mechanistic research also ensures that the Agency remains abreast of advances in areas of molecular biology, cell biology and genetics that are leading to a fuller understanding of the origins of cancer.

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. Defects in molecules involved in DNA damage response, repair and recombination after exposure to endogenous and environmental carcinogens play an important role in human cancer development. The studies presented here are investigating the role of various gene products in the detection of DNA damage and in signal-transduction pathways, with particular emphasis on those involved in sensing and repairing DNA damage following exposure to genotoxic agents, including double- and single-strand breaks as well as accumulation of DNA adducts formed by lipid peroxidation.

Characterization of *ATM* mutations in children with ataxia telangiectasia

S. Angèle, M. Fernet, N. Moullan, B. Chapot, M. Vuillaume, J. Hall; in collaboration with D. Stoppa-Lyonnet, Paris, France; J.-O. Bay, Clermont-Ferrand, France

A collaborative project is being conducted to examine the *ATM* mutation profile in children from over 70 ataxia telangiectasia (AT) families living in France over the period 1977–2001. Mutation analysis of the *ATM* gene is being carried out using either cDNA-based techniques (protein truncation test (PTT), restriction endonuclease fingerprinting (REF) and fluorescence-assisted mismatch analysis) or, where only genomic DNA is available, by SSCP analysis; all the alterations are confirmed by direct sequencing. The mutations detected so far appear to be scattered throughout the whole *ATM* gene and demonstrate extensive allelic heterogeneity of AT in French patients. The cellular response (cell survival, cell-cycle progression, induction of apoptosis and ATM kinase activity) of lymphoblastoid cell lines established from AT patients carrying different *ATM* mutations following exposure to ionizing radiation is being assessed to establish possible genotype/phenotype relationships.

Role of the *ATM* gene in breast cancer

S. Angèle, S. Gutierrez Enriquez, M. Fernet, N. Moullan, B. Chapot, M. Vuillaume, J. Hall, M.D. Friesen, O. Sinilnikova, P. Tanière; in collaboration with A.-L. Borressøn-Dale, Oslo, Norway; A. Brémond, J.P. Gérard, P. Romestaing, C. Lasset, I. Treilleux, Lyon, France; T. Dork, Hannover, Germany; C. Jones, S. Lakhani, London, UK. Supported by the Association pour la Recherche sur le Cancer (ARC), Electricité de France (EDF)

To assess the contribution of the *ATM* gene to breast cancer, two approaches have been adopted. Firstly, expression of the ATM protein has been studied using immunohistochemistry in infiltrating duct and *in situ* carcinomas of the breast. In normal breast ducts, nuclear expression of ATM was seen in epithelial cells but not in myoepithelial cells. In contrast, this nuclear expression was absent or low in the epithelial cancer cells in 31 (77%) of the tumours studied. Positive immunostaining for p53 was found in 20 tumours. Sixteen tumours had both low ATM expression and positive p53 immunostaining. Our results indicate that in the majority (35/40) of the sporadic breast carcinomas examined not only would the functionality of the ATM/p53-mediated DNA damage response be compromised, but also other signalling pathways activated by these two multifunctional proteins could contribute to tumour development and progression [5]. The expression of other proteins implicated in the repair of DNA strand breaks such as BRCA1, hp95, hMRE11, is being investigated, as are the expression patterns in myoepithelial breast tumours.

The second approach has involved establishing lymphoblastoid cell lines from patients with breast cancer who were or were not radiosensitive when treated with radiotherapy. These lines have been characterized in terms of their cell survival and the functionality of the p53 response to DNA damage after exposure to ionizing radiation, ATM protein expression and mutational status of the *ATM* gene using the PTT and REF techniques. In some of the cell lines established from breast cancer patients, the level of cell survival and the p53 induction after exposure to ionizing radiation are lower than those observed in control cell lines, indicating an alteration in the ATM signalling pathway.

One truncating mutation has been found among the 37 patients with radiosensitive breast cancer in which the entire ATM open reading frame has been examined, and eight different missense sequence alterations, two of which are novel changes, have been identified. The biological significance of these missense alterations and their frequency in our study group of 231 breast cancer patients and 300 controls is under investigation.

A cytokinesis-blocked micronucleus test has been established in order to examine the level of radiation-induced chromosome breaks in lymphoblastoid cell lines from breast cancer patients carrying these *ATM* missense sequence alterations and compare it with the level in those carrying a wild *ATM* gene (Figure 27).

Role of the *ATM* gene in ocular telangiectasias

M. Vuillaume, N. Moullan, B. Chapot, S. Angèle, J. Hall, M.D. Friesen; in collaboration with M. Mauget-Faÿsse, M. Quaranta, Lyon, France. Supported by the

Ligue National Contre le Cancer, Comité Départemental du Rhône (France)

One clinical characteristic of AT is the development of telangiectasias in the eyes and ears. Although this disease is extremely rare, *ATM* heterozygotes have been estimated to make up 1% of the general population, and these individuals fall into two groups distinguished by their *ATM* mutation profile. It has been predicted that carriers of a missense allele have an increased risk of cancer or perhaps of developing clinical phenotypes associated with AT, such as radiation sensitivity and telangiectasias. In a pilot study, we have investigated whether 30 individuals with no family history of AT, who developed ocular telangiectasias, were carriers of *ATM* mutations. A lymphoblastoid cell line was established for each patient and RNA from this cell line was used to screen the *ATM* open reading frame for sequence alterations using the REF cDNA approach. All fragments with an altered REF pattern were sequenced to determine the exact modifications. The frequency of each change was then assessed in a French control population. A total of 21 *ATM* sequence variants, at 10 different sites on the *ATM* gene, were found in 17/30 cell lines examined. All were missense alterations, 8/10 of which would be predicted to result in an amino acid substitution in the ATM protein at a conserved position. This result supports the hypothesis that missense ATM variants could confer an AT-like phenotype acting in a dominant negative fashion by enhancing radiation sensitivity and the formation of retinal and choroidal vascular abnormalities.

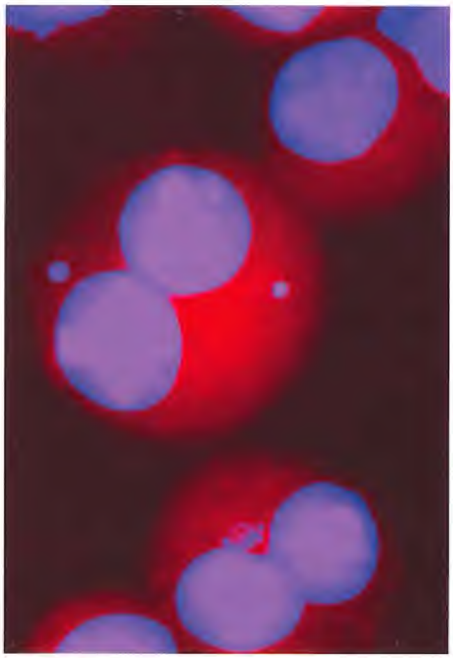

Figure 27. Binucleated cell with two micronuclei. The cytoplasm (red) was stained with propidium iodide and both nuclei and micronuclei (pink/blue) with DAPI stain

Role of the *ATM* gene in prostate cancer

J. Hall, S. Angèle, B. Chapot, N. Moullan, P. Tanière, M. Friesen; in collaboration with M. Colombel, Lyon, France; R. Eeles, A. Falconer, Sutton, UK; M. McKay, Melbourne, Australia. Supported by the Association for International Cancer Research (AICR)

Although the etiology of carcinoma of the prostate remains largely unknown, several risk factors have been identified. These include genes involved in androgen homeostasis, the vitamin D signalling cascade, mutations in the *PTEN/MMAC 1*, *BRCA1, BRCA2, TP53, RB* and *CDKN2* genes and a susceptibility locus on chromosome 1.

Our pilot project aims to investigate whether the *ATM* gene is associated with development of prostate cancer and/or the extreme radiation sensitivity seen in some prostate cancer patients, following the finding by Hall *et al.* (1998, *Cancer J.*, **4**, 385–389) of germline *ATM* alterations in prostate cancer patients. In a first approach, the ATM protein expression profile is being characterized in prostate tumour samples and compared with that of normal prostate using immunohistochemical techniques. Secondly, the frequency of specific missense alterations in the *ATM* gene is being compared between prostate cancer patients, some of whom have shown extreme radiosensitivity during their treatment, and age-matched controls.

Repair of DNA etheno adducts and carcinogenesis

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Etheno adducts such as 1,N^6-ethenoadenine (εA) and 3,N^4-ethenocytosine

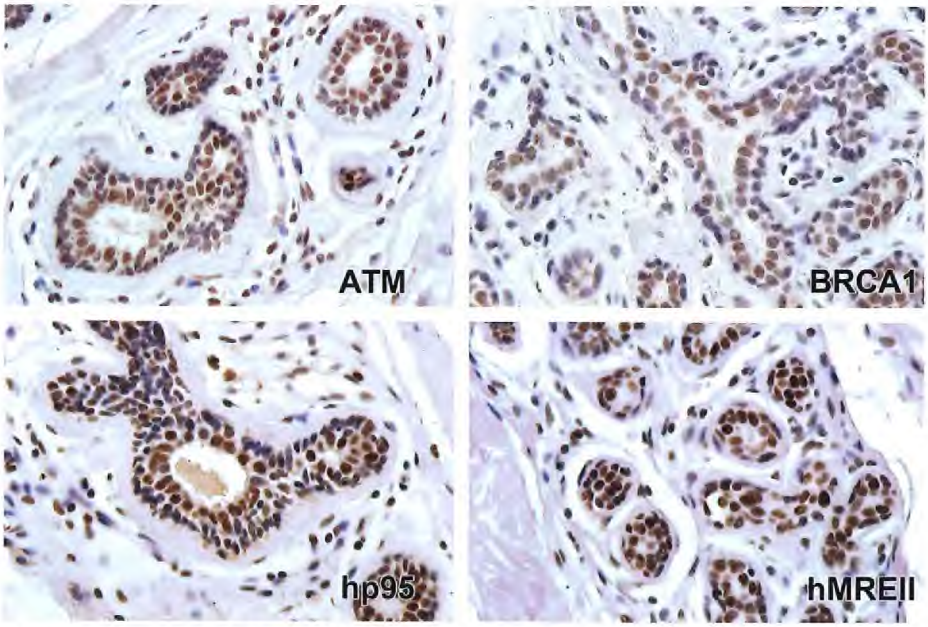

Figure 28. Immunostaining for ATM, BRCA1, hp95 and hMre11 protein in normal mammary tissue (×400).

(εC) are promutagenic DNA lesions [15] formed by some environmental carcinogens and by the lipid peroxidation product *trans*-4-hydroxy-2-nonenal (HNE) [539]. We are studying some host factors that may modulate the formation, persistence and biological consequences of these lesions.

DNA etheno adducts in human tissues

Background levels of DNA damage in humans have, in general, been measured in one selected tissue but have rarely been compared between different tissues of the same individual. To obtain data on variations in background DNA damage between different tissues in humans, a pilot study has been implemented, to measure etheno adduct levels in several tissues obtained during autopsy examination. Levels of εA and εC in DNA from liver, lung, kidney, colon, colon mucosa, cerebellum, brain cortex and brain medulla from ten individuals were analysed. With the exception of one liver sample and one lung sample, ranges and median values of both etheno adducts differed little between the liver, lung, kidney, colon, colon mucosa and cerebellum, but levels were higher in the brain cortex and medulla. This suggests that brain tissues may be more susceptible than other tissues to DNA damage associated with lipid peroxidation. The same DNA samples are now being analysed for abasic sites, which are thought to represent the major DNA lesion. The aim is to subsequently determine whether higher levels of DNA damage (etheno adducts and/or abasic sites) are associated with the pathology or known exposures of the individuals.

In collaboration with the Institute of Biochemistry and Biophysics (Warsaw, Poland), a series of DNA samples from lung cancer patients has been analysed for εA and εC, in order to assess the role of oxidative stress and lipid peroxidation in the etiology of lung cancer. The DNA samples were from normal and tumorous lung tissue and from circulating lymphocytes obtained from 33 lung cancer patients. Preliminary data suggest that etheno adduct levels (medians and ranges) are similar in healthy and tumorous lung tissue, but slightly higher in lymphocytes. For lung DNA, the levels of εA and εC are similar in tissue samples obtained by autopsy and at surgery. The etheno adduct levels will be compared with the activities of DNA glycosylases (including those involved in removal of εA and εC from DNA) and with other oxidative DNA lesions measured in the same tissue samples. DNA damage and DNA repair activities in circulating lymphocytes from healthy volunteers will be similarly analysed.

Repair of etheno adducts in vivo

In vitro, ethenobases can be processed by the base excision repair pathway: εA is excised by the mammalian 3-methyladenine DNA glycosylase (APNG) protein, whereas a different DNA glycosylase is involved in the removal of εC from DNA. To assess the role of APNG in the repair of εA and εC, the persistence of these two adducts was measured in wild-type and APNG knock-out mice after repeated exposure to vinyl carbamate. Six hours after the last exposure, levels of εA in liver and lung DNA from the knock-out animals were two-fold higher than in the wild type, but levels of εC were similar in both strains and lower than levels of εA. The disappearance of εA was two- to three-fold slower in the knock-out animals, with half-lives of about 60 h in the liver and lung, while there was no significant difference between the rates of removal of εC between the knock-out and wild-type mice. These data demonstrate that the base excision repair pathway is involved (through the APNG protein) in the repair of εA *in vivo*. However, there is a back-up repair system which remains to be identified.

To identify possible alternative pathways for the repair of εA and εC, the formation and persistence of these adducts is being investigated in mice deficient in mismatch repair (MSH2 knock-out mice) or in nucleotide excision repair (XPA and XPC knock-out mice) after treatment with vinyl carbamate. Preliminary results indicate that εA is formed at higher levels in DNA from pre-weaning MSH2 mice compared with wild-type mice, suggesting that the mismatch repair system is involved in the removal of εA from DNA.

Effects of DNA repair deficiency on genotoxic effects of lipid peroxidation products

The effects of repair deficiencies on DNA damage induced by HNE and its oxidation product 2,3-epoxy-4-hydroxynonanal (EH) are being investigated in cell cultures derived from wild-type mice and from knock-out mice deficient in the mismatch repair protein MSH2.

Following treatment of $MSH2^{+/+}$, $MSH2^{+/-}$ and $MSH2^{-/-}$ primary and immortalized cells with HNE or EH, DNA strand breaks and alkali-sensitive sites were measured with the single cell gel electrophoresis (Comet) assay, and εA and εC were analysed by immunoaffinity/^{32}P-postlabelling. HNE and EH both increased DNA damage, as measured by the Comet assay, in primary and established cells, and a dose–response relationship was found for HNE. Formation of εA and εC was induced by HNE in these cell cultures, probably through stimulation of cellular oxidative stress and lipid peroxidation, as shown with the fluorescent probe diphenyl-1-pyrenylphosphine.

Carcinogenesis in PARP-deficient mice

Susceptibility to urethane-induced carcinogenesis has been compared in wild-type and PARP knock-out mice with a 129/Sv × C57BL/6 genetic background. Mice given a single injection of urethane at 12 days of age died earlier than controls. In treated males, the median survival times did not differ significantly, while in females, survival was slightly longer in wild-type than in knock-out mice. Urethane induced lymphomas and tumours in the liver and lungs in all treated groups and also tumours of the uterus and ovaries in females. No significant difference in the types and incidence of tumours was observed between the two strains. These data suggest that the base excision repair pathway is not essential for protecting mice from the carcinogenicity of urethane.

RAD52 and RAD52B proteins in DNA double-strand break repair

E. Van Dyck, Y.-G. Yang, S. Hamimes, J. Michelon; in collaboration with J.-M. Buerstedde, Hamburg, Germany; A. Stasiak, Lausanne, Switzerland

DNA double-strand breaks can lead to genomic instability and cancer. Double-strand break repair in eukaryotic cells requires RAD52, a protein that plays a critical role in homologous recombination. This protein forms ring structures that bind single-stranded DNA as well as DNA ends and promote homologous pairing and the annealing of complementary single strands. We are conducting biochemical and genetic studies to elucidate the roles of RAD52 in double-strand break repair.

Protein partners of human RAD52 and its ring-formation and DNA-binding properties

We have used the yeast two-hybrid assay to identify proteins that interact with human RAD52 to mediate double-strand break repair. Screening of a human testis cDNA library uncovered several candidates, and their identification is well advanced. Once interaction of these proteins with RAD52 is confirmed, we will characterize them, with the aim of finding new avenues to study RAD52 and elucidate the repair pathways it mediates. The DNA-binding and self-interaction domains of RAD52 have been mapped to the well-conserved N-terminal half of the protein. In order to examine the function of these domains, we have used site-directed mutagenesis to generate variants of the human RAD52 protein and are now preparing purified recombinant proteins to analyse their DNA-binding properties, as well as their ability to form rings.

Biochemical characterization and functional analysis of RAD52B

Recently, a novel chicken gene, called *RAD52B*, has been identified, which encodes a protein having some amino acid similarities with RAD52. Chicken cells lacking the *RAD52B* gene are viable and their phenotype suggests a role in DNA recombination and repair. To examine what reactions RAD52 and RAD52B mediate and the extent to which the biochemical properties and roles of these proteins overlap, we have undertaken the biochemical characterization of the RAD52B protein. Our data indicate that purified recombinant chicken RAD52B binds single-stranded DNA and resected double-strand breaks. In addition, we have identified a human homologue of RAD52B, which suggests conservation of RAD52B function among vertebrates and used a PCR-based method to isolate a full-length human *RAD52B* cDNA. We have studied the mRNA expression pattern of *hRAD52B* and prepared recombinant human RAD52B protein to further explore its biochemical properties and its role in DNA metabolism. Using the yeast two-hybrid assay to identify partners of hRAD52B, we have uncovered several interacting candidates that are now being characterized. The biochemical and enzymatic properties of the various complexes containing RAD52 and/or RAD52B will be assayed and the identity of its members will be determined.

4.2 Genetic determinants of specific cancers

The programme on genetic susceptibility to cancer is evaluating the role and importance of inherited conditions that predispose to cancer, using molecular, familial and population-genetic approaches. Probably less than 5% of cancers occur in individuals with strong predisposition to a particular cancer type. Molecular epidemiological studies may allow identification of low-penetrance predisposing genes. Such information would be of importance for more common non-familial forms of cancer which may also be associated with genetic predisposition. IARC has helped to identy genes predisposing to familial medullary thyroid cancer (multiple endocrine neoplasia type 2), to neurofibromatosis type 2 and to familial breast cancer. Major efforts have been put into identification of the X-linked lymphoproliferative syndrome (XLP) gene and mapping of papillary thyroid carcinoma susceptibility genes.

Genetic susceptibility to breast and ovarian cancer

O. Sinilnikova, C. Szabo, D. Hughes, S. Ginholac, M. Leone; in collaboration with G. Lenoir, D. Stoppa-Lyonnet, Paris, France; H. Lynch, Omaha, NE USA; S. Mazoyer, C. Lasset, Lyon, France; K Nathanson Philadelphia, PA, USA; S de SanJose, Barcelona Spain; and the Breast Cancer Linkage Consortium

Although great progress has been made in elucidating the role of two major high-risk genes, *BRCA1* and *BRCA2*, in the etiology of breast and ovarian cancer, several questions remain to be answered. There is a growing number of reports of rare missense and intronic *BRCA1* and *BRCA2* alterations of unknown significance in familial and early onset breast cancer cases as compared to deleterious truncating mutations. This first type of *BRCA1* and *BRCA2* germline lesions, with some exceptions, has not been considered in the etiology of cancer due to the absence of functional assays allowing their evaluation. In our study of population-based series of early-onset breast cancer patients (Rhône, France; Tarragona and Gerona, Spain), we found that approximately 10% of these patients had clearly deleterious mutations in *BRCA1* or *BRCA2* and that another 15% had *BRCA1* and *BRCA2* alterations of unknown significance. It is clear that at least some of these sequence variants must be disease-causing, but others are neutral polymorphisms. The functional relevance of these alterations is being evaluated through a study of corresponding lymphoblastoid cell lines (stability and splicing of mutant transcripts, sensitivity to ionizing radiation, double-strand break DNA repair rate) and tumours (loss of heterozygosity (LOH) at *BRCA1* or *BRCA2* loci, *TP53* mutations and expression) (see Section 4.1). Another question we are addressing relates to the variability of cancer risk

associated with *BRCA1* and *BRCA2* germline mutations. Although mutations in these genes confer high risk of breast and ovarian cancer, wide variability in the age at diagnosis and cancer site is observed, even between carriers of the same mutation. We have created a bank of DNA samples from individual carriers of clearly deleterious *BRCA1* or *BRCA2* mutations and used it for two studies. In one, an association of breast cancer risk with a repeat-length polymorphism in the androgen receptor gene was confirmed, while the second study found a protective effect on risk of ovarian cancer of two polymorphisms in the 17β-hydroxysteroid dehydrogenase 2 gene (*EDH17B2*). We are also testing a region on chromosome 5q using a linkage-based approach in families segregating a *BRCA1* or *BRCA2* mutation.

The international *BRCA 1* and *2* gene carrier cohort study (IBCCS)

D.E. Goldgar, M. Corbex, A.J. Sasco; in collaboration with the IBCCS Consortium. Supported by the European Union Europe Against Cancer programme

In order to precisely determine cancer risks due to mutations in the *BRCA1* and *BRCA2* breast cancer predisposition genes, examine the role of other known risk factors in modifying these risks, and gauge the efficacy of various prevention strategies, we are conducting a multicentric observational prospective study of identified carriers of these genes [167]. There are currently 14 participating centres in 11 countries including three large national centres in France, the Netherlands and the United Kingdom. Data collection and transfer are managed using the ORACLE relational database system. The IBCCS project is now integrated within the large European Breast Cancer Network. The questionnaire and protocol have been finalized and since enrolment into the study began in November 1998, approximately 1000 subjects have been enrolled (halfway to the target of 2000 carriers). The first follow-up of the subjects enrolled in 1998 has begun. A set of retrospective interim statistical analyses is now being carried out.

Mapping of non-*BRCA1* and *2* breast cancer susceptibility loci

D.E. Goldgar, C. Szabo; in collaboration with P. Devilee, Leiden, Netherlands; D.F. Easton, Cambridge, UK; M.R. Stratton, Sutton, UK; and the International BRCA3 Linkage Consortium. Supported by the Association for International Cancer Research and the SwissBridge Foundation

Although germline mutations in the *BRCA1* and *BRCA2* genes are thought to be involved in the vast majority of cancer predisposition in families with multiple cases of breast and ovarian cancer, these genes explain only a minority of the excess familial aggregation observed for premenopausal breast cancer. The goal of this project is to identify the chromosomal location of one or more additional breast susceptibility loci and to estimate the frequency and risks due to such genes. Together with our collaborators, we have collected DNA samples from 138 families which meet the criteria of having three sampled cases of breast cancer diagnosed under age 60 years with no identified mutation in the *BRCA1* or *BRCA2* gene. At the high-throughput capillary sequencing facility at the Sanger Centre (Cambridge, United Kingdom) a total of 576 samples have been genotyped for a set of 400 STR markers scattered throughout the genome. We have also evaluated a reported localization of a new breast cancer susceptibility locus on chromosome 13q21 in a set of Scandinavian families. We found no evidence of this in our families and can exclude the possibility that such a locus accounts for more than 13% of all breast cancer families [478].

As an adjunct to the linkage studies, an approach based on genome mismatch scanning will be applied to DNA samples from distantly related individuals with clear inherited breast cancer, in order to identify genomic fragments which are shared identical by descent.

Genetic and family studies of cancers of the head and neck

D.E. Goldgar; in collaboration with R. Eeles, S. Jefferies, Sutton, UK; W. Foulkes, Montreal, Canada

A case–control study has been carried out to assess the familial risks of squamous cell carcinomas of the head and neck (SCCHN) and to identify potential tumour suppressor loci which may be involved in the development of these tumours. The focus is 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 provided questionnaire data on personal alcohol and tobacco usage and other relevant demographic and risk factor data, as well as data on smoking and alcohol consumption by each of their first-degree relatives and information on any cancers that occurred in their relatives. To date, 86 cases of multiple primary tumours have signed the consent form and filled out the study questionnaire as well as an equal number of single primary tumour cases and controls. In a subset of the cases screened for germline mutations in the *p16* gene, none were found [202]. Examination of epidemiological risk factors in families with two or more cases of related cancers versus families with negative cancer histories has allowed assessment of potential gene–environment interactions. In addition to significant effects of family history and smoking, we also discovered an association between SCCHN and a polymorphism at the glutathione peroxidase (GPX1) locus. These results suggest that polymorphisms in the *GPX1* gene may be a marker for development of multiple primary tumours.

Genetic and functional studies of *SH2D1A* and related genes in X-linked lymphoproliferative disease (XLP) and in other EBV-associated diseases

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X-linked lymphoproliferative disease (XLP) is an inherited immunodeficiency characterized by selective susceptibility to Epstein–Barr virus (EBV). EBV is also implicated in other lymphoid diseases, namely Burkitt lymphoma, Hodgkin disease, non-Hodgkin lymphoma (NHL)

and lymphomas in patients with immunodeficiency, including AIDS patients and organ-transplant recipients who have undergone immunosuppressive therapy, as well as in nasopharyngeal carcinoma (NPC) (*IARC Monographs*, Vol. 70, 1997). Defective immune response to EBV infection seems to be the common mechanism underlying the development of these malignancies. In 1998, we and others identified inactivating mutations in the *SH2D1A* (or *SAP* or *DSHP*) gene in XLP patients. The SH2D1A protein interacts with the cytoplasmic domains of several proteins, including SLAM, which are all members of the CD2 receptor family belonging to the immunoglobulin superfamily. Furthermore, SH2D1A associates with Dok1 and activates NF-κB [459]. It is reasonable to hypothesize that alterations of SH2D1A and its related molecules affecting signal transduction may be responsible for the various EBV-associated diseases.

Genetic association studies

By genetic approaches, we are investigating the involvement of *SH2D1A* and *SLAM* in EBV-associated pathologies. We have previously established the genetic structure of the *SLAM* gene and identified intragenic polymorphisms in *SH2D1A* and *SLAM*. DNA samples from 100 NPC patients and from 100 matched normal controls have been collected, in collaboration with the Cancer Center of the Sun Yat-Sen University Medical School, Guangzhou, China, which we are now using for genetic association studies.

XLP knock-out mouse studies

We have studied the biological role of *SH2D1A* by functional approaches using an XLP knock-out mouse generated at IARC. In embryo development, absence of the gene does not cause any apparent abnormality. The development of the lymphoid organs and the maturation of the lymphocytes were also apparently normal. However, *sh2d1a*-deficient mice with a BALB/c genetic background showed consistently lower proportions of T cells, particularly $CD4^+$ T cells, and a higher proportion of $CD19^+$ B cells in spleen and peripheral blood compared with their normal littermates. The molecular mechanism underlying this phenomenon is under study.

We have investigated XLP-equivalent phenotypes in *sh2d1a*-deficient mice. The phenotype of hypogammaglobulinaemia G of XLP patients were reproduced, but malignant lymphoma and aplastic anaemia, observed in 24% and 3% of XLP patients respectively, were not seen in *sh2d1a*-deficient mice up to 16 months. To test their susceptibility to EBV infection, the mutant and normal mice were infected with murine gammaherpesvirus (MHV) 68, which is homologous to EBV. Exacerbated proliferation of activated $CD8^+$ cells was observed in *sh2d1a*-deficient mice. As a consequence, the grade of splenomegaly was higher in mutant mice. While most XLP patients are unable to control lymphoproliferation after EBV infection, fulminant infectious mononucleosis in *sh2d1a*-deficient mice was self-limiting. Lymphocyte infiltration in liver, kidney and lung was significantly more frequent and more serious in *sh2d1a*-deficient mice, but they were not more morbid than their normal littermates. We are studying further the immune responses of *sh2d1a*-deficient mice against MHV-68, particularly their capacity for long-term virus control. Development of spontaneous and viral-induced malignancies is being monitored and possible alterations of the SH2D1A-related signal transduction pathways in the mutant mice are being studied.

Role of Dok1 protein

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We have reported that SH2D1A associates with several phosphotyrosine proteins including p62dok (Dok1) and that it activates NF-κB [459]. An SH2D1A mutant found in XLP patients failed to bind to Dok1, suggesting that the SH2D1A/Dok1 association might be relevant to the XLP disease [459]. Dok1 is an adaptor protein that associates with a number of signalling molecules such as RasGAP, Csk, Nck and SHIP2. Dok1 is constitutively tyrosine-phosphorylated in various transformed cells and in T cells overexpressing SH2D1A and inhibits cell proliferation and MAP kinase signalling (Latour *et al.*, 2001, *Nature Immunol.*, **2,** 681–690) Tyrosine phosphorylation of Dok1 is also induced in B- and T-cell signalling.

In order to further elucidate the biological function of SH2D1A and the physiological significance of the SH2D1A/Dok1 interaction in relation to XLP and other EBV-associated disorders, we are studying the effects of SH2D1A and Dok1 on T-cell activation and proliferation in relation to NF-κB and MAP kinase signalling pathways. We are also searching for additional partners of SH2D1A and potential molecules that compete with SH2D1A for Dok1 binding, using the yeast two-hybrid screening of a thymus cDNA library. We have also investigated the role of Dok1 in human cancer by looking for alterations of Dok1 in EBV-associated and -non-associated tumours. A number of Burkitt lymphoma and lymphoblastoid cell lines of XLP patients have been selected for mutation searching.

Genetic predisposition to low-penetrance and high-penetrance thyroid cancer

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Non-medullary thyroid carcinoma (NMTC) accounts for ~90% of all thyroid cancers (age-adjusted prevalence 0.5–5 per 100 000 in most populations) and originates from the follicular cells of the thyroid. Papillary thyroid carcinoma (PTC) and follicular carcinoma (FC) are the two main variants of NMTC. Epidemiological studies indicate familial clustering of NMTC. Familial NMTC (FNMTC) has more aggressive behaviour than the sporadic tumour. It follows an incompletely penetrant autosomal dominant mode of inheritance, and is thought to represent ~5% of all cases of thyroid cancer. Very little is

known about genetic predisposition to NMTC. On the other hand, *RET* has been found to be activated in 66% of sporadic PTC observed in Ukraine and Belarus 10 years after the Chernobyl accident. This activation derives from somatic mutations, namely chromosomal translocations or inversions resulting in rearrangements of the protooncogene *RET* with different genes (Figure 29).

In order to map genes predisposing to NMTC, the International Consortium for the Genetics of FNMTC, organized by IARC, has collected 225 pedigrees. Two loci predisposing to FNMTC have been identified: one on chromosome 19 (Canzian *et al.*, 1998, *Am. J. Hum. Genet.*, **63**, 1743–1748) in a French family with an unusual form of NMTC with cell oxyphilia and a second one on chromosome 14 (Wooster *et al.*, 1995, *Nature*, **378**, 789–792) in a large Canadian family with multinodular goitre and low recurrence of NMTC. However, neither of these accounts for a significant fraction of FNMTC pedigrees.

More recently an extensive genome-wide scan carried out in our laboratory has revealed a common haplotype on chromosome 2q21 in seven out of the eight PTC patients from a large Tasmanian pedigree (Tas1) with recurrence of PTC [283]. In order to verify the significance of this third locus, genetic analysis based on the method of linkage was performed in 80 of our pedigrees and confirmed the significance of the finding. In addition, a histological stratification based on the presence of at least one case of the follicular variant of PTC (fvPTC), the phenotype observed in the Tas1 family, confirmed the existence of a major locus for susceptibility to NMTC which has been denominated NMTC1 [283].

In contrast, six candidate genes, *RET, TRK, MET, TSHR, APC* and *PTEN* as well as *TCO* and *MNG1*, were excluded as major susceptibility genes in a large sample of families by using microsatellites that are positioned in or close to these genes. In order to determine whether some variants of *RET* or a combination of them predispose to PTC, we looked for association of *RET* haplotype(s) in PTC cases and in controls matched for sex, age and population. Four single-nucleotide polymorphisms (SNPs) across the *RET* coding sequence were typed and haplotypes reconstructed for sporadic PTC cases and controls. Eleven unique haplotypes were obtained, which show different distributions in patients and in controls. Our data suggest that some variants of *RET* and some specific haplotypes are associated with predisposition to sporadic as well as familial PTC.

We are also collecting tumour material from familial and sporadic cases of NMTC and studying rearrangements of *RET* in direct tumour preparations of familial NMTCs using fluorescence *in situ* hybridization (FISH), which allows detection of *RET* abnormalities at the single-cell level in interphase nuclei extracted from frozen tumours or in archival paraffin-embedded tissue sections [95]. Somatic rearrangements of *RET* were found in 19% and 5% of sporadic and familial PTC, respectively [100]. Although we found *RET* rearrangements in FPTC, we confirmed that *RET* was not involved in the inherited predisposition to NMTC. Such rearrangements were observed in more than 50% of microcarcinomas, indicating that *RET* activation may not be necessary for microcarcinomas to progress into PTC, but represents an early event (Figure 30) [101].

The FISH approach allowed us to detect a novel translocation involving the *RET* region, that was not detectable by RT-PCR with specific primers for known rearrangements [99]. This led to identification of the fusion gene, which involves the 5′ portion of *PCM-1*, a gene coding for a centrosomal protein with a distinct cell-cycle distribution, and the RET tyrosine kinase (TK) domain. FISH analysis confirmed the chromosomal localization of *PCM-1* on chromosome 8p21-22, a region commonly deleted in several tumours. We found a greatly increased level and altered subcellular localization of the PCM-1 protein in thyroid tumour tissue compared with normal tissue and are investigating whether this differential

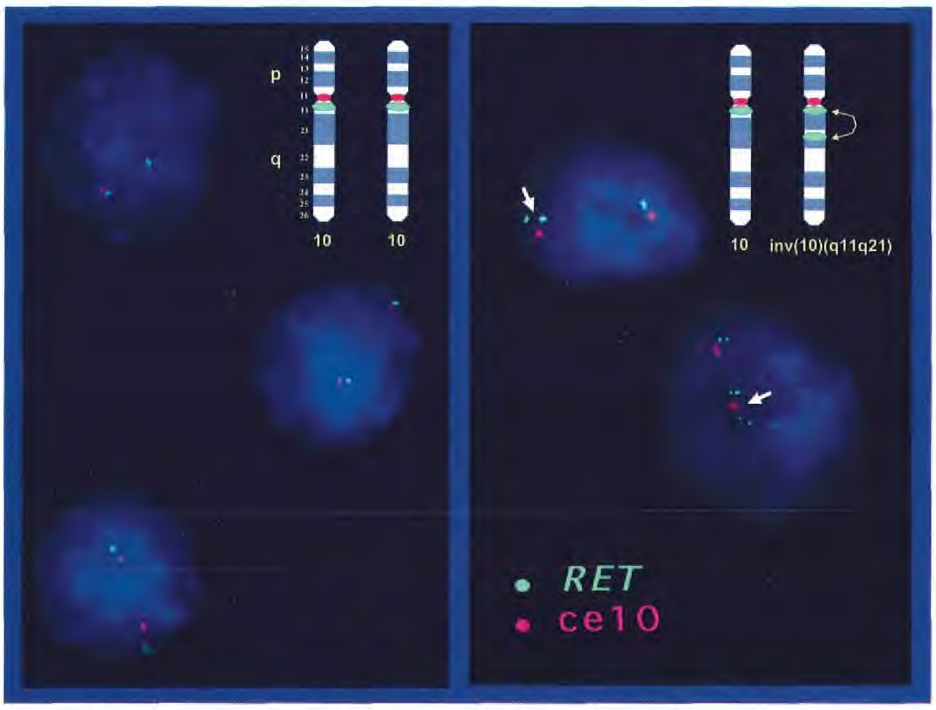

Figure 29. Status of the protooncogene *RET* in thyroid nuclei. *RET* was detected with fluorescein-conjugated avidin (green) and α-satellite DNA with anti-digoxigenin–rhodamine Fab fragments (red) Left: Normal status of *RET*; signals are associated with the two centromeres. Right: Inversion; arrows indicate the rearranged copies of *RET*

expression is associated with centrosome abnormalities. Recent evidence suggests that at least some cancers arise because centrosome malfunction leads to chromosome missorting and damage. Different *PCM-1* expression patterns were observed between tumours and normal tissues by western blot. The expression patterns were also different in various types of tissue, maybe due in part to alternative splicing. Screening of different types of cancer cDNAs on a cancer profiling array revealed an increase in *PCM-1* expression in thyroid cancer and a drastic reduction in renal carcinomas compared with normal tissues. In order to correlate these data with a molecular alteration in the tumours, we analysed loss of heterozygosity using microsatellite markers of the chromosome 8 region that surrounds *PCM-1*. No loss was observed in thyroid tumours, but loss of the *PCM-1* region was found in renal and liver carcinomas. These data are consistent with the data on expression of *PCM-1*. PCM-1 protein was completely absent in liver carcinomas, suggesting that one allele is lost and the second is probably inactivated.

We are extending our studies of the highly penetrant medullary thyroid carcinoma (MTC), using a knock-in mouse model, constructed at IARC, that carries the Cys620Phe mutation, which in humans causes both Hirschsprung disease and MTC. Although the MTC phenotype is observed in newborn homozygous mice (which die soon after birth), it is not seen in heterozygous adult mice at 2½ years of age; this discrepancy between the human and mouse phenotypes is now under investigation.

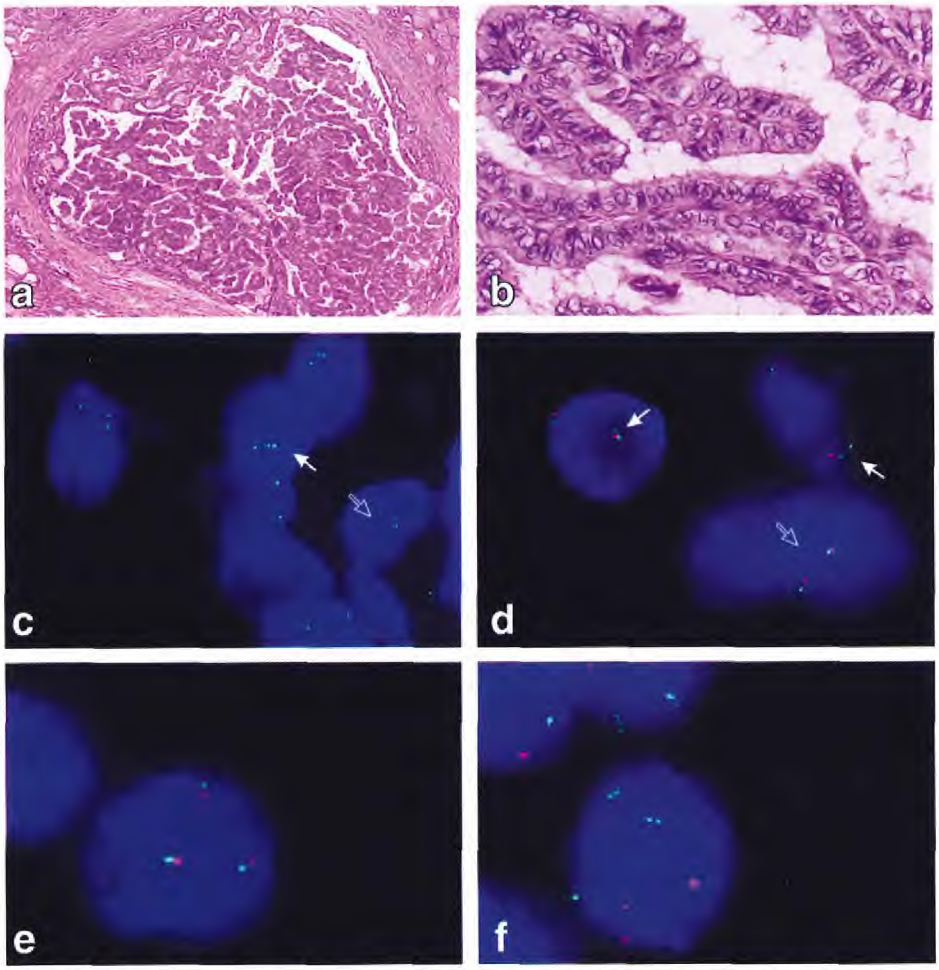

Figure 30. Histopathological and FISH analysis of microcarcinomas. (a, b) Haematoxylin and eosin staining of a microcarcinoma (×100 and ×400, respectively). Microcarcinoma sections were cohybridized with probes for RET (green) and centromere 10 (red). (c, d) Microcarcinomas showing an inversion involving the RET gene. Solid arrow: rearranged RET (inversion); hollow arrow: nuclei carrying two apparently normal copies of RET. (e) Nucleus harbouring chromosome 10 trisomy. (f) Nuclei of a microcarcinoma hybridized with α-satellite DNA for centromere 6 (green) and centromere 12 (red) are trisomic for both chromosomes

Cancer occurrence in relation to selected genetic conditions

A.J. Sasco; in collaboration with D. Satgé, Tulle, France

Following on from studies on the occurrence of childhood tumours in relation to genetically defined conditions (see Section 1.3), our work on Down syndrome has been extended to adults. For example, a pertinent case report of a brain tumour has been published [418], as well as a general review of tumoral profile [420].

A study based on the French national database of death certificates is currently in progress. For deaths at all ages and taking into account the reduced life expectancy of subjects with Down syndrome, preliminary results demonstrate a clear deficit of breast cancer deaths. Other cancer sites will be evaluated. In a similar vein, other genetic conditions, such as those linked to an abnormal number of X chromosomes are being explored [419].

Genetic variability in the arachidonic acid metabolism pathway in relation to risk of gastrointestinal tract cancer

D.G. Cox, S. Landi, F. Canzian; in collaboration with B. Crusius, S. Peña, Amsterdam, Netherlands; M. De Marchi, Turin, Italy; V. Moreno, C.A. González, Barcelona, Spain; and the EPIC collaborators

Prostaglandins are believed to play a role in carcinogenesis through mechanisms including increased cell proliferation, promoted angiogenesis, enhanced carcinogen metabolism or modulation of the immune system. Two isoforms of prostaglandin synthase (also known as cyclooxygenase), *PTGS1* and *PTGS2* (*COX1* and *COX2*), catalyse the bisoxygenation of arachidonic acid to form prostaglandin G2

and the peroxidative reduction of the latter to form prostaglandin H2.

Prostaglandin synthases are involved in pathophysiological processes through their function as rate-limiting enzymes for prostaglandin and thromboxane formation and their role as procarcinogen and mutagen bioactivators. Non-steroidal anti-inflammatory drugs (NSAIDs) act primarily by inhibiting the activity of these enzymes, leading to a marked decrease in prostaglandin production, and persons who regularly use NSAIDs have a 40–50% decrease in colon cancer risk; a similar trend has been observed for stomach cancer. In addition, *PTGS2* is expressed at high levels in colon and stomach cancer in humans and rodents. Studies of inter-individual variations in the activity of the key genes of this metabolic pathway should lead to a better understanding of disease predisposition and treatment variability.

Some polymorphisms of *PTGS1* and *PTGS2* have been reported (Halushka *et al.*, 1999, *Nature Genet.,* **22**, 239–247). In order to characterize polymorphisms in the *PTGS2* gene more completely, we have scanned all the coding regions, the 5′ and 3′ untranslated regions and the promoter of the gene with denaturing high-performance liquid chromatography (DHPLC), leading to identification of 25 new polymorphisms [102]. The new polymorphisms have been further characterized by genotyping in a larger series of samples (mostly Europeans, plus Japanese and black Africans) already available at IARC. This has allowed better estimation of the allelic frequencies in the major ethnic groups and reconstruction of haplotypes by computer-assisted analysis [103], in order to obtain estimates of the conservation of linkage disequilibrium within the gene. We have thus identified five polymorphisms that represent most of the genetic variability within the *PTGS2* gene. These polymorphisms, together with three polymorphisms in the *IL1B* gene (interleukin 1 is the major inducer of *COX2* expression), have been studied using a case–control approach, in two series of cases of inflammatory bowel disease (which is a risk factor for colorectal cancer) from the Netherlands and from Italy, and controls matched for age, sex and ethnic background (a total of 250 cases and 400 controls). The results indicate that homozygosity for one polymorphism of *PTGS2* is associated with a strong risk of developing inflammatory bowel disease.

We have also studied the same polymorphisms in 300 cases of colorectal cancer and 300 controls in Spain. No association with *PTGS2* polymorphisms was found in this group, but homozygosity for one polymorphism of *IL1B* showed a strong association with rectal cancer, in interaction with smoking.

A case–control study of gastric cancer nested in the EPIC cohort is in progress; one of its aims is to elucidate the role of polymorphisms of genes of the arachidonic acid metabolism pathway.

4.3 Role of oxidative stress in carcinogenesis

Oxidative stress contributes to cancer, ageing and various pathophysiological disorders. Mammalian cells produce a variety of reactive oxygen and nitrogen species such as nitric oxide (NO), superoxide ($O_2^{\cdot-}$) and hypochlorous acid (HOCl), which contribute to oxidative stress by damaging proteins, lipids and nucleic acids. We are studying the role of these reactive species in carcinogenesis from various points of view.

Helicobacter pylori infection, oxidative stress and stomach cancer

Oxidative and nitrative stress associated with cagA*-positive* H. pylori *infection and inflammation*

B. Pignatelli, C.-Q. Li, H. Ohshima, C. Malaveille, M. Laval, N. Lyandrat; in collaboration with A. Covacci, Siena, Italy

H. pylori infection is considered to be a risk factor for gastric cancer (*IARC Monographs,* Vol. 61, pp. 177–240, 1994), but the mechanisms underlying its carcinogenic potential are unclear. Oxidative and nitrative stress and DNA damage caused by *H. pylori* infection may play an important role. We have measured oxidized (carbonyl-containing) and nitrated (nitrotyrosine (NTYR)-containing) proteins as markers of oxidative and nitrative stress in 216 human gastric biopsies using dot and western immunoblots, and correlated the results with *H. pylori*, *cag*A status, expression of interleukin-8 (IL-8) and inducible nitric oxide synthase (iNOS) mRNAs and gastric pathology [261, 262]. Higher levels of both oxidized and nitrated proteins were found in patients with either chronic gastritis or duodenal ulcer than in those with normal mucosa. The levels of modified proteins were significantly higher in inflamed samples infected with *H. pylori*, especially *cag*A-positive strains, and in those with expression of IL-8 and iNOS mRNAs than in those without. These results indicate that infection with *cag*A-positive *H. pylori* (toxic strain) induces significant oxidative and nitrative stress in stomach mucosa, contributing to the pathogenesis of *H. pylori*-associated gastroduodenal diseases.

We have also studied the role in gastric oxidative stress of the *cag*A, *cag*E and *Vir*B11 genes located in the *cag* pathogenicity island. Prevalence of expression of IL-8 and iNOS mRNAs and levels of oxidized and nitrated proteins were especially high in gastric specimens infected with *H. pylori* strains containing all three genes.

H. pylori *eradication attenuates oxidative stress in human gastric mucosa*

B. Pignatelli, H. Ohshima, M. Plummer, M. Laval, N. Lyandrat; in collaboration with B. Bancel, L.-M. Patricot, Lyon, France; S. Toyokuni, Kyoto, Japan

We have investigated the effects of *H. pylori* eradication on oxidative stress by measuring changes of relevant markers in

antral biopsies from 34 patients with chronic atrophic gastritis and peptic ulcer disease before and after bacterial eradication. The expression of iNOS and levels of NTYR and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dGuo) were assessed immunohistochemically as markers of NO production and of damage to proteins and DNA, respectively. NTYR staining was significantly associated with the intensity of inflammation and gastritis activity and the prevalence of 8-oxo-dGuo tended to be associated with that of NTYR. After successful eradication of *H. pylori*, the prevalence of iNOS and NTYR (in mild gastritis) staining decreased. 8-Oxo-dGuo staining disappeared in 24% of cases but appeared in 18% of previously negative cases in spite of eradication. We conclude that targets of oxidative stress associated with *H. pylori* infection are inflammatory and deep foveolar cells and lymphoid follicles, and that 8-oxo-dGuo is localized in lymphoid follicles in gastric mucosa. Oxidative stress is reduced by bacterial eradication in the first stages of mild gastritis. The effects of moderate or severe gastritis on iNOS may be reversible by bacterial eradication, but those on NTYR and 8-oxo-dGuo partly irreversible [350].

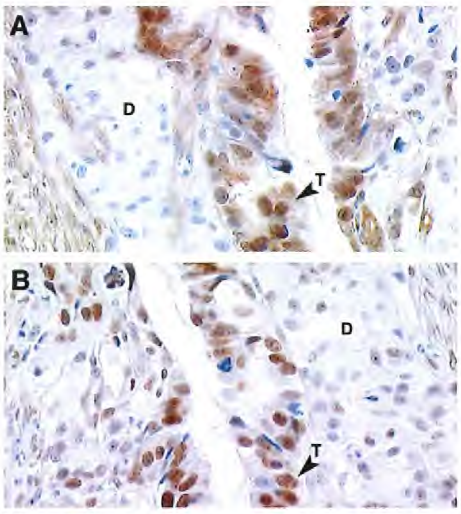

Figure 31. Immunostaining of nitrotyrosine (A) and 8-hydroxy-2'-deoxyguanosine (B) in a human mixed gastric adenocarcinoma associating two sub-types: the tubular-type component (T) is immunoreactive with both antibodies. The diffuse-type one (D) is not stained.

Oxidative and nitrative stress in dysplasia and gastric adenocarcinoma

B. Pignatelli, H. Ohshima, M. Laval, N. Lyandrat; in collaboration with B. Bancel, L.-M. Patricot, Lyon, France; S. Toyokuni, Kyoto, Japan

We have investigated the extent of oxidative and nitrative stress in dysplasia and different types of adenocarcinoma of the human stomach. The expression of iNOS and levels of nitrated proteins and 8-oxo-dGuo in nuclear DNA were assessed immunohistochemically in biopsies from 110 French patients (Figure 31). The lesions were classified histologically as: dysplasia ($n = 24$), tubular (intestinal type, $n = 52$), signet-ring cell (diffuse type, $n = 21$) and mixed ($n = 13$) adenocarcinomas. iNOS was expressed in half of dysplasia and tubular adenocarcinoma cases, but only in 30% of mixed and 17% of signet-ring cell adenocarcinomas. The prevalence of both nitrated proteins and 8-oxo-dGuo was higher in dysplasia (85 and 75%, respectively). The prevalence of nitrated proteins was 67% in tubular, 57% in signet-ring cell and 44% in mixed adenocarcinomas. The prevalence of 8-oxo-dGuo was similar in tubular (37%), signet-ring cell (42%) and mixed (36%) adenocarcinomas.

The degree of protein and DNA damage, reflected by NTYR and 8-oxo-dGuo immunostaining, is high in dysplasia and does not depend on the type of adenocarcinoma. In contrast, iNOS expression varies in the various forms of gastric carcinoma, being high in the intestinal type and its precancerous stage (dysplasia) and nearly absent in the diffuse type. These findings suggest that, in addition to inducing formation of oxidative and nitrative species, iNOS may play another role in carcinogenesis, for example in angiogenesis.

Nitrated and oxidized plasma proteins as biomarkers of oxidative stress

Nitrated and oxidized plasma proteins in smokers and lung cancer patients

B. Pignatelli, C.-Q. Li, C. Malaveille, P. Boffetta, H. Ohshima; in collaboration with W. Ahrens, Bremen, Germany; I. Bruske-Hohlfeld, Munich, Germany; Q. Chen, H. Ischiropoulos, Philadelphia, PA, USA; V. Constantinescu, Bucharest, Romania; C. Fortes, Rome, Italy; A. Mukeria, Moscow, Russian Federation; F. Nyberg, Stockholm, Sweden

Oxidants either present in cigarette smoke and/or formed in the lung of smokers may trigger oxidative and nitrative damage to DNA and cellular components, contributing to carcinogenesis. We have developed new simple and sensitive methods, requiring only 20 µg of protein, to measure oxidized (carbonyl-containing) and nitrated (NTYR-containing) proteins in human plasma or tissues using immuno-dot blot assays and applied them for analysis of plasma samples collected from 52 lung cancer patients and 43 control subjects (heavy and light smokers, non-smokers with or without exposure to environmental tobacco smoke) (see Section 3.7). The levels of nitrated proteins were significantly higher in lung cancer patients than in controls ($p = 0.003$), while the levels of oxidized proteins were significantly higher in smokers than in non-smokers ($p < 0.001$). Among non-smokers, exposure to passive smoking was associated with increased levels of oxidized proteins. We identified fibrinogen, transferrin, plasminogen and ceruloplasmin as nitrated proteins and fibrinogen as the only oxidized protein present in human plasma of lung cancer patients and smokers. Our results clearly show that cigarette smoking increases oxidative stress and that during lung cancer development, formation of reactive nitrogen species results in nitration and oxidation of plasma proteins. In the same subjects, we analysed genetic polymorphisms of myeloperoxidase, manganese superoxide dismutase and glutathione *S*-transferases (M1 and P1 forms). The relationships between genotypes, levels of modified proteins and tobacco exposure are being evaluated.

Nitrated and oxidized plasma proteins as biomarkers for chemoprevention trials

S. Baflast, I. Gilibert, B. Pignatelli, H. Vainio, H. Ohshima; in collaboration with I. Kato, Z. Djuric, Detroit, MI, USA; P. Srivatanakul, Bangkok, Thailand; J. Virtamo, Helsinki, Finland

DNA and tissue damage caused by reactive oxygen and nitrogen species has

been associated with cancer risk at various sites. Dietary antioxidants inhibit such damage. We are measuring oxidized and nitrated proteins in studies of liver fluke infection, inflammation and liver cancer in Thailand, of dietary habits and breast cancer risk in the United States and of the efficacy of chemopreventive agents (β-carotene, α-tocopherol) in Finnish smokers (the ATBC study). In addition, we plan to study effects of smoking cessation and betel-quid chewing on oxidative and nitrative stress.

Suppression of intestinal polyposis in $Apc^{Min/+}$ mice by inhibiting NO production

H., Ohshima, M.P. Cros, M. Laval, N. Lyandrat; in collaboration with B. Ahn, Seoul, Korea

Increased expression of iNOS has been associated with some pathological conditions such as ulcerative colitis, colon adenomas and carcinomas in human subjects. $Apc^{Min/+}$ mice spontaneously develop multiple polyps in the small and large intestines at the age of 10–12 weeks and thus provide a useful animal model for studies of human familial adenomatous polyposis (FAP) and sporadic colorectal cancers. We have shown by RT-PCR and immunohistochemistry that iNOS is expressed in normal mucosa and adenoma of the small and large intestines of $Apc^{Min/+}$ mice. Experimental strategies to suppress iNOS include (*a*) pharmacological treatment with the iNOS-selective inhibitor aminoguanidine, (*b*) nutritional restriction of the iNOS substrate L-arginine and (*c*) generation of iNOS knockout p53-deficient mice. Administration of aminoguanidine (1.5 g/L) in drinking water or an L-arginine-deficient diet to $Apc^{Min/+}$ mice resulted in significantly decreased adenoma development in the small intestine (Figure 32). Similarly, iNOS-gene knock-out $Apc^{Min/+}$ mice ($Apc^{Min/+}iNOS^{-/-}$ or $Apc^{Min/+}iNOS^{-/+}$) developed significantly fewer adenomas in both small and large intestines than $Apc^{Min/+}iNOS^{+/+}$ mice. These results suggest that iNOS-selective inhibitors may have potential as chemopreventive agents against colorectal cancers [2].

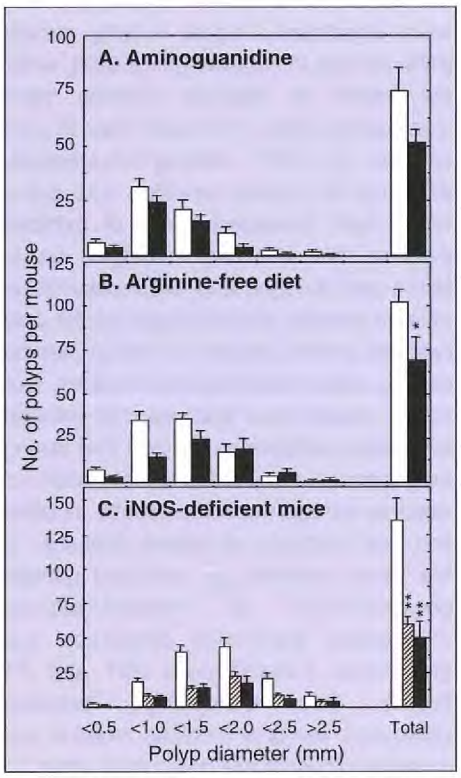

Figure 32. Size distribution of polyps in the small intestine of Min mice. (A) Effect of iNOS inhibitor aminoguanidine in drinking water (solid bars) and control (open bars); (B) effect of arginine-free diet (solid bars) and control amino acid diet (open bars) and (C) effect of different iNOS genotypes, $Apc^{Min/+}iNOS^{+/+}$ (open bars), $Apc^{Min/+}iNOS^{-/+}$ (hatched bars) or $Apc^{Min/+}iNOS^{-/-}$ (solid bars)

*, **, Significantly different from controls at $p < 0.05$ and $p < 0.0005$, respectively.

Role of iNOS in tumour development in p53-deficient mice

H. Ohshima, M. Masuda, M. Saleem Bhat, M. Tatemichi, M.P. Cros, M. Laval, N. Lyandrat, H. Ohgaki

Overproduction of NO is involved in the pathogenesis of cancer at various organ sites in both rodents and humans. Recent studies suggest that there is interaction between iNOS and the p53 tumour-suppressor protein. In order to study the role of iNOS in development of lymphoma and sarcoma in p53-deficient mice, we are studying the effects of iNOS inhibition. Our preliminary results suggest that mice lacking both the *iNOS* and *TP53* genes develop lymphoma, but not sarcoma, less frequently than iNOS-wild-type p53-deficient mice.

Modification of functions of p53 by NO

L. Chazotte-Aubert, H. Ohshima O. Pluquet, P. Hainaut

Mammalian cells incubated with excess NO accumulate p53 protein but concomitantly this p53 loses its capacity for binding to its DNA consensus sequence (Calmels *et al.*, 1997, *Cancer Res.*, **57**, 3365–3369). We have shown that tyrosine residues of p53 protein extracted from a breast cancer cell line (MCF-7) treated with an NO-releasing compound (*S*-nitrosoglutathione (GSNO)) were nitrated, suggesting that nitrated p53 protein lost its normal tumour-suppressor function [89], in a similar manner to the functional impairment of many other proteins by nitration. MCF-7 cells preincubated in the presence of GSNO before γ-irradiation failed to arrest in the G1 phase of the cell cycle, whereas those γ-irradiated without GSNO exhibited normal cell cycle arrest [90]. The GSNO-treated cells did not express the p53 target gene $p21^{waf1}$ after γ-irradiation, although this gene was strongly expressed in cells irradiated in the absence of GSNO. These results strongly support the notion that NO impairs the function of p53, possibly via conformational change and/or amino acid modifications. On the other hand, cells incubated for 16 h in the presence of GSNO underwent apoptosis with accumulation of the pro-apoptotic protein Bax. This Bax accumulation, however, was shown to occur via a p53-independent pathway [90].

Post-translational modification of p53 by nitric oxide

K. Fukunaga, R. Fukunaga, H. Ohshima, P. Hainaut; in collaboration with H. Arakawa, Y. Taya, Tokyo, Japan

NO has been attributed diverse functions in many cell types. We are investigating effects of NO on post-translational modifications of p53 protein, including nitration, phosphorylation and acetylation, which play important roles in regulating the biological activity of p53. We have detected two types of p53 phosphorylation site in MCF-7 cells treated with GSNO: an early type and a delayed

type. Different p53 kinase pathways may be involved in these two modes of phosphorylation. We are also studying association between NO-induced post-translational modifications of p53 and the expression of p53 target genes. These include a new ribonucleotide reductase (p53R2), implicated in the repair of damaged DNA (Tanaka *et al.*, 2000, *Nature*, **404**, 42–49), and p53-regulated apoptosis-inducing protein 1 (p53A1P1) (Oda *et al.*, 2000, *Cell*, **102**, 849–862). p53R2 protein was found to be strongly induced in NO-treated cells (Figure 33).

Apoptosis and oxidative DNA damage caused by nitroxyl anion and hydrogen peroxide

L. Chazotte-Aubert, I. Gilibert, M. Saleem Bhat, H. Ohshima

Nitroxyl anion (NO^-), the one-electron reduction product of nitric oxide ($NO^\cdot$), can act as a reducing agent to generate the hydroxyl radical in the presence of hydrogen peroxide (H_2O_2) and transition metal ions. We have observed that MCF-7 cells incubated with Angeli's salt (an NO^--generating compound) plus H_2O_2 undergo apoptotic cell death, as shown by DNA ladder formation, chromatin condensation and nuclear fragmentation. Cells incubated with either Angeli's salt or H_2O_2 alone did not undergo apoptosis. Similarly, intracellular production of oxidants and nuclear levels of 8-oxo-dGuo, a marker of oxidative DNA damage, were significantly elevated in cells incubated with Angeli's salt and H_2O_2, but not in cells incubated with either compound alone. Diethylamine-NONOate (an $NO^\cdot$-releasing compound) plus H_2O_2 similarly induced apoptosis and produced intracellular oxidants, but did not cause oxidative DNA damage in MCF-7 cells; however diethylamine-NONOate, H_2O_2 and Fe(III)-EDTA did not form oxidant(s) *in vitro*. These results suggest that $NO^\cdot$ is converted to NO^- in cells, possibly in mitochondria, and exerts cytotoxic effects in the presence of H_2O_2. Thus, NO^- plays an important role in the tissue damage induced by excess NO in inflammation.

Formation of carcinogenic N*-nitrosamines and* N*-nitramines by the reaction of secondary amines with reactive nitrogen species*

M. Masuda, B. Pignatelli, I. Celan, M.D. Friesen, H. Ohshima; in collaboration with H.F. Mower, Hawaii, USA, H. Nishino, Kyoto, Japan

Reactive nitrogen species, including nitrogen oxides (N_2O_3, N_2O_4), peroxynitrite ($ONOO^-$) and nitryl chloride (NO_2Cl), have been implicated as causes of inflammation and cancer. We have found that both *N*-nitrosamines and *N*-nitramines were formed in reactions of secondary amines with peroxynitrite [272]. On the basis of kinetic studies, we have proposed a free-radical mechanism involving one-electron oxidation by peroxynitrite of secondary amines to form amino radicals ($R_2N^\cdot$), that react with $NO^\cdot$ or nitrogen dioxide ($^\cdot NO_2$) to yield nitroso- and nitro-secondary amines, respectively. Such reactions of secondary amines with reactive nitrogen species generated in inflamed tissues might generate carcinogenic *N*-nitrosamines and *N*-nitramines. Levels of nitrated secondary amines such as *N*-nitroproline could also be determined as specific markers for endogenous nitration mediated by reactive nitrogen species.

Products formed by reaction of tryptophan with peroxynitrite as a biomarker of amino acid or protein damage caused by reactive nitrogen species

T. Suzuki, M.D. Friesen, H. Ohshima; in collaboration with H.F. Mower, Hawaii, USA

Peroxynitrite ($ONOO^-$), generated from nitric oxide (NO) and superoxide ($O_2^{\cdot-}$), plays an important role in inflammatory tissue injury. The reaction of tyrosine with peroxynitrite generates the nitrated derivative 3-nitrotyrosine, that is now analysed as a biomarker for tissue damage caused by reactive nitrogen species. Tryptophan is another important target amino acid for protein damage caused by peroxynitrite, since it reacts with peroxynitrite more readily than tyrosine. We have studied the reaction of *N*-acetyltryptophan with peroxynitrite and identified several products including 1-nitrosotryptophan, 6-nitrotryptophan and *N*′-formylkynurenine (Figure 34). 6-Nitrotryptophan is the most stable of these products under physiological conditions and thus may be suitable as a biomarker of protein alteration caused by peroxynitrite and possibly by other reactive nitrogen species.

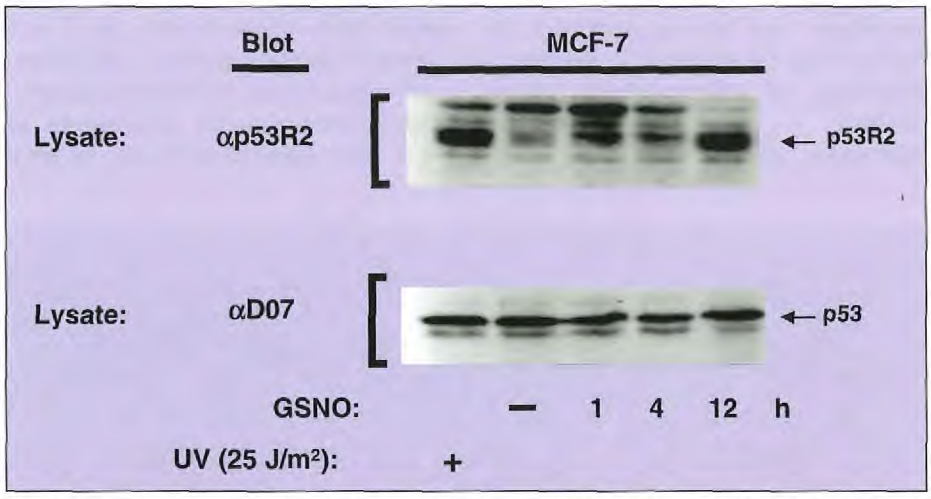

Figure 33. Time-dependent expression of endogenous p53R2 protein in MCF-7 cells treated with *S*-nitrosoglutathione (GSNO). MCF-7 cells incubated with *S*-nitrosoglutathione were analysed by western blot analysis using a polyclonal antibody against p53R2.

Myeloperoxidase in carcinogenesis

Chlorination of guanosine and other nucleosides by hypochlorous acid and myeloperoxidase

M. Masuda, T. Suzuki, T. Nakano, M.D. Friesen, B. Pignatelli, H. Ohshima; in collaboration with H.

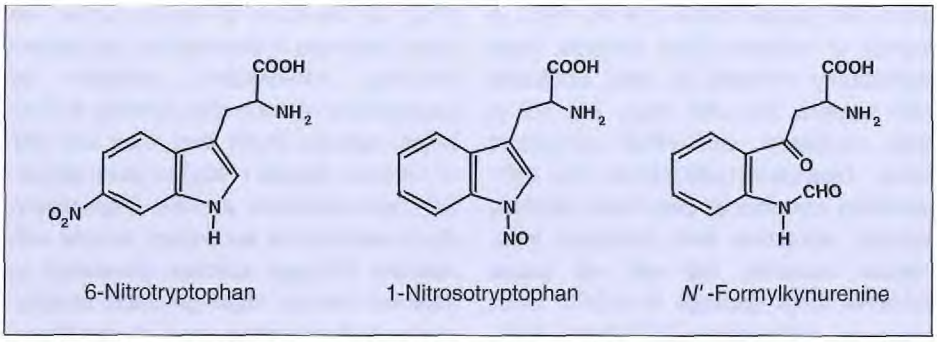

Figure 34. Products generated from the reaction of tryptophan with peroxynitrite.

Nishino, Kyoto, Japan; J.-L. Ravanat, J. Cadet, Grenoble, France

Activated human neutrophils secrete myeloperoxidase, which generates hypochlorous acid (HOCl) from hydrogen peroxide (H_2O_2) and chloride ion (Cl^-). We have found that various (2′-deoxy)-nucleosides react with HOCl to form chlorinated (2′-deoxy)nucleosides, including 8-chloro(2′-deoxy)guanosine, 5-chloro(2′-deoxy)cytidine and 8-chloro(2′-deoxy)adenosine [274]. When we treated guanosine with HOCl, myeloperoxidase and activated human neutrophils in the presence or absence of nitrite, 8-chloroguanosine was always more easily formed than 8-oxo- or 8-nitro-guanosine. Using electrospray ionization tandem mass spectrometry, we found that several chlorinated nucleosides including 8-chloro(2′-deoxy)guanosine were formed following exposure of isolated DNA or RNA to HOCl (Figure 35). Micromolar concentrations of tertiary amines such as nicotine and trimethylamine dramatically enhanced the chlorination of free (2′-deoxy)nucleosides and nucleosides in RNA by HOCl. Reduced expression of myeloperoxidase mRNA due to a known polymorphism of the *MPO* gene is associated with lower risk of lung cancer, suggesting that chlorination damage of DNA, RNA or nucleosides by myeloperoxidase and its enhancement by nicotine may be important in the pathophysiology of tobacco-related human diseases.

Substances that can scavenge HOCl-generating oxidants, inhibit MPO activities or prevent activation of neutrophils could be potentially useful to reduce DNA or tissue damage in inflamed tissues. We are screening naturally occurring substances and drugs which have such inhibitory activities as possible chemopreventive agents against inflammation-associated human cancer.

Similarly, tyrosine residues in proteins are chlorinated by the human MPO/HOCl system to form 3-chlorotyrosine. Immunoassays to detect chlorinated proteins in inflamed tissues and biological fluids are being developed.

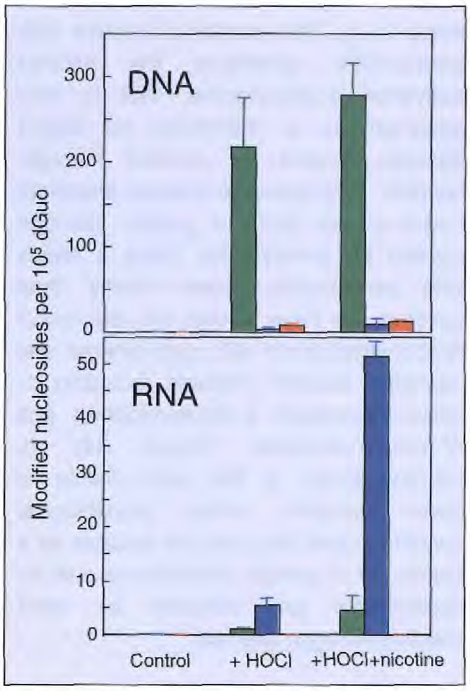

Figure 35. Analyses of chlorinated nucleosides formed in DNA and RNA (1 mg/ml) following exposure to 200 μM HOCl with or without 20 μM nicotine at 37°C for 15 min, by HPLC associated with tandem mass spectrometry ■ 5-Chlorocytosine, ■ 8-chloroguanine, ■ 8-chloroadenine

New reaction products formed from 2′-deoxyguanosine with hypochlorous acid or a myeloperoxidase–H_2O_2–Cl^- system

T. Suzuki, M. Masuda, M.D. Friesen, H. Ohshima; in collaboration with B. Fenet, Lyon, France

We have found that among four naturally occurring nucleosides, 2'-deoxyguanosine (dGuo) reacts most easily with HOCl to form several products including 8-chloro-2′-deoxyguanosine (8-Cl-dGuo). However, the yield of 8-Cl-dGuo did not account fully for the consumption of dGuo. Two other products were also generated in this system (Figure 36). One is an imidazolone nucleoside (dIz) previously reported as a product of dGuo formed with hydroxyl radical or by one-electron oxidation under aerobic conditions. The other product was identified on the basis of spectrometric measurements as a new diimino-imidazole nucleoside, 2,5-diimino-4-[(2-deoxy-β-D-*erythro*-pentofuranosyl)-amino]-2*H*,5*H*-imidazole (abbreviated as dDiz). The yields of dDiz and dIz were

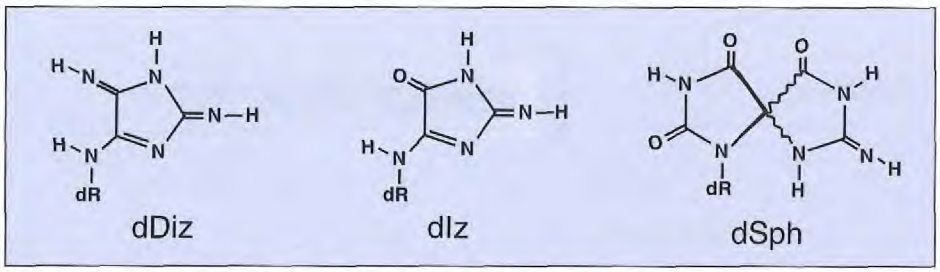

Figure 36. The structures of the diimino-imidazole nucleoside (dDiz), imidazolone nucleoside (dIz) and spiroiminodihydantoin deoxyribonucleoside (dSph) identified as reaction products of 2′-deoxyguanosine with hypochlorous acid or a myeloperoxidase–H_2O_2–Cl^- system. dR denotes 2′-deoxyribose.

similar to that of 8-Cl-dGuo. The same three products were also formed in the reaction of dGuo with myeloperoxidase in the presence of H_2O_2 and Cl^- under mildly acidic conditions.

HOCl also reacts easily with 8-oxo-dGuo to form spiroiminodihydantoin deoxyribonucleoside (dSph) [458] (Figure 36). Identification was based on various spectrometric measurements. The conversion of 8-oxo-dGuo to dSph proceeded almost quantitatively without producing any by-products, and much faster than the reaction with dGuo. dSph was also formed by reaction of 8-oxo-dGuo with myeloperoxidase in the presence of H_2O_2 and Cl^-.

Our results imply that dDiz, dIz and dSph may be important DNA lesions formed by HOCl and other reactive oxygen species in inflamed tissues. Genotoxic effects of these modified nucleosides that may be formed in the nucleotide pool and DNA in cells are being assessed.

4.4 Role of cell–cell interactions 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 studied at IARC.

Mutations of connexin genes and human colon carcinogenesis

V. Krutovskikh; in collaboration with M.V. Dubina, D.E. Popov, N.A. Iaitckii, St Petersburg, Russian Federation

The connexin (Cx) gap junction proteins are considered to act as tumour-suppressors. Their function or expression is frequently aberrant in tumour cells and several mechanisms appear to be involved. It is not yet certain whether irreversible mutational alterations of connexin genes are among these mechanisms. Recent findings that the tumour-suppressive ability of individual members of the connexin protein family is fairly different between different tissues may help to explain why certain Cx genes have not been found mutated in certain types of tumour. It also suggests that mutational deactivation of Cx proteins in tumours could be rather tissue- and connexin-species-specific.

Twenty-nine human colon tumours with different degrees of progression towards malignancy (from benign adenomatous polyps to poorly differentiated invasive carcinomas) along with surrounding non-tumour colon mucosa were analysed. Immunostaining revealed that both connexins 32 and 43 were expressed in normal human enterocytes. About two thirds of the tumours analysed also tested positive for these connexins. In these colon tumours, mutations of the *Cx32* gene were not detected, whereas the part of the *Cx43* gene corresponding to the C-tail of the protein from colon tumour samples was found to contain mutations. A pseudogene origin of these mutations was excluded. In two out of three moderately differentiated adenocarcinomas, a single nucleotide deletion in codon 310 was detected that caused a shift of reading frame and a premature stop codon. Another shift of reading frame due to a single nucleotide insertion in codon 358 was found in another colon tumour.

Double immunostaining with a pair of antibodies against different epitopes of Cx43 revealed selective expression of mutated Cx43 in tumour glands prone to invasion (Figure 37). Taken together, our data indicate that Cx43 mutations may arise at a rather late stage of human colon tumour development, giving a spur towards malignancy.

Adhesive determinants of plakoglobin in tumour suppression

V. Krutovskikh, C. Piccoli; in collaboration with S. Troyanovsky, St Louis, MO, USA

Plakoglobin (γ-catenin, Pg) is a member of the armadillo protein family with striking structural similarity to the oncoprotein β-catenin. However, unlike β-catenin, it has not been found frequently mutated in human tumours and is considered to act as a tumour-suppressor. Our experiments have shown that in human fibrosarcoma cells (HT1080) normally negative for this protein, restoration of Pg expression inhibited their tumorigenicity in nude mice. Plakoglobin and β-catenin are multifunctional proteins: interacting with different cadherins and other catenins, they form adherens junctions and desmosomes, which provide intercellular adhesiveness. In addition, these proteins take part in the Wnt signal transduction pathway. Both these functions could be critical for either tumour suppression or progression. The principal functional difference between Pg (a tumour suppressor) and β-catenin (an oncoprotein) is a predominance of its role in adhesion over its signalling capacity. We have therefore proposed that some adhesive properties of Pg may be critical for inhibition of tumour growth. Various domains of the Pg protein responsible for its interaction with other cell adhesion proteins have recently been identified. Using several point mutants of Pg that are deficient for interaction either selectively with α-catenin or desmosomal cadherins (desmoglein and desmocollin), or simultaneously with all these three proteins, we found that loss of binding activity diminished but did not abolish the anti-growth properties of Pg. Next, we are planning to compare the signalling abilities of mutated and intact Pg and their interaction with certain transcription factors. The results will show whether the tumour-suppressive properties of Pg depend on its role in cell-cell contacts or on a direct action in regulation of transcription.

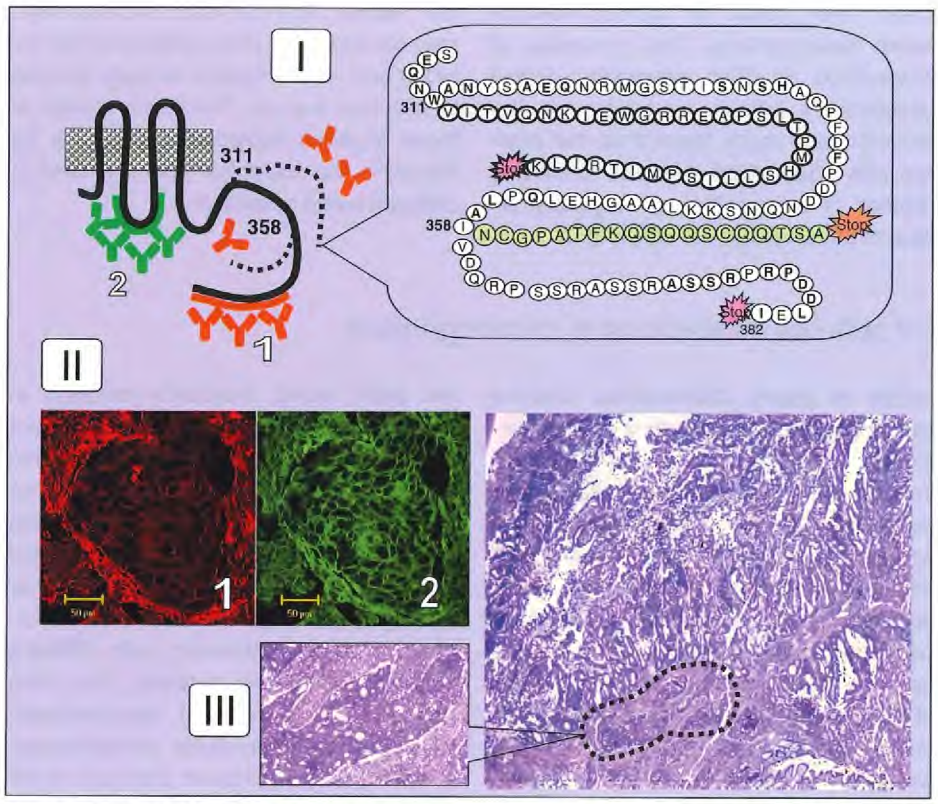

Figure 37. Connexin (Cx43) mutations in human colon cancer. I, Frameshift mutations due to either single nucleotide deletion (Δ) in codon 310 or insertion in codon 358 result in changed composition of the C-tail of the protein. II, Double immunostaining with antibodies recognizing either non-mutated (1) or both mutated and non-mutated (2) Cx43 revealed that mutated Cx43 is selectively expressed in morphologically distinct glands in the invasive front of tumours (III).

Roles of different cadherins in regulation of metastatic phenotype of cancer cells

V. Krutovskikh, C. Piccoli; in collaboration with S. Troyanovsky, St Louis, MO, USA

Cadherins comprise a family of transmembrane proteins essential for intercellular adhesion. Due to homophilic interaction of their intercellular domains, they help to maintain tissue integrity. In addition, cadherins (via interaction with the intercellular catenin proteins) possess signalling capacity via intracytoplasmic domains. Tumour cells with altered cadherin function acquire a metastatic phenotype. Several mechanisms have been reported to be responsible for tumour-associated alteration of cadherins. In particular, it has been found that a shift of expression from E-cadherin to the structurally similar N-cadherin is involved in the acquisition of metastatic properties by tumour cells.

To elucidate whether the adhesiveness or signalling function of cadherin proteins is more critical in controlling the metastatic properties of tumour cells, the highly metastatic human breast carcinoma cell line SKBR3, that lacks both E- and N-cadherins, has been transfected with cDNA of either E- or N-cadherin. The growth, morphology and metastatic capacity of the resulting stable clones in nude mice were examined. Although neither the parental cells nor the tested clones gave rise to tumour nodules at the site of cell inoculation, all formed metastatic nodules in the axilla. However, E-cadherin expression diminished the metastatic capacity of SKBR3 cells, whereas expression of N-cadherin enhanced it. In order to find which domains of different cadherins are critical for regulation of metastatic behaviour, chimeric constructions with exchanged extracellular domains from both E- and N-cadherins have been created and stably transfected into SKBR3 cells. The growth and metastatic properties of the clones obtained are now being assessed.

4.5 *Mutator phenotype and carcinogenesis*

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 and sporadic, and subsequently for many other cancers, including those of the endometrium, stomach and oesophagus.

Genomic instability in oral cancer patients from India

S. Zienolddiny, A.-M. Aguelon, N. Mironov, R. Sankaranarayanan, H. Yamasaki

Genomic instability is exhibited by a variety of cancer types. This may concern large segments of the genomic DNA or single nucleotides. An increased degree of genomic instability may affect the stability of the many cancer-related genes which harbour microsatellite sequences within their coding sequences. In addition, genes located between these sequences may be a target of genetic alterations such as a high frequency of deletions and amplifications. A modified PCR approach known as inter-simple sequence repeat (inter-SSR) was used to screen tumours from 37 Indian oral cancer patients for genomic instability in sequences flanked by CA and GT dinucleotide repeats scattered throughout the genome. In these tumours, 38% had genomic alterations in sequences flanked by $(CA)_8$ and $(GT)_8$ dinucleotides. Patients with tumours harbouring genomic alterations had a

two-fold higher frequency of betel-quid chewing (12.1 chewings/day; 95% CI 3.4–20.8) than patients with tumours lacking genomic alterations (6.2 chewings/day; 95% CI 3.5–8.9). These patients also had an almost two-fold higher number of lifetime chewings (121×10^3; 95% CI 44.5–197.4×10^3) than patients without genomic alterations (66.1×10^3; 95% CI 30.1–102.1×10^3). The patients were also screened for microsatellite instability within specific $(CA)_n$ repeats located on four different chromosomes. Tumour DNA from five patients (13.5%) showed alterations in at least one microsatellite marker. Two of the five tumours with microsatellite instability had alterations in at least two markers and therefore could be defined as high in microsatellite instability. However, there was no relationship between the microsatellite status of the tumours and betel-quid chewing habits of the patients. These data indicate that exposure to carcinogens present in the betel-quid may have an adverse effect on the stability of repeated DNA sequences scattered throughout the genome.

Relationship between cytosine methylation and microsatellite instability

Q. Xiong, A.-M. Aguelon, N. Mironov, H. Yamasaki

Regulation of gene expression through epigenetic mechanisms such as regulation of promoter methylation has been reported for several cancer types. Recent data suggest a correlation between replication error-positive (RER^+) phenotype and aberrant promoter methylation of some genes.

The *Cx32* gene is transcribed from two alternative promoters, P1 and P2. The methylation status of the promoters was investigated in human colon cancer cell lines as well as in matched normal and colon tumour tissues. Methylation of P1 was detected in three out of six cell lines, whereas P2 was methylated in four. Two of the six showed methylation of both promoters and both of these cell lines showed an RER^+ phenotype with a high degree of microsatellite instability. These data suggest that epigenetic inactivation of the *Cx32* gene plays an important role in tumorigenesis and demonstrate a correlation between *Cx32* promoter methylation and microsatellite instability.

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.

Functional analysis of DNA end-binding proteins

Tumour suppression by poly(ADP-ribose) polymerase (PARP) in humans and in mouse models

W.-M. Tong, Z. Herceg, U. Cortes, V. Petrilli, P.-O. Frappart, C. Cuenin, C. Piccoli, C. Granier, A. Barbin, Z.-Q. Wang; in collaboration with P. Hande, New York, USA; S. Jackson, Cambridge, UK; P. Lansdorp, Vancouver, Canada

PARP, which catalyses poly-ADP-ribosylation of nuclear proteins upon DNA damage, is proposed to play a role in chromosomal integrity, DNA repair and recombination, cell proliferation and cell death [184]. While PARP mutant mice develop normally and show normal fertility, they are hypersensitive to γ-radiation [480], indicating a role of PARP in DNA damage response. This defect can be reversed by the human homologue of PARP. In addition, we have shown that PARP mutant cells exhibit high levels of sister chromatid exchange and micronucleus formation in response to DNA damage, telomere shortening and chromosomal aberrations, indicative of genomic instability [184, 433]. Although PARP mutant mice develop spontaneous tumours at a low frequency and in a strain-dependent manner, they are susceptible to chemically induced liver carcinogenesis. These data indicate that PARP may function as a tumour suppressor.

To further test the role of PARP in tumorigenesis, mice were generated that lacked both PARP and p53. The tumour spectrum of these $PARP^{-/-}p53^{-/-}$ mice was wider than that of $p53^{-/-}$ controls, including brain tumours and carcinomas of the colon, pancreas, skin and liver. $p53^{+/-}$ mice with a PARP-deficient background also developed a high frequency of mammary gland carcinomas and brain tumours, reminiscent of the Li–Fraumeni syndrome in humans [481]. The enhanced tumorigenesis was probably caused by telomere dysfunction and chromosomal instability mediated by the absence of PARP and p53. While $PARP^{-/-}$ cells exhibited telomere shortening, in $p53^{-/-}$ cells telomere length was normal. However, inactivation 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 [481].

Ku80 is a major DNA end-binding molecule and $Ku80^{-/-}$ cells show severe shortening of telomeres and prominent chromosomal aberrations such as fusions, fragmentation and breaks, as well as loss of telomeric signals, suggesting that Ku80 is important in telomere function and chromosome stability [105]. PARP and Ku80 interact at DNA strand

interruption and are believed to cooperate to stabilize the genome. To study the biological significance of this interaction *in vivo*, $PARP^{+/-}Ku80^{+/-}$ mice were intercrossed to generate doubly mutant mice. PARP/Ku80 doubly null mice died at embryonic day 9.5, suggesting that genetic cooperation of both genes is required in early embryonic development. While $Ku80^{-/-}$ mice are generally not tumour-prone (developing a low frequency of tumours), haplo-insufficiency of Ku80 in $PARP^{-/-}$ mice results in multi-organ epithelial hyperplasia or dysplasia and a high frequency of hepatoma and hepatocellular carcinoma (HCC). These tumours exhibit multi-stage progression, characterized by loss of E-cadherin during transition from adenoma to carcinoma (Figure 38), mutations of β-catenin and a high rate of chromosome aberrations, as in human HCC. It is thus clear that the functional synergism of PARP and Ku80 plays an important role in development and in suppressing liver tumorigenesis.

Genetic studies of human HCC have revealed frequent abnormalities in chromosome 1q, such as trisomy and translocation and also loss of heterozygosity (LOH) at chromosome 1q42-43 and 2q35-37. Since PARP and Ku80 are located at human chromosome 1q41-42 and 2q33-34, respectively, we are investigating whether the imbalance or loss of chromosome 1q may alter human PARP gene expression or its ADP-ribosylation activity, and whether imbalance of 2q35-37 in humans can lead to Ku80 deficiency, contributing to HCC formation. Taken together, these data demonstrate that PARP deficiency promotes tumour development, most likely due to genome instability and dysfunction of telomeres, and that PARP serves as a cofactor for suppressing tumorigenesis.

Study of molecules responsible for DNA repair/damage response and generation of mouse models for human Nijmegen breakage syndrome

V. Dumon, G. Schmid, P.-O. Frappart, Z. Herceg, W.-M. Tong, G. Sajithlal, Z.-Q. Wang; in collaboration with M. Digweed, Berlin, Germany

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disease characterized by microcephaly, growth retardation, chromosomal instability, immunodeficiency, radiosensitivity and predisposition to cancer. The protein nibrin (Nbs1) has been proposed to play a role in DNA double-strand break repair and cell-cycle checkpoints and has been shown to be involved in telomere function. In response to DNA damage, Nbs1 can be activated by ATM, a DNA damage-signalling molecule that is mutated in ataxia telangiectasia cells. This activation may further activate downstream molecules including p53 and BRCA1.

To investigate the physiological function of Nbs1 *in vivo* and to establish an animal model for this human disease, we disrupted the murine homologue (Nbn) of Nbs1 by homologous recombination. Mice lacking nibrin ($Nbn^{-/-}$) die between embryonic stages E3.5 and E7.5, suggesting an essential role for this molecule in the basic function of cells. Culture of $Nbn^{-/-}$ blastocysts revealed a growth deficiency of the inner cell mass and enhanced apoptosis in these cells. However, embryonic stem (ES) cells devoid of nibrin are capable of forming most somatic tissues, except cerebral cortex, in chimeric mice, suggesting that nibrin is dispensable for proliferation and DNA replication. $Nbn^{-/-}$ ES cells subjected to ionizing radiation accumulate massive DNA breaks and show high susceptibility to chromosome aberrations. $Nbn^{-/-}$ cells show radioresistant DNA synthesis and a defective G2/M checkpoint. These results demonstrate that although nibrin is dispensable for DNA replication during cell proliferation, it is required for embryonic development. Moreover, these data confirm the role of Nbs1 in humans in DNA repair, S-phase checkpoint and chromosome stability. We have observed a high frequency of tumour development in aged Nbn heterozygous mice. Southern blot analysis showed the remaining wild-type allele in the tumours, suggesting that haplo-insufficiency of Nbn causes tumour development, which would be consistent with the tumour susceptibility of NBS patients.

To avoid the early lethal effect of knocking out Nbn in mice and to further study the role of Nbn in DNA damage response, genomic recombination and tumorigenesis, we have taken a 'conditional' gene targeting approach to introduce a null mutation of Nbn in specific tissues and at specific developmental stages.

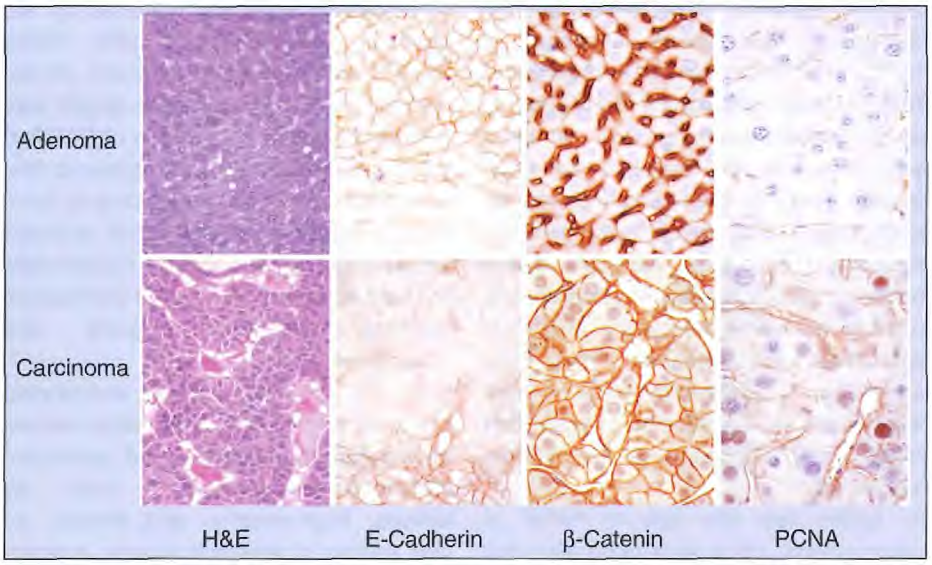

Figure 38. Liver tumours in $PARP^{-/-}$ $Ku80^{+/-}$ mice, showing a distinct trabecular pattern and areas with glandular structure. Immunostaining of adjacent section from hepatocellular adenoma, and carcinoma with antibodies against E-cadherin or β-catenin reveals focal loss of E-cadherin and translocation of β-catenin to the nucleus in the carcinomas.

Functional study of molecules in cell-cycle control and mitotic checkpoint

Z. Herceg, H. Li, C. Cuenin, Z.-Q. Wang; in collaboration with S. Jackson, Cambridge, UK

The basic task of the cell cycle is to ensure that DNA is faithfully replicated during S phase and that identical chromosomal copies are distributed to daughter cells during mitosis. Cells possess checkpoints to monitor DNA replication, chromosomal segregation and cytokinesis in the correct order and to ensure cell-cycle progression based on successful completion of preceding events. Crucial insight into cell cycle control came with the discovery that many human tumour-suppressor genes, including *ATM* and *TP53*, which block S phase initiation when DNA is damaged or block DNA re-replication when the mitotic spindle is damaged, are critical components of distinct surveillance mechanisms. Mutations, deletions or amplifications of the pivotal genes of cell-cycle checkpoints frequently lead to aberrant cell function and tumour development.

Transformation/transcription domain-associated protein (TRRAP) is a newly identified member of the ATM/PI3-kinase superfamily and acts as a cofactor for c-myc and E2F oncoproteins. It is a component of chromatin-remodelling complexes harbouring histone acetyltransferase (HAT) activity, suggesting that it may play a role in cell viability, proliferation and oncogenic transformation. In order to study the biological function of TRRAP and how it controls proliferation, we inactivated the gene in embryonic stem cells and mice. Null mutation of Trrap in mice resulted in peri-implantation embryonic lethality due to blocked proliferation of blastocysts. We demonstrated that loss of Trrap causes a complete block of cell proliferation due to aberrant mitotic exit accompanied by failure of cytokinesis and endoreduplication. Trrap-deficient cells fail to delay mitotic entry despite chromosome missegregation and disrupted spindle assembly associated with compromised activity of mitotic kinase cdk1 (Figure 39) [183]. These results confirm that Trrap is essential for early development, mitotic checkpoints and normal cell-cycle progression.

The mitotic checkpoint monitors chromosome integrity and segregation. Mutations in any of the mitotic checkpoint genes (such as *BUB1* and *MAD2*) impair cell-cycle arrest, causing premature cell-cycle progression, aneuploidy and genomic instability. Therefore exit from mitosis with compromised checkpoint results in uncontrolled cell-cycle progression, aneuploidy and eventually neoplastic transformation. To study the biological consequences of Trrap deletion in tumour and disease development, we have generated mice by a 'conditional' knock-out approach with gene mutations in specific organs in order to study their effects on tumour development.

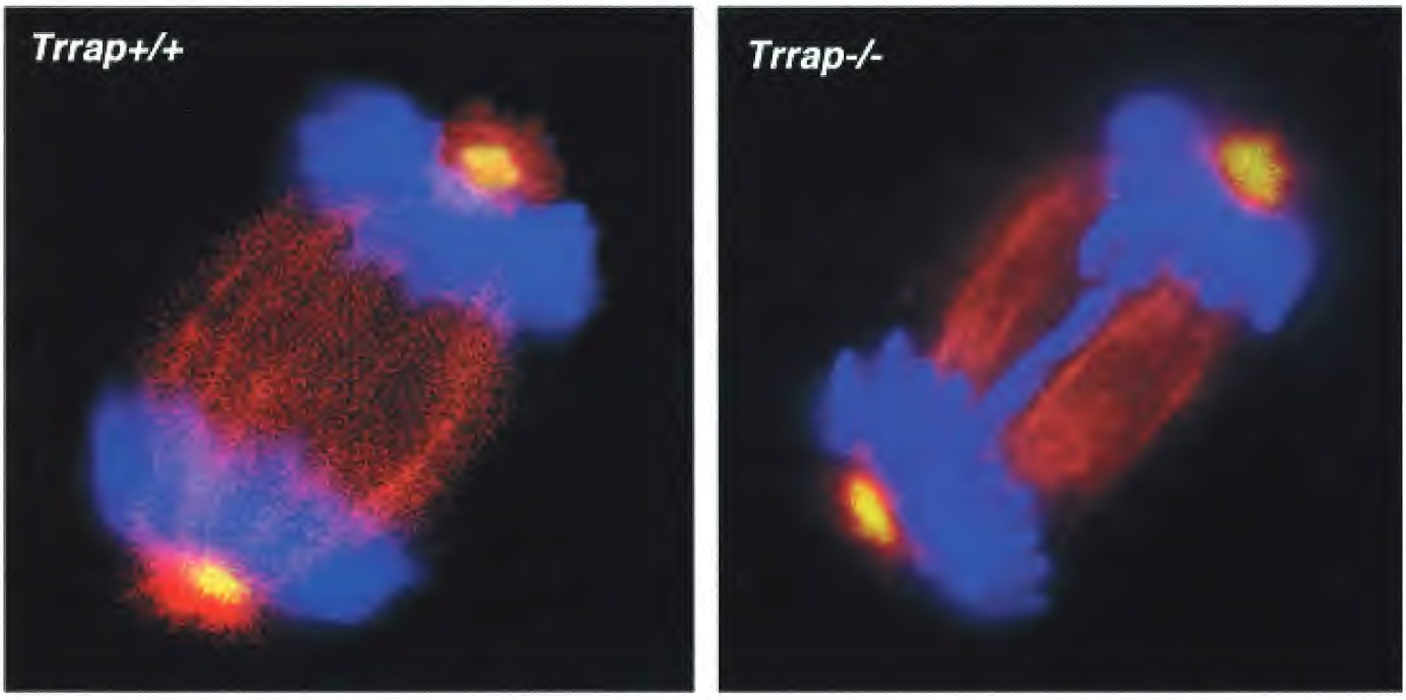

Figure 39. Trrap-deficient cells exhibit mitotic checkpoint defects. Trrap deletion was induced by Cre-mediated recombination in mouse embryonic fibroblasts and chromosome segregation errors (lagging chromosome) were detected in cells captured at anaphase by fluorescent microscopy after staining with anti-α-tubulin antibody (spindle, red), anti-γ-tubulin antibody (centrosome, green) and DAPI (blue).

The *TP53* tumour-suppressor gene encodes a nuclear phosphoprotein with cancer-inhibiting properties. Development of human cancer often involves inactivation of this suppressor function. *TP53* 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, scattered over more than 250 codons are common in most forms of human cancer.

Research on *TP53* at IARC includes analysis of mutations in inherited and sporadic forms of cancer, in particular cancer of the oesophagus (Section 3.1), liver (Section 3.3), brain (Section 3.5) and lung (Section 3.7), as well as studies on p53 protein structure, function and regulation, in relation to cellular response to DNA damage (Section 4.1) and to the action of nitric oxide (Section 4.3). A database of *TP53* mutations in human cancers is maintained.

Regulation of p53 protein conformation and activity by redox factors and metal compounds

O. Pluquet, S. North, S. Seemann, S. Courtois, D. Maurici, P. Hainaut; in collaboration with W. Deppert, Hamburg, Germany; T. Frebourg, Rouen, France; G. Fronza, Genoa, Italy; K. Mann, Anchorage, AK, USA; M. Oren, V. Rotter, Rehovot, Israel; A. Sacchi, Rome, Italy; T. Soussi, Paris, France

The p53 protein is intrinsically flexible and most mutations induce drastic changes in its conformation. Understanding the biochemical factors that affect and control the conformation of the p53 protein may allow the design of pharmacological approaches to stabilize wild-type p53 activity or to restore the activity of mutant p53. We have shown that binding of metals (zinc) and reduction of thiol groups are both essential for maintenance of p53 protein conformation and that the conformation is very sensitive to stress-induced changes in the cellular environment, such as oxidative or heavy metal stress. Thus, it is possible that many environmental risk factors affect p53 function by modulating the conformation and activity of the protein.

We have recently observed that the aminothiol amifostine, a drug used clinically as a radio- and chemo-protector, can stabilize the conformation of the p53 protein and activate its capacity to induce cell-cycle arrest. The classical model of p53 induction is that this protein is activated in response to DNA damage through disruption of its interaction with the protein mdm2, which is a negative regulator of p53 stability. We have found that amifostine activates p53 through a completely different pathway, which does not involve the formation of detectable DNA damage and is independent of the mdm2 protein. The main effector in this new pathway is a kinase induced in response to many forms of stress, c-Jun N-terminal kinase (JNK). Inactive JNK binds p53 and induces its degradation. When JNK is activated, this complex dissociates, allowing p53 to escape degradation. We have found that a dominant-negative form of JNK can at least partially block the activation of p53 by amifostine. This new, non-genotoxic pathway of p53 activation may be of interest as a target for development of chemo-protective or chemopreventive drugs.

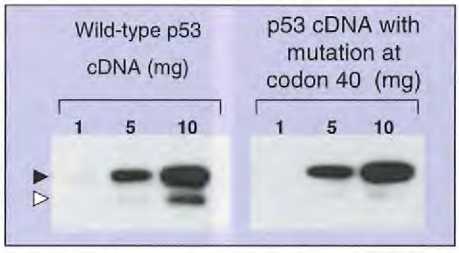

Figure 40. Demonstration of the existence of a shorter form of p53, lacking the N-terminus. In cells transfected with wild-type p53 cDNA (left), two forms of the protein are found: the full-length form (black arrow) and a shorter isoform (white arrow). In cells transfected with a p53 cDNA carrying a mutation at codon 40 (right), the shorter form is no longer seen. This shows that codon 40 in p53 acts as an initiation site for transcription of the short form, which may be important as a regulator of p53 function.

We have also developed yeast-based assays to analyse the phenotype of specific *TP53* mutants. Using yeast equipped with reporter genes under the control of promoter sequences derived from various human genes regulated by p53, we can determine whether a particular mutant has totally lost transcriptional activity or can still bind the promoters of some of the physiological p53-target genes. These assays can also be used to search for drugs that modulate the conformation of p53 or restore the activity of mutant p53 *in vitro*. For example, we have shown that amifostine can restore the activity of several rare forms of mutant p53. We are now using this assay to establish the functional profile of mutant forms of p53 expressed in human cancer. These studies are part of a project supported by the European Union that involves five other laboratories working on different aspects of p53 protein regulation.

During these experiments, we discovered that p53 can be expressed in the form of a shorter protein lacking the extreme N-terminal domain. We have fully characterized this new protein variant, which we have called ΔNp53. The ΔNp53 variant arises through internal initiation of translation at an in-frame ATG located at codon 40 (Figure 40). The protein is stable, binds to specific DNA with high affinity and counteracts the transcriptional activity of full-length, wild-type p53. It thus behaves as an 'anti-suppressor' and blocks the anti-proliferative effects of wild-type p53 transfected into human cancer cell lines. We have also shown that ΔNp53 is naturally expressed in a cell-cycle-dependent manner, with a peak at the late G1/early S stage. This is compatible with the hypothesis that it plays a role in keeping p53 function in check during the normal cell-division cycle. Thus, ΔNp53 may contribute to switching off p53 function so as to bypass a cell-cycle checkpoint in cells undergoing normal proliferation.

IARC database of *TP53* mutations in human cancer

M. Olivier, P. Hainaut; in collaboration with D. DeMarini, Research Triangle Park, NC, USA; M. Hollstein, Heidelberg, Germany; M. Khan, C.C. Harris, Bethesda, MD, USA; A. Martin, Reading, UK; J. Thornton; London, UK; G. Pfeifer; Duarte, USA

The IARC *TP53* mutation database is now recognized as a central resource for the identification of carcinogen 'fingerprints' in human cancer. The database was updated in July 2001 and currently contains over 15 000 mutations. A major effort has been devoted to improving the quality of annotations on individual exposure. A new web site has been designed, featuring a comprehensive search system that allows a user to query the database, to retrieve and sort the data as required, and to obtain search results in various graphic and tabular formats (Figure 41).

The main focus of the database is to provide data for research on mutation patterns. We have re-evaluated the patterns of mutations in breast cancers. Overall, this pattern does not reveal any particular mutation hotspot or mutation type. However, there are important differences between the patterns of mutations from Caucasian (Europe, United States) and Japanese women. In particular, the tumours of Caucasian women contain a greater proportion of transversions, suggesting a possible role of unspecified environmental carcinogens.

Several studies, including ours, have shown that the position of G to T transversions in lung cancers from smokers is compatible with the site of formation of adducts by metabolites of polycyclic aromatic hydrocarbons (PAHs) in cultured bronchial cells. This view has been contradicted in recent publications that claimed to have assessed the data in the IARC *TP53* database. This controversy prompted us to re-assess and confirm our interpretation [178] (Figure 42). Several lines of evidence indicate that the excess G to T transversions observed in smokers are directly caused by tobacco carcinogens. Furthermore, we have collaborated with Dr DeMarini (US Environmental Protection Agency) in an interpretation of mutation patterns in lung cancers of non-smoking women highly exposed to PAHs from barbecue fumes. This pattern shows an extremely high prevalence of mutations occurring at putative sites of formation of PAH–DNA adducts.

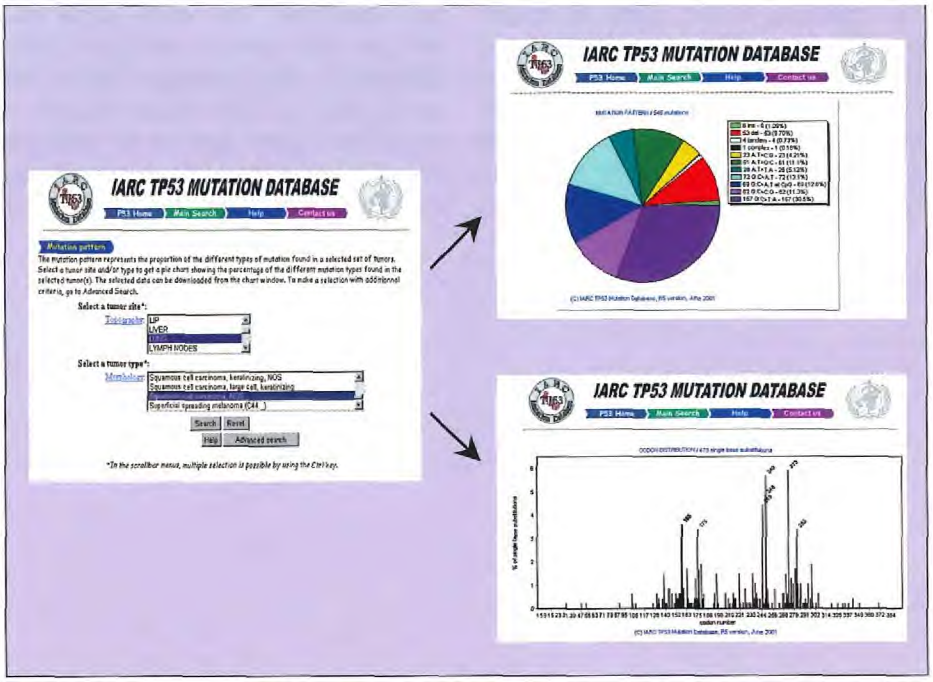

Figure 41. Searching the IARC TP53 mutation database. Simple queries can be made using pre-formatted menus (left) and the results can be displayed as pie charts showing the proportion of various types of mutation along the coding sequence (bottom right)

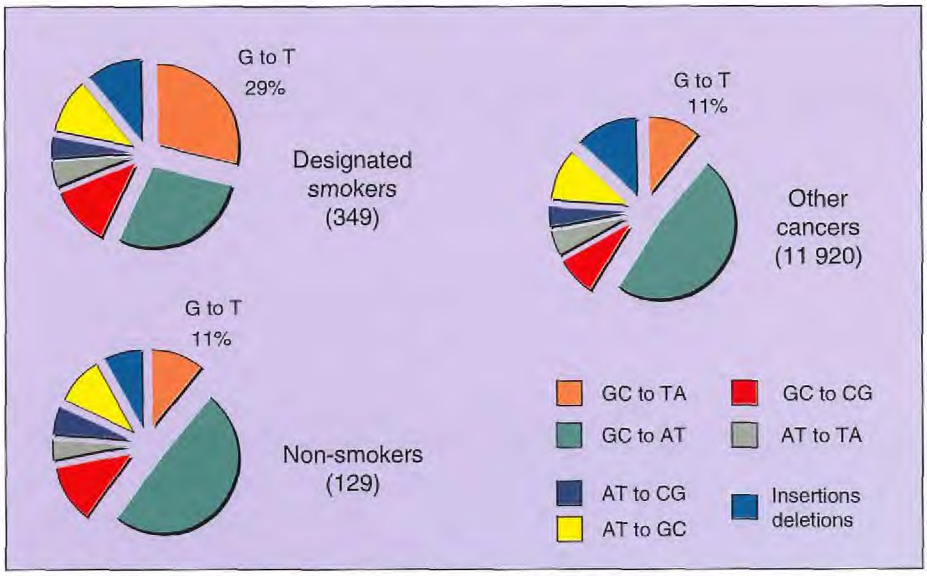

Figure 42. TP53 mutation patterns in lung cancers of smokers and non-smokers (left) and in cancers at other sites (right). Lung cancers of smokers show an excess of G to T transversions (29%) compared with non-smokers or with cancers at other sites (11%).

The database is also useful to analyse correlations between mutations and tumour phenotype. To better classify the mutations, we have carried out an extensive structural analysis of all the mutations reported to date, based on computer modelling and structure prediction algorithms. The results show that, although most common mutations can be predicted to have structural effects that would influence DNA-binding capacity of the protein, about 30% of all mutations reported do not have a predictable impact on the protein structure. We suggest that the latter type of mutants may partially retain wild-type function, or the mutations may inactivate protein activities other than DNA binding. We are currently assessing these hypotheses by examining the expression of human p53 mutants in functional, yeast-based assays.

Part 5

Prevention and early detection of cancer

Prevention of cancer is the ultimate aim of all of IARC's research. Cancers may be prevented by avoiding exposure to agents and lifestyle factors known to increase cancer risk (primary prevention). However, even after exposure to a carcinogen, the multi-step process of cancer development may be slowed, halted or even reversed by a variety of strategies, thus preventing progression to clinical disease. Detection of early stages on the pathway to cancer is therefore important (secondary prevention).

IARC conducts research to identify preventive strategies and evaluate trials to establish their efficacy in actually reducing cancer incidence or mortality, particularly in human target groups known to be at relatively high risk. Its aim is to provide evidence on which health authorities can base suitable policy and practice for cancer prevention in their specific populations.

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, can lead to undesirable side-effects that negate any cancer-preventive benefit. It is therefore 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 15 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.

A chemoprevention trial to evaluate the effect of antioxidant vitamins in prevention or regression of precancerous lesions of the stomach is in progress in Venezuela.

Directory of On-going Research in Cancer Prevention

E. Démaret, R. Sankaranarayanan, M.T. Valdivieso H. Vainio; in collaboration with N. Becker, J. Wahrendorf, Heidelberg, Germany

The Directory of On-going Research in Cancer Prevention, produced jointly with the German Cancer Research Centre, Heidelberg, is a unique source of information on current work in human cancer prevention, for scientists, clinicians, public health professionals and policy-makers. For the purpose of inclusion in the Directory, cancer prevention studies are defined as interventions addressing a change in incidence of or mortality from cancer or modulation of intermediate endpoints 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. Updating of the Directory is in progress, with extensive efforts to expand the list of potential contributors.

Gambia Hepatitis Intervention Study

D.M. Parkin, P. Hainaut, E. Bah, G. Kirk, O. Lesi; in collaboration with H.C. Whittle, M. van der Sande, M. Mendy, Fajara, The Gambia; A.J. Hall, London, UK; 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 laboratories of the United Kingdom Medical Research Council (MRC) in the Gambia. The first phase of the GHIS involved the introduction over a five-year period (1986–90) of vaccine against hepatitis B virus (HBV) into the expanded programme of vaccination (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 effectiveness of vaccination will be judged by following these two cohorts over a period of 35 years or longer. In phase II of the study, surveys conducted in 1996–97 assessed the short-term effectiveness of vaccination in preventing infection and chronic carriage with HBV. 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

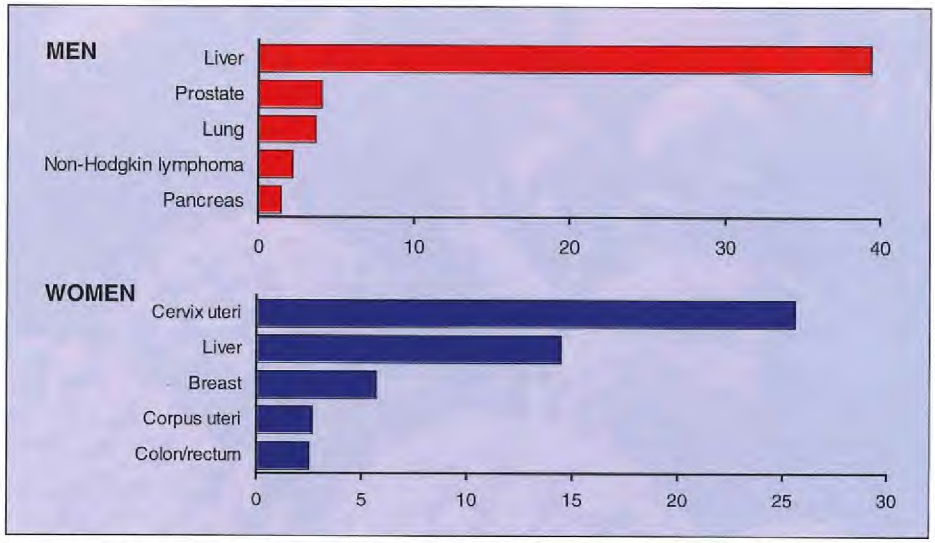

Figure 43. The Gambia: age-standardized incidence of the five most common cancers in men and in women

vaccination on the incidence of hepatocellular carcinoma. For this purpose, 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) in the Gambia concerned with diagnosis of liver disease, to optimize case finding and management.

An analysis of almost 3000 cases from 10 years of registration (1988–97) [11] shows that two cancers predominate: liver cancer, comprising 58% of all cancers in men (incidence rate 35.7 per 100 000) and 19.4% of cancers in women, and cervical cancer, comprising 34% of cancers in women (incidence rate 18.9 per 100 000) (Figure 43). Few liver cancer cases are biopsied (only 4%), the majority being diagnosed by ultrasound and alpha-fetoprotein examination; as a result, the overall proportion of cancer cases with histological proof of diagnosis was only 21%. The registry is participating in the studies of cancer survival in Africa (Section 1.4) and of HIV/AIDS-related cancers (Section 2.6).

The success of the evaluation of vaccination efficacy will depend upon linkage between the incident cases of liver cancer and chronic liver disease (cirrhosis) identified in the age groups potentially enrolled into the vaccination and control cohorts, and the GHIS study database. Personal identifiers, site of vaccination scar and foot and palm prints are used for this purpose. Several studies of these methods of linkage procedures have been undertaken. As pilot work for the planned adolescent booster study (see below), a sample of 133 children aged 10–16 years was interviewed at home in early 2001. Overall, based on demographic identifiers alone, some 66% of potential members of the GHIS cohorts could be identified in the database. Of the 19% of cases that were unmatched, almost half had no clear date of birth recorded.

The location of the vaccination scar has not proved a reliable indicator of whether the child had received HBV vaccine or was a member of the control cohort.

The utility of the stored foot and palm prints for record linkage purposes has been investigated (Figure 44). The digital prints were deemed to be of variable quality and non-standard format, and therefore could not be scanned with existing equipment; a realistic use for the prints is in resolving uncertain matches thrown up by the record linkages based on demographic identifiers. This involves visual comparison of a set of prints with several possible matching sets from the database. A trial of this procedure was successfully conducted in 2000.

Alongside the main GHIS study, several ancillary studies are in progress, utilizing the main GHIS infrastructure. A randomized trial of hepatitis B booster vaccination in adolescents aged 13–15 years (the Gambia Hepatitis Adolescent Booster Study) has been proposed for funding by MRC, Gambia.

A case–control study, supported the United States National Cancer Institute, has investigated the role of other risk factors in liver cancer: exposure to aflatoxins and their interaction with HBV; hepatitis C virus and HBV variants (see Section 3.3). Associated with this project is an evaluation of the accuracy of estimating alpha-fetoprotein on dried spot blood on filter paper for diagnosis of primary liver cancer.

Serum from individuals in The Gambia is being analysed to assess the prevalence of the ^{249}Ser mutation in the *TP53* gene, that is indicative of past exposure to aflatoxin B_1.

Studies of mutant hepatitis viruses are in progress in collaboration with the MRC and the School of Veterinary Medicine, London. Genomic changes in the virus that could permit it to escape neutralization by the immune response to the current vaccine type would have obvious public health implications.

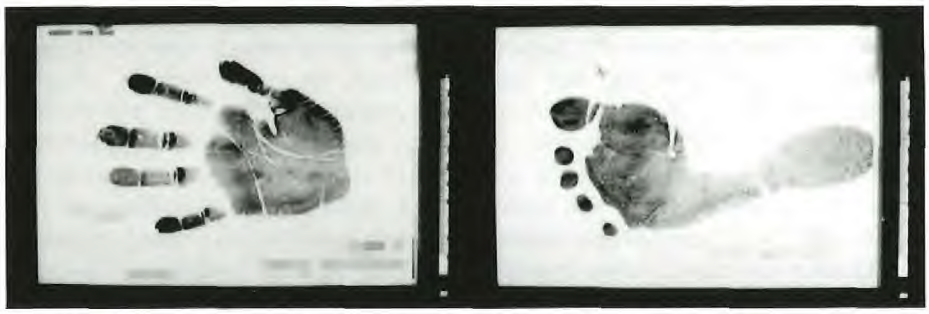

Figure 44. Palm and foot prints taken at enrolment into the GHIS for use in identification of subjects

Chemoprevention trial on precancerous lesions of the stomach in Venezuela

M. Plummer, N. Muñoz, C. Lavé, S. Franceschi; in collaboration with C. Aebischer, Basel, Switzerland; O. Andrade, E. Cano, D. Castro, G. Lopez, W. Oliver, V. Sanchez, J. Vivas, San Cristobal, Venezuela; J. Torrado, San Sebastian, Spain

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 anti-oxidant vitamins can block progression through these precancerous stages. The trial is taking place in Tachira state, Venezuela, in a population at high risk of stomach cancer (see also Section 3.2), taking advantage of the infrastructure created by the gastric cancer control programme there, in particular the presence of highly skilled endoscopists.

The original design of the trial included a phase of treatment for *Helicobacter pylori* infection (94% of subjects were *H. pylori*-

positive at baseline). However, following two pilot studies that showed poor rates of eradication of *H. pylori*, possibly due either to differences in *H. pylori* strains or to frequent reinfection, the anti-*H. pylori* treatment phase was deleted from the protocol. The trial started in May 1992. The target for recruitment of 2200 subjects was achieved in February 1995 and treatment completed in March 1999. By June 1999, 1263 subjects had completed treatment and had a gastroscopy, 217 completed treatment but had no final gastroscopy and 720 had withdrawn from the trial.

Subjects were randomized to treatment with anti-oxidant 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, a gastroscopy was performed, taking five biopsies from pre-specified areas of the stomach, and blood and urine specimens were collected from each patient. Since the results of various randomized trials 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.

Severity of intestinal metaplasia correlated strongly with anomalous expression of Lewis a antigen. 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 [486].

The randomization code has not yet been broken since the analysis of the trial will use the results of a validation study that is still in progress. In order to eliminate inter-observer variation, the biopsies of all subjects who returned for at least one follow-up gastroscopy have been reviewed by a single pathologist (G. Lopez).

HPV vaccines for cervical neoplasia

S. Franceschi, M. Plummer, E. Weiderpass, J. Smith; in collaboration with C. Banura, E. Mbidde, Kampala, Uganda; P. Coursaget, Tours, France; S. Pagliusi, T. Aguado, T. Cherian, Geneva, Switzerland; T. Rajkumar, Chennai, India; R. Rajkumar, Ambillikai, India; S. Sukvirach, Bangkok, Thailand

The phase III (efficacy) trials for HPV vaccines which are planned to start in 2001 in the United States and Latin America are expensive and complex studies, in which participating women will be followed up intensively and, possibly, over-treated for suspicious cervical lesions. This suggests a need for further trials to demonstrate the effectiveness of an HPV vaccination programme under field conditions in developing countries. By conducting such trials, we aim to accelerate the adoption of HPV vaccination as part of cancer control programmes in populations that need it most. HPV prevalence surveys are a prerequisite for such programmes.

Detailed plans for field trials of vaccination cannot yet be made, but they are likely to include (*a*) randomization of HPV vaccine by areas with populations of approximately 2000 individuals; (*b*) use of HBV or a similar vaccine in the control group, instead of placebo; (*c*) vaccination of both sexes at around ages 10–19 years; and (*d*) assessment of outcome by, among other things, monitoring women (and, if possible, their partners) at the times of giving birth and of children's vaccinations.

Except for the one in Colombia, none of the previous IARC surveys of HPV prevalence focused on adolescents and young women, nor included young men. We are, therefore, conducting some new surveys in order to determine (*a*) the age at which females and males first become seropositive for HPV-16; (*b*) the age-specific prevalence of HPV DNA of different types; (*c*) the degree of population mixing between different age groups and different villages and towns; (*d*) the suitability of perinatal care centres as a location for follow-up visits in future HPV vaccine trials; and (*e*) the attitude of study participants towards taking part in eventual HPV vaccine trials.

Field trips and negotiations with funding agencies have taken place during 2001 and local personnel are being trained. The largest survey is being conducted in a rural area of Tamil Nadu State, southern India, covered by the Ambillikai Cancer Registry. The area includes 384 villages and a population of approximately 360 000. The study population consists of young women and men aged 13–29 years. This rural region has a very high incidence rate of cervical cancer and a cancer hospital with facilities for cervical cancer diagnosis and treatment. A randomized trial in this region is being conducted to evaluate the efficacy of visual inspection of the cervix uteri with acetic acid as a cervical screening method (see Section 5.3).

All individuals aged 13–29 years from 15 health areas who are permanent residents and do not suffer from mental or physical disability will be invited to participate, and the expected final sample size is 3000 females and 3000 males. After the interview, all subjects will be asked if they are willing to provide 10 mL blood, in order to obtain three aliquots of plasma and one of Buffy coat, as well as exfoliated cells from the cervix uteri in married women or exfoliated cells from the coronal sulcus and the prepuce in men, for HPV DNA detection.

A cluster sampling design has been chosen to reflect the design of an eventual vaccination trial, which will include approximately 10 times more women and men than the survey.

As only sparse data exist on the prevalence and type distribution of HPV infection in Africa, an HPV survey of 1200 sexually active women aged 10–24 years has been set up in Kampala, Uganda. This study population differs from those in which previous IARC surveys were conducted in that it is heavily affected by the AIDS epidemic (the prevalence of HIV infection at first test in unselected women aged 15–24 years in Kampala was 23% in 1994 and 12% in 1999).

5.2 Evaluation of cancer-preventive agents

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 are of relevance to the public health aspects of cancer prevention are also being evaluated.

H. Vainio, F. Bianchini. The following members of other units have contributed to the programme: R. Baan, P. Boffetta, P. Brennan, J. Cheney, S. Franceschi, M.D. Friesen, Y. Grosse, J. Hall, R. Kaaks, V. Krutovskikh, A. Lukanova, A.B. Miller, H. Ohshima, C. Partensky, B. Pignatelli, A.J. Sasco, N. Slimani, E. Suonio, J.D. Wilbourn

Biomarkers in Cancer Chemoprevention

An international workshop on 'Use of Biomarkers in Chemoprevention of Cancer' was held at the German Cancer Research Center (DKFZ) in Heidelberg on 27–29 February 2000. Over 50 scientists participated in the workshop; there were presentations by 21 invited speakers, and formal group discussions involving the invited speakers, the organizers and other participants.

Clinical trials to evaluate chemopreventive agents usually require large study populations and long-term commitment of resources, because cancer is an infrequent event and because clinically overt disease may take many years to develop. Biomarkers are cellular, biochemical, molecular or genetic alterations measurable in biological media. They may be used to identify individuals who are at increased risk for cancer resulting either from exposure to exogenous or endogenous carcinogens or from certain genetic susceptibilities, thus enabling chemoprevention studies to be carried out in smaller high-risk populations and still have adequate statistical power to detect intervention effects. Because cancer can arise through multiple pathways that may proceed in parallel at different rates in various types of cells, characterizing the cellular, biochemical, molecular and genetic events involved is critically important to the rational development of effective chemoprevention strategies. The identification of valid intermediate-effect biomarkers that are part of the cancer pathways and causally related to cancer, and could thus serve as surrogate end-points for clinical disease, would make it possible to carry out chemoprevention trials in less time than is currently feasible.

The workshop was generally considered to be very productive, with high level discussions. The papers and conclusions from the Workshop, including a consensus statement, have been published as IARC Scientific Publication No. 154.

Sunscreens

Sunscreens were originally developed to prevent sunburn, and contain chemicals that reduce the amount of ultraviolet radiation (UVR) reaching the skin. A major issue regarding sunscreen use is whether they protect against other harmful effects of sunlight, including skin cancer. Skin cancers (melanoma, basal-cell carcinoma and squamous-cell carcinoma) are very common and there is now sufficient evidence that sunlight, and possibly UVR, is the major cause.

An international working group of experts was convened on 11–18 April 2000 in Lyon to evaluate the preventive effects of sunscreens against skin cancer and to compile the fifth volume of the *IARC Handbooks of Cancer Prevention*.

Sunscreens have been shown to protect against UVR-induced carcinogenesis in experimental animals, but the epidemiological data are contradictory. Three case–control studies showed significantly lower risk and eight studies significantly higher risk for melanoma in users compared with non-users; four other case–control studies provided little evidence of an effect. The formation of non-melanocytic naevi, precursors of some cutaneous melanoma, was found to be decreased in one randomized trial, but four cross-sectional studies reported no reduction or a higher naevus count in children using sunscreens. In one randomized trial, sunscreen users had significantly less squamous-cell carcinoma, but not basal-cell carcinoma, than non-users, while two others showed a significant protective effect of sunscreens against actinic keratoses, precursor lesions for squamous-cell carcinoma.

The working group concluded that there is *inadequate evidence* for a cancer-preventive effect of sunscreens in humans against cutaneous malignant melanoma and basal-cell carcinoma of the skin, and *limited evidence* against squamous-cell carcinoma. There is *sufficient evidence* for a cancer-preventive effect of sunscreens in animals.

The working group warned about the use of sunscreens to extend the duration of intentional sun exposure, as such extension may increase the risk for cutaneous malignant melanoma. The working group also recommended that sunscreens (generally with a sun protection factor higher than 15) be used only as one part of a comprehensive sun-avoidance strategy, which includes seeking shade and use of appropriate clothing (Figure 45).

The results of the meeting have been published as Volume 5 of the *IARC Handbooks of Cancer Prevention*.

Figure 45. T-shirt and sign advertising the 'SunSmart' campaign on a beach in Australia

Weight control and physical activity

The prevalence of obesity and overweight is rising worldwide. Obesity is a clearly established risk factor for various chronic diseases, including type II diabetes, cardiovascular diseases and possibly some cancers. Weight control appears to be becoming more and more difficult, not only in industrialized but also in developing countries. In Europe and North America, more than 50% of the adult population has a body mass index (BMI) of at least 25 kg/m^2, and 20% of individuals are obese (BMI at least 30 kg/m^2). At the same time, an increasing fraction of the population is not physically active either at work or during their leisure.

IARC convened an international working group of experts to evaluate the evidence for the role of weight control and physical activity in cancer prevention and to identify priorities for research and public health action in relation to the primary prevention of cancer, in Lyon in February 2001. This group concluded that limiting weight gain during adult life, thereby avoiding overweight and obesity, reduces the risk of postmenopausal breast cancer and of cancers of the colon, endometrium, kidney (renal cell) and oesophagus (adenocarcinoma). Weight loss among overweight or obese persons possibly reduces risks of these cancers, but no definite conclusion could be drawn because of the paucity of the epidemiological evidence.

The working group also concluded that there was *sufficient evidence* for the role of physical activity in preventing colon and breast cancers, and *limited evidence* for cancers of the prostate and endometrium. Some of these effects are independent of that of weight control.

Taken together, the working group considered that excess body weight and physical inactivity account for approximately one fourth to one third of cancers of the colon, breast, endometrium, kidney (renal cell), and oesophagus (adenocarcinoma). Thus adiposity and physical inactivity appear to be the most important avoidable causes of these cancers.

The results of the meeting are being published as Volume 6 of the *IARC Handbooks of Cancer Prevention*.

5.3 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 a screening programme is established if it leads to a significant reduction in mortality from the disease without incurring enormous 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.

Early detection of cervix cancer in developing countries

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Several early detection methods such as visual inspection with acetic acid without (VIA) and with magnification (VIAM), visual inspection with Lugol's iodine (VILI), conventional cytology and HPV

testing are being evaluated in cluster randomized intervention trials and cross-sectional studies for their accuracy in detecting high-grade cervical precursor lesions and in preventing invasive cervical cancer.

In a cluster randomized intervention trial in Osmanabad district, Maharashtra, India, eligible women (30–59 years, N = 160 000) living in 502 villages under 52 primary health centres (PHC) in the district have been randomized (randomization unit: PHC) to receive either VIA, conventional cytology or HPV DNA testing, or to join a control group. A large infrastructure consisting of a field office, laboratories, screening clinics, colposcopy and treatment clinics and liaison offices has been established. Staff have been recruited and trained. Quality control of various procedures has been completed. Three fourths of the invited women attend for screening. The detection rates of high-grade cervical neoplasia (CIN II, III and invasive cancer) are similar with the three screening methods. Recruitment and screening will be completed in 2003.

Table 6. Preliminary results of health education intervention, Solapur District, India

	Intervention	Control
Total women	96 908	76 084
Women-years	352 628	380 805
Incident cervical cancers	80	64
% Stage I and II cancers	65.1	32.8
Age-standardized incidence rate	26.3/100 000	18.7/100 000
Deaths from cervical cancer	17	30
Age-standardized mortality rate	5.6/100 000	8.6/100 000

Incidence rate ratio: 1.41 (95% CI 1.00–1.98)
Mortality rate ratio: 0.65 (95% CI 0.36–1.18)

Eligible women (30–59 years, N = 74 500) living in 113 village clusters (*panchayaths*) in Dindigul district, Tamil Nadu, India have been randomized either to receive screening with VIA or to a control group. A field office, histopathology laboratory, screening clinics, colposcopy and treatment clinics and liaison offices have been established. The detection rate of cervical precancers by VIA is around 3.5%. Overall, 735 women have been treated with cryotherapy and 21 with loop excision electrosurgical procedure (LEEP)/conization.

Figure 46. Women being interviewed and invited for screening in Osmanabad district, India

The role of improved awareness in the early detection and control of cervical cancer is being evaluated in two sub-districts in Maharashtra State, western India, where literacy among women is less than 20%. Person-to-person and group health education on cervical cancer were provided to 97 000 women in Madha Tehsil, while 79 000 women in Karmala Tehsil (Solapur district) served as the control population. This programme was initiated in 1995; preliminary results for the period 1995–99 show that a much higher proportion of women with cervical cancer presented in earlier stages with significantly reduced case fatality in the intervention sub-district than in the control area (Table 6).

The accuracy of various screening tests such as VIA, VIAM, VILI, cytology and HPV DNA testing is being evaluated in cross-sectional programmes in Burkina Faso, Republic of Congo, Guinea, India (*Mumbai, Calcutta, Jaipur, Trivandrum*), Mali, Niger and Nigeria. The necessary infrastructure has been organized in each site. These programmes also provide a framework to introduce early detection services and as a focal point of training in the regions or countries concerned. Two studies (Calcutta and Trivandrum) have been completed and the data have been analysed. Results from some of the completed studies are given in Table 7.

More than 1800 women have received cryotherapy and around 500 women have been treated with LEEP in the context of the above studies. These women are being followed up to document treatment-

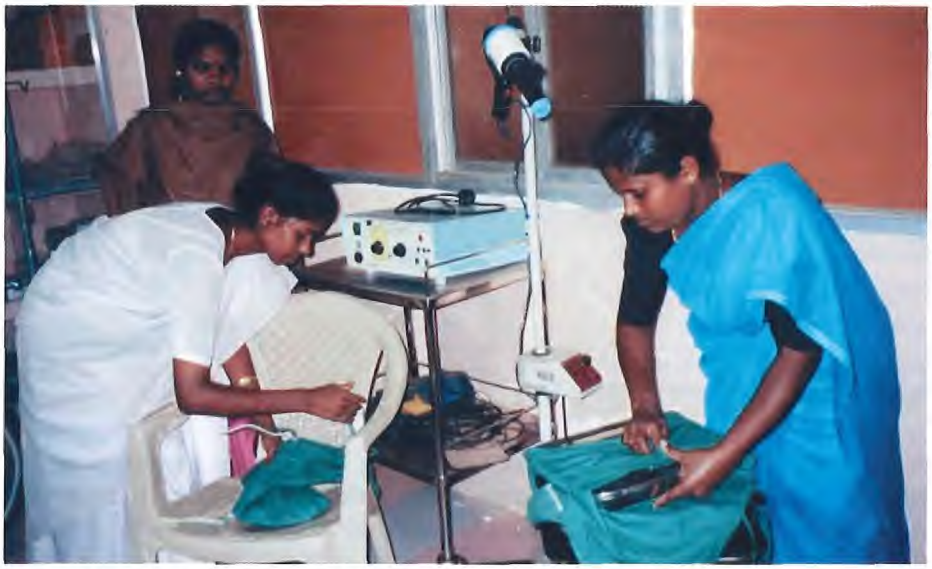


Figure 47. Nurses preparing to sterilize instruments in the screening clinic, Ambillikai, India

Figure 48. Laboratory for HPV testing , Barshi, Osmanabad district, India

related outcomes. Short-term complications following cryotherapy seem to be less than 4%. The impact of different methods of encouraging women to participate in screening, perceptions of women and related socioeconomic issues are also being addressed.

Training facilities have been organized in India (Barshi, Mumbai, Calcutta, Trivandrum), and Guinea (Conakry) to train personnel in various aspects (screening techniques, cytology, colposcopy, histopathology, treatment of precursors, etc.) of cervical cancer prevention.

Cervical screening and prevention was the subject of a meeting in Tunis [288]. The integration of early detection methods into health services in developing countries [392] and existing cervical cancer screening programmes in developing countries have been reviewed [394].

Oral cancer screening in developing countries

R. Sankaranarayanan, D.M. Parkin, P. Pisani; in collaboration with L. Fernandez Garrotte, J. Lence, R. Camacho, Havana, Cuba; B. Mathew, K. Ramadas, P. Sebestian, M. Pandey, T. Somanathan, E. Abraham, G. Thomas, B. Kuruvilla, N. Sreedevi Amma, M.K. Nair, Trivandrum, India; R. Rajkumar, J. Cherian, Ambillikai, India

A community-based cluster randomized trial in Trivandrum district, India, is currently addressing whether screening with visual oral inspection will lead to reduction in incidence of and mortality from oral cancer. A total of three rounds of screening at three-year intervals have been planned. In the second round of screening, initiated in October 1998, 41 468 subjects have been screened. Of the 558 screen positives referred for confirmatory examination by dentists, 355 (63.6%) complied with referral. 317 were subjected for biopsy and 29 oral cancers and 131 high-grade dysplasias (moderate and severe dysplasia) were diagnosed among them. Results of surgical management of oral leukoplakia cases detected in this study have been evaluated [329]. Two nested case–control studies within the oral cancer intervention cohort have examined risk factors for erythroplakia

Table 7. Performance of different screening tests in detection of high-grade cervical precancerous lesions and cancer

Location (number)	No. CIN II [a]	VIA	VIA [b]	VIAM	VILI	Cyto	HPV
Trivandrum, India (3752)	157	91.1	–		93.0	84.7	
		77.5			80.7	87.3	
Calcutta, India (6399)	135	63.0	–	66.7	–	41.1	50.0
		84.4		85.3		85.4	91.8
Burkina Faso, Congo, Guinea, Mali, Niger (8995)	211	78.7	84.4	–	95.3	–	–
		75.6	77.8		84.3		

Upper values (%) indicate sensitivity and lower values specificity
[a] Number of cases of CIN II and advanced disease; [b] by doctors

and leukoplakia [180, 181]. Tobacco chewing, smoking and alcohol drinking emerged as major risk factors for oral precancers. An inverse dose–response relationship was indicated between body mass index and the risk of oral leukoplakia and erythroplakia.

In a case–control study to evaluate the Cuban oral cancer screening programme [395], the odds ratio for advanced oral cancer associated with screening was 0.67, indicating that screening can reduce the risk of advanced disease. Further descriptive evaluation of this programme is continuing.

Screening for cancer of the breast in the Philippines

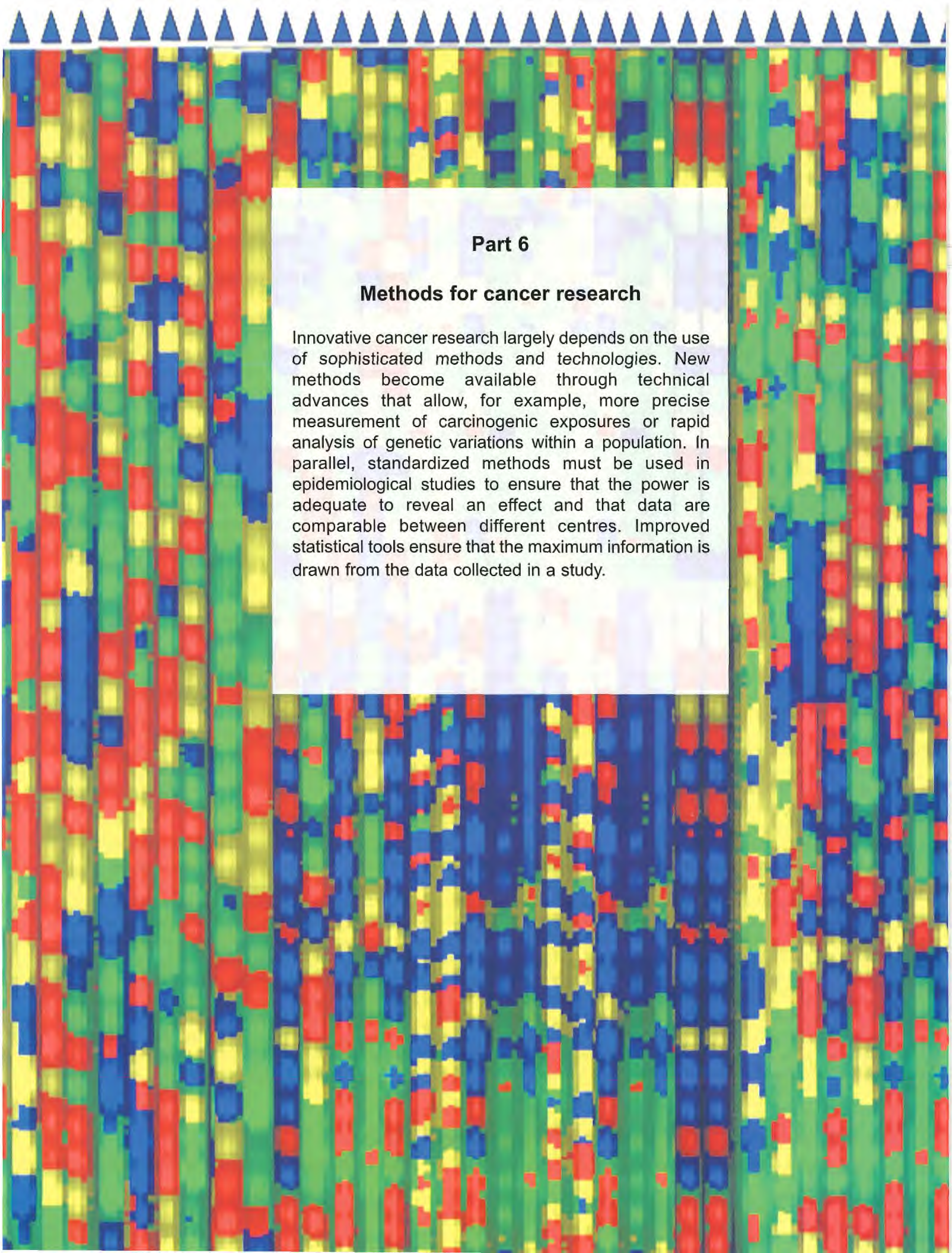
D.M. Parkin, P. Pisani, A. Bautista; in collaboration with D.B. Esteban, C.A. Ngelangel, A.V. Laudico, Manila, Philippines

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, with support from the United States Army Medical Research Development Command.

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 were 219 000 and 190 000 in the intervention and control groups respectively.

By the end of 1997, the first round of examinations was completed. In view of the very low rate of compliance with referral of women detected positive at physical examination, the intervention was discontinued after completion of the first screening round and follow-up of the target population was undertaken.

Follow-up of the 154 000 women interviewed is being undertaken by the two population-based cancer registries serving the Manila area. For breast cancer cases, a special case-finding mechanism has been established and for all incident cancers information on size and extent at diagnosis is recorded. Within the six months after examination, 43 malignant breast cancers were diagnosed in the intervention population: 27 among screen-positive women, 12 among screen-negative and 4 among those who refused the examination. Overall, 105 new cases of invasive breast cancer occurred in the study population after an average of three years of follow-up. The proportion of cases diagnosed at stage I or IIA increased by 9% after the intervention. The excess incidence attributable to known risk factors is being evaluated by means of a nested case–control study.



Part 6

Methods for cancer research

Innovative cancer research largely depends on the use of sophisticated methods and technologies. New methods become available through technical advances that allow, for example, more precise measurement of carcinogenic exposures or rapid analysis of genetic variations within a population. In parallel, standardized methods must be used in epidemiological studies to ensure that the power is adequate to reveal an effect and that data are comparable between different centres. Improved statistical tools ensure that the maximum information is drawn from the data collected in a study.

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.

Mass spectrometric analysis of mutations

M.D. Friesen, S. Michel, S. Angèle, N. Moullan, B. Chapot, J. Hall, P. Hainaut; in collaboration with J.D. Groopman, P. Strickland, P. Jackson, Baltimore, MD, USA

A method called short oligonucleotide mass analysis (SOMA) has been developed for analysis of defined DNA variations by mass spectrometry. The method is generally applicable to any DNA variant, is highly accurate and directly measures the mass of the variant DNA sequence. Multiple single nucleotide polymorphisms (SNPs) in the *ATM* gene have been reliably genotyped after multiplex SOMA (see Section 4.1).

The SOMA technique has been used to detect low levels of mutated DNA in plasma [201]. A specific missense mutation resulting from a G→T transversion in codon 249 of the *TP53* tumour-suppressor gene has been found in 10–70% of hepatocellular carcinomas from areas of high dietary exposure to aflatoxin B_1 (see Section 3.3). Analysis of 20 plasma and tumour pairs showed 11 tumours containing the specific mutation and this change was detected in six of the paired plasma samples. Four other plasma samples had detectable levels of the mutation, but the tumours were negative, suggesting the possible presence of multiple independent carcinomas. The SOMA technique thus has potential for use in prevention trials and in early diagnosis of hepatocellular carcinoma.

Mass spectrometric measurement of human exposure to the heterocyclic amine food mutagen PhIP

M.D. Friesen; in collaboration with J.D. Groopman, P. Strickland, Baltimore, MD, USA

Heterocyclic aromatic amines are carcinogenic combustion products formed during cooking of meat at high temperature. We have used a highly sensitive gas chromatography/mass spectrometry method to measure levels of the commonly formed heterocyclic amine 2-amino-1-methyl-6-imidazo[4,5-*b*]pyridine (PhIP) in alkali-hydrolysed urine from 10 healthy non-smoking male volunteers who consumed equal amounts of broiled ground beef on five consecutive days [157]. The results were similar to those obtained with a less sensitive HPLC method with fluorescence detection [455]. The morning after initial consumption of broiled beef, urinary concentrations of PhIP increased 14- to 38-fold over the mean pre-feed concentrations. Comparison of the proportions of alkali-labile PhIP metabolites and parent PhIP in human urine revealed large inter-individual differences in PhIP metabolism. The results indicate that significant amounts of PhIP are bioavailable from ingestion of broiled ground beef.

Serum DNA as a marker in lung cancer

E. Gormally, E. Derrepiere, G. Tchoun, P. Hainaut; in collaboration with E. Brambilla, Grenoble, France; P. Vineis, Turin, Italy

Building on our expertise in analysis of plasma DNA, developed in the course of studies on liver cancer (see Section 3.3), we are applying a similar approach to the detection of molecular alterations in plasma DNA of lung cancer and precancer patients. The genes under investigation are *TP53* (point mutations), *p16* (INK4a/CDKN2a; hypermethylation) and K-*RAS* (point mutations). Small numbers of paired plasma and tumour tissue DNA samples are being analysed to determine whether there is a good correlation between mutations in tumour and plasma samples for these three genes. These methods will be applied in the European GENAIR project (coordinator: P. Vineis, Turin), aimed at studying the etiology of lung cancers and head-and-neck cancers in non-smokers. This is a nested case–control study within the EPIC cohort (see Section 2.3). Over 2000 plasma specimens from individuals who developed lung or head-and-neck cancers will be analysed and the results will be correlated with detailed individual information as well as with molecular data on multiple polymorphisms in candidate susceptibility genes.

Generation of mouse models for molecular epidemiology studies

W.-M. Tong, D. Galendo, J. Michelon, Z.-Q. Wang; in collaboration with M. Hollstein, Heidelberg, Germany

The p53 protein is dysfunctional or absent in the majority of human tumours, usually due to single point mutations in the gene. The great diversity in p53 point mutation spectra in tumours of distinct etiopathology offers a novel approach for investigating environmental and endogenous origins of human cancer mutations, but experimental induction of mutations in the

human *TP53* gene *in vivo* has not been possible up to now. The mouse and human *TP53* genes differ in the core domain (codon 102 in exon 4 to codon 292 in exon 8) where most of the 14 000 mutations in human tumours have been found (IARC *TP53* mutation database, Release 4, June 2000; see Section 4.7). Thus, genetically engineered mice carrying a 'humanized' *TP53* gene, expressed at physiological levels and with a core domain identical to that of the human protein, would be of value in screening compounds that may be carcinogenic to humans.

We have constructed a human p53 knock-in (*hupki*) mouse strain in which exons 4–9 of the endogenous mouse *TP53* alleles have been replaced with the human counterpart. These mice, harbouring a chimeric p53 protein, retain various p53 cellular functions and are phenotypically normal. The chimeric *TP53* allele is properly spliced and transcribed at levels corresponding to those in wild-type mice [267]. The hupki protein binds to p53 consensus sequences in gel mobility shift assays with anti-p53 antibody PAb421. Following γ-irradiation of homozygous *hupki* ($p53^{ki/ki}$) mice, expression patterns of p53-regulated genes in the spleen and the kinetics of p53-dependent apoptosis in thymocytes are similar to those with wild-type ($p53^{+/+}$) mice [267], indicating that p53 is functional in the *hupki* strain.

The major etiological agent contributing to human non-melanoma skin cancer is sunlight and in these tumours, the *TP53* gene usually contains single or tandem transitions at dipyrimidine sequences in the DNA-binding domain that are a characteristic effect of ultraviolet (UV) irradiation. We have validated the use of the *hupki* mouse model by correlating UV-induced p53 mutations with the mutation spectra in humans. When epidermal cells of *hupki* mice ($p53^{ki/ki}$) were irradiated *in vivo* with a single dose of UVB light, UV photoproducts accumulated at the same locations of the *TP53* gene as in human cells. Chronic exposure of *hupki* mice resulted in the appearance of cell patches that stained intensely with anti-p53 antiserum CM1. DNA extracted from the epidermis of treated mice had C to T and CC to TT mutations at codons 278–279, and at codons 247–248, which are the most frequent UVB-associated mutation sites in humans [266]. These observations validate the *hupki* mouse as a tool for molecular epidemiology and biomedical research (reviewed in Hollstein *et al.*, 1999, *Mutat. Res.*, **431**, 199–209), which can be used to examine spontaneous and induced mutations in human *TP53* gene sequences *in vivo* for comparison with published *TP53* mutation spectra in human tumours. In addition, the *hupki* mouse strain paves the way for development of rodent assays for preclinical testing of cancer drugs designed to modulate the DNA-binding activity of the human *TP53* core domain.

Development of a tool for genotyping of polymorphisms of genes related to xenobiotic metabolism and DNA repair

F. Gemignani, S. Zienolddiny, S. Landi, F. Vivant, A. Llewellyn, J.-C. Hung, P. Brennan, F. Canzian; in collaboration with S. Chanock, Bethesda, MD, USA; A. Haugen, Oslo, Norway; A. Metspalu, Tartu, Estonia; P. Vineis, Turin, Italy

Understanding the interaction of genetic variants with each other and with environmental exposures (such as tobacco, alcohol and air pollution) is important for the identification of high-risk groups at the population level and for evaluation of profiles of risk for several neoplasias, such as lung and head and neck (see Sections 3.7 and 3.8) at the individual level. For large-scale association studies of such interactions (see Sections 2.3, 3.7 and 3.8) and for wider testing in the pharmacogenetic field, a fast, cheap and reliable tool is needed to determine large numbers of genotypes of polymorphisms in metabolizing enzymes. The present project aims at the development of a genotyping DNA microarray for such purposes.

A set of 54 candidate genes for enzymes of various pathways of xenobiotic metabolism (phase I detoxification, including several cytochrome P450s and phase II detoxification, including several glutathione-*S*-transferases and *N*-acetyltransferases, and alcohol-metabolizing enzymes), DNA repair and cell cycle control, have been selected. A thorough search for known polymorphisms in the candidate genes has been performed, through searches of the literature and of publicly available databases. For each polymorphism, we have recorded the exact position in the gene, the nature of the genetic variation and the allelic frequencies in various human populations. A total of 343 single nucleotide polymorphisms (SNPs) have been listed. A subset of 166 SNPs with high allele frequency (> 5%) in Caucasians or other major ethnic groups and SNPs with a previously reported association for cancer ($p < 0.05$) have been selected for further studies (Figure 49). On the basis of this

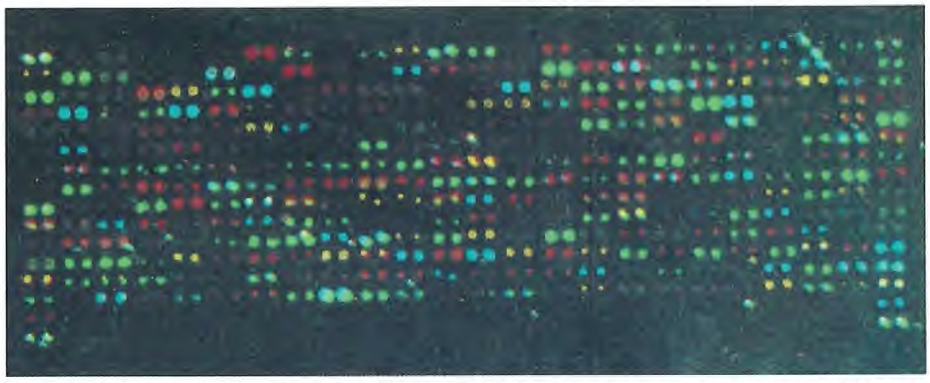


Figure 49. Four-colour composite image of a DNA microarray which allows the simultaneous genotyping of 166 single nucleotide polymorphisms

knowledge, a genotyping DNA microarray with the arrayed primer extension technology (Kurg *et al.*, 2000, *Genet. Test.*, **4**, 1–7) has been prepared. Multiplex PCR conditions have been established. Validation of the microarray with a set of samples genotyped at the same 166 SNPs with reference techniques is in progress.

6.2 *Epidemiological methods*

Development and evaluation of analytical methods for genetic epidemiology

D.E. Goldgar, F. Vogl; in collaboration with D. Easton, Cambridge UK; J. Hopper, Melbourne, Australia; Y. Shugart, Baltimore, MD, USA. Supported by the US National Institutes of Health and National Cancer Institute

This project explores many of the important analytical, statistical, and design issues in cancer genetic epidemiology. Specifically, we are involved in the following set of studies: (*a*) investigations of optimal sampling and analysis strategies for mapping loci under high levels of heterogeneity; (*b*) implementation of a likelihood-based approach to combined linkage and association testing on general pedigree structures; (*c*) examination of the power of existing data sets for detecting the presence of modifier genes in high-risk breast cancer families; (*d*) mathematical models for determining the age of specific recurrent mutations based on multilocus haplotype data in mutation carriers. 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, while others involve analyses of specific data-sets which currently exist or will be generated in our laboratory. Current studies include the analysis of a large (~1700 member) family with a mutation in the *BRCA1* gene. We have focused our efforts on the estimation of risk using different statistical models and methods, in order to define the inherent variability in such estimates. We have also been examining the relationship between family history, family size and penetrance, in order to better interpret family history data from population-based cases screened for mutations in particular genes. These studies will help family cancer clinics set guidelines for family history in deciding who should be eligible for genetic testing.

Part 7

Publications, education and training

Among the statutory missions of IARC are the collection and dissemination of information on the epidemiology of cancer, on cancer research and on the prevention and causation of cancer throughout the world and the education and training of personnel for cancer research.

Dissemination of information is achieved both through publications in external peer-reviewed journal articles and in the form of books and electronic publications prepared and published by the Agency itself. The Internet is inceasingly used as a medium for making information accessible worldwide.

Education and training are provided by awarding fellowships to young researchers that allow them to pursue their studies in a different country and by organizing specialized courses at IARC and in other countries on aspects of cancer research, particularly epidemiology.

7.1 Publications

While it is widely recognized that any major institution needs to have a coherent approach to information transfer, it is part of the statutory mission of IARC to "collect and disseminate information on the epidemiology of cancer, on cancer research and on the prevention and causation of cancer throughout the world". In order to streamline and integrate related but previously dispersed activities, a support unit responsible for the area of communications was established in January 2001. This brings together within one group the management of all activities dealing with publications, both printed and electronic, the IARCPress sales and distribution service in Lyon and Washington, the development and maintenance of the Internet and Intranet sites, the public relations office and the translation and language training facilities. The resulting unit has responsibility for the presentation of a homogeneous image of all aspects of IARC work to the scientific community, the media and the general public, as well as providing a service to the scientifc units in all matters related to information.

The Communications unit thus assists the scientific units in dissemination of the results from their research projects, by providing advice and editorial help for publications of articles in the primary international scientific journals and through its own publications under the IARCPress imprint. The latter appear in the series of IARC Scientific Publications and the IARC Technical Publications. In addition, the IARCPress initiates publications to be generated with external scientific assistance that are deemed to be required by the international scientific community. The most prominent of these is the WHO Classification of Tumours, of which the first three volumes had been published by the end of 2001, with considerable success. These provide authoritative and profusely illustrated descriptions of tumours for histological and genetic typing of human tumours.

The IARCPress sales service has continued to increase its turnover, through additional marketing efforts by direct mailings and displays at scientific meetings. A notable innovation has been the establishment of an office in Washing-

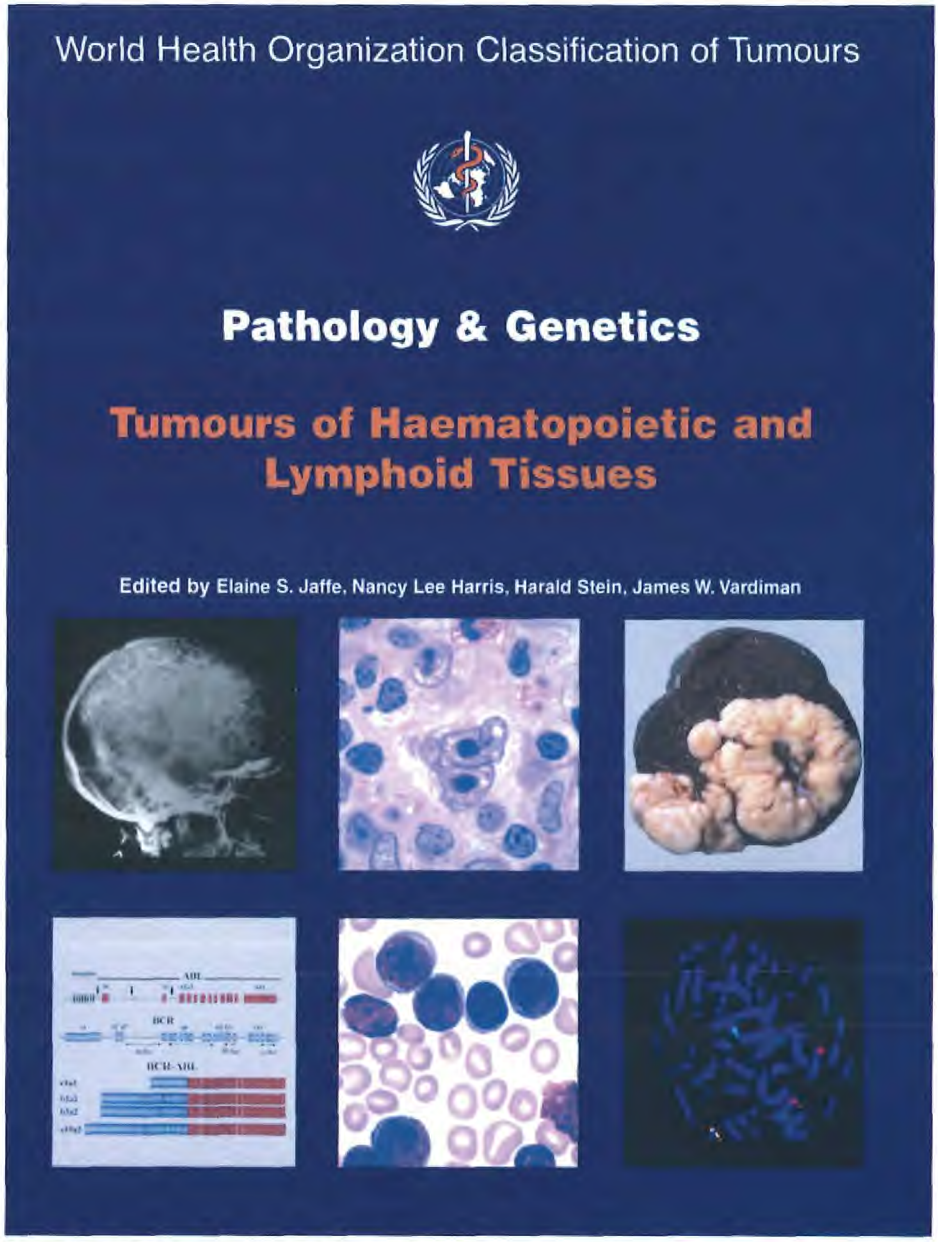


Figure 50. The latest volume in the WHO Classification of Tumours series

ton, DC, to handle promotional activities and sales in North America, as well as to generally enhance the visibility of IARC throughout the continent.

Press releases are issued periodically covering significant developments that are likely to be of wide public interest, and the public relations office is also responsible for handling external enquires about any aspect of the Agency's work.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

This programme is described in detail in Section 2.1. Much information from earlier volumes of the Monographs series has been made available on the Internet and a CD-ROM carrying most volumes of the Monographs was issued (see below).

Five new volumes were published during the period under review:

Volume 75, *Ionizing Radiation*, Part I: *X- and Gamma (γ)-Radiation, and Neutrons*

Volume 76, *Some Antiviral and Antineoplastic Drugs and Other Pharmaceutical Agents*

Volume 77, *Some Industrial Chemicals*

Volume 78, *Ionizing Radiation, part 2: Some Internally Deposited Radionuclides*

Volume 79, *Some Thyrotropic Chemicals*

IARC Scientific Publications

One new volume was published:

Biomarkers in Cancer Chemoprevention (IARC Scientific Publications No. 154)

IARC Handbooks of Cancer Prevention

This programme is fully described in Section 5.2. One new volume was published:

Volume 5. *Sunscreens*

WHO Classification of Tumours

The third edition of the WHO 'blue book' series on histopathological and genetic typing of human tumours was launched in 2000, and three volumes have been published to date (Figure 50):

Pathology and Genetics of Tumours of the Nervous System

Pathology and Genetics of Tumours of the Digestive System

Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues

IARC Reports

The following IARC Internal Reports were produced during the biennium:

Update of the Follow-up of Mortality and Cancer Incidence among European Workers Employed in the Vinyl Chloride Industry

Interphone. International Case–Control Study of Tumours of the Brain and the Salivary Glands. Protocol

Multiple Primaries

A Case–control Study of Lung Cancer among European Rock and Slag Wool Production Workers. Final Report

Depleted Uranium and other Exposures in Conflict Areas. I. The Balkans: Exposures, Possible Health Effects and Outline of Epidemiologic Feasibility Studies

INTERPHONE. International Case–control Study of Tumours of the Brain and Salivary Glands. Protocol, Rev. 1

IARC Epidemiological Study of Cancer Mortality among European Asphalt Workers

Electronic publications

An ever-increasing range of general information about IARC and scientific data resulting from its research activities is available through the IARC web site (http://www.iarc.fr/) (Figure 51). The web site has been redesigned, to enhance its appearance, navigability and information content, in view of the ever-growing importance of this form of communication. Useful new features include a powerful Boolean-capable search engine, FTP access, registration and feedback forms and a searchable on-line catalogue of publications in portable document format (PDF). Forthcoming events, fellowships, job vacancies and new publications are routinely announced through this channel.

A large amount of epidemiological data can be accessed through the CANCERMondial web site (http://www-dep.iarc.fr) (see below). The latter also hosts the web sites of the International Association of Cancer Registries (Section 1.1), the European Network of Cancer Registries (Section 1.1), the Automated Childhood Cancer Information System (Section 1.3) and the Directory of On-going Research in Cancer Prevention (Section 5.1). Summaries and evaluations from all IARC Monographs are available online (Section 2.1), while the *TP53* database is another unique data resource that is disseminated only in electronic form (Section 4.7).

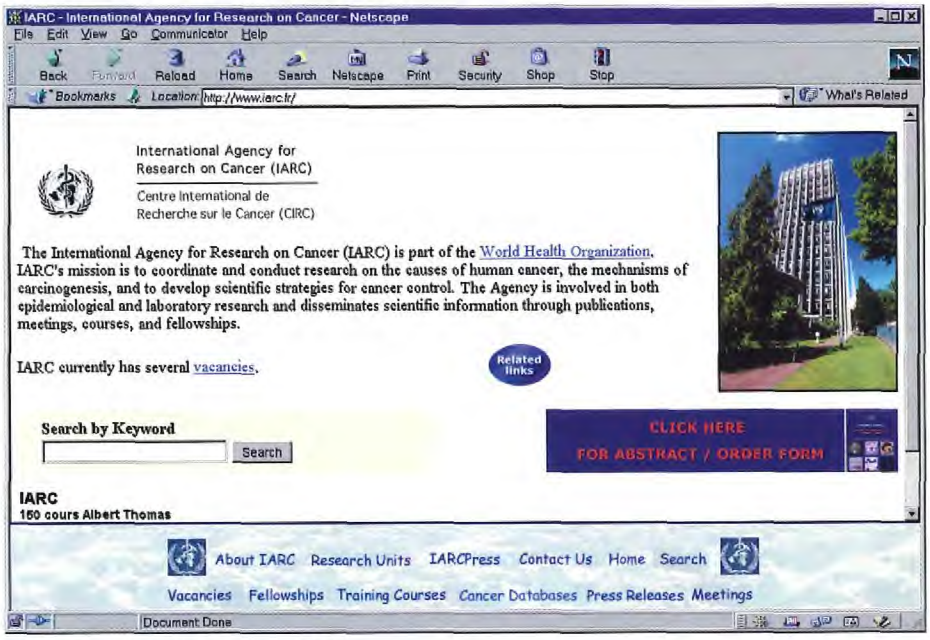


Figure 51. The Internet home page of IARC

One new electronic publication has been issued on CD-ROM. GLOBOCAN 2000, the fifth volume of the 'Cancerbase' series, is a graphic package providing estimates on the incidence and prevalence of, and mortality from, 26 major cancers for all countries of the world in 2000. Data can be extracted and presented as tables or graphs (Figure 52), and grouped as desired. Updates of the database will be made available for registered users through the Internet.

Simplified versions of GLOBOCAN 2000 and EUCAN with limited statistics and options are available through the Internet at the CANCERMondial web page, which also provides access to mortality data extracted from the WHO cancer mortality databank: data can be extracted using a simple menu-driven interface, then presented in various tabular and graphic formats.

Version 1 of a CD-ROM containing volumes 43 to 74 plus Supplement 7 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* was issued in 2000 by GMA Industries Inc. (Annapolis, MD, USA), and the same content can be obtained on the Internet at http://www.gmai.com. Version 1.1 contains additional earlier and later volumes, and a further issue carrying all volumes up to volume 78 is in preparation.

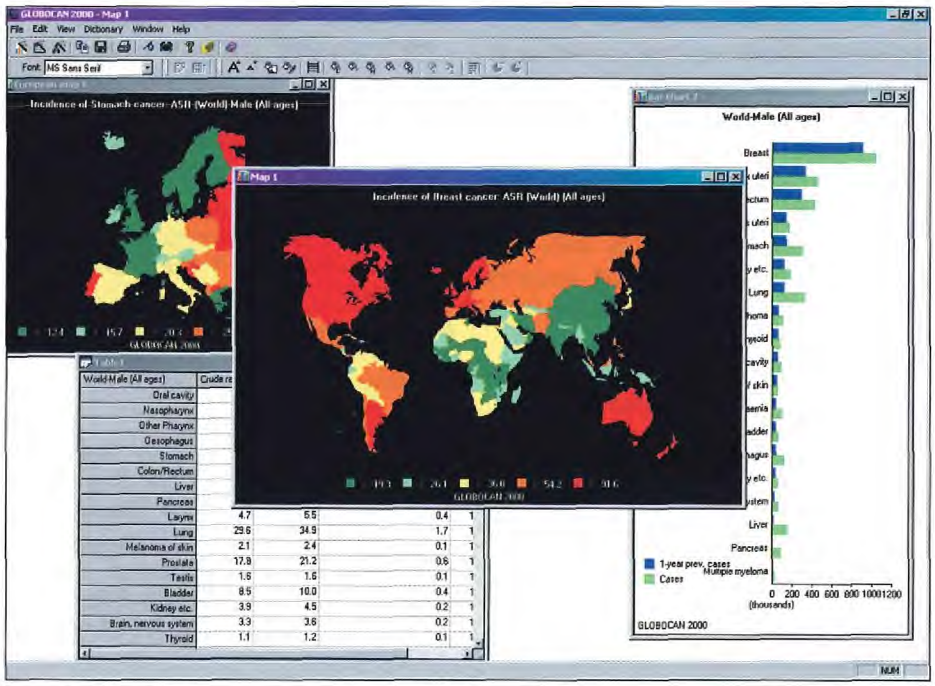


Figure 52. Examples of graphs created using the GLOBOCAN 2000 software.

7.2 *Cancer research fellowships*

IARC Research Training Fellowships

D.E. Goldgar and E. El Akroud

The aim of this programme is to provide young postdoctoral scientists, from any country, 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 develop programmes in cancer research or cancer control. The majority (63%) of the 501 fellows who have received awards since 1966 have come from western Europe, Japan, North America, Israel, Australia and New Zealand, while 18% came from eastern Europe and 18% from Africa, Asia and South America (Figure 53). Host laboratories have been mainly located in western Europe (51%) and North America (49%). The programme is one of the few to provide training in epidemiology, and the 105 fellowships awarded so far in this discipline have contributed substantially to the development of cancer epidemiology in a number of countries.

The Fellowships Selection Committee met twice in Lyon during the 2000–01 biennium to review applications; the members of the Committee were:

Dr M. Hollstein (2000, 2001)
German Cancer Research Center
Heidelberg, Germany

Dr K. Nilsson (2000, 2001) (*UICC Representative*)
Uppsala University Hospital,
Uppsala, Sweden

Dr T.E. Pangestu (2000, 2001) (*WHO Representative*)
Division of Evidence and Information for Policy, World Health Organization,
Geneva, Switzerland

Dr M.A. Pierotti (2000, 2001) (*Chairman*)
Istituto Nazionale per lo Studio e la Cura dei Tumori,
Milan, Italy

Dr J. Pouysségur (2000, 2001)
Centre de Biochimie, Faculté des Sciences,
Nice, France

Dr K. Sikora (2000, 2001)
Global Clinical Research (Oncology),
Pharmacia and Upjohn,
Milan, Italy

Dr P. Swann (2001)
University College London,
London, United Kingdom

Dr H. Tsuda (2000, 2001)
National Cancer Center Research Institute,
Tokyo, Japan

Dr J. M. Vasiliev (2000, 2001)
Russian Cancer Research Center,
Moscow, Russian Federation

The IARC representatives were Dr D.E. Goldgar and Dr E. Riboli (2000, 2001).
In 2000, among a total of 62 candidates, 28 were declared eligible and 9 finally received an award; in 2001, among a total of 80 candidates, 34 were declared eligible and 10 received an award. The distribution of fellowships awarded by discipline is given in Table 8 and the list of fellows in Table 9.
The Italian Association for Cancer Research continued its generous support of the Fellowships programme, providing a total of US$100 000 over the two-year period.

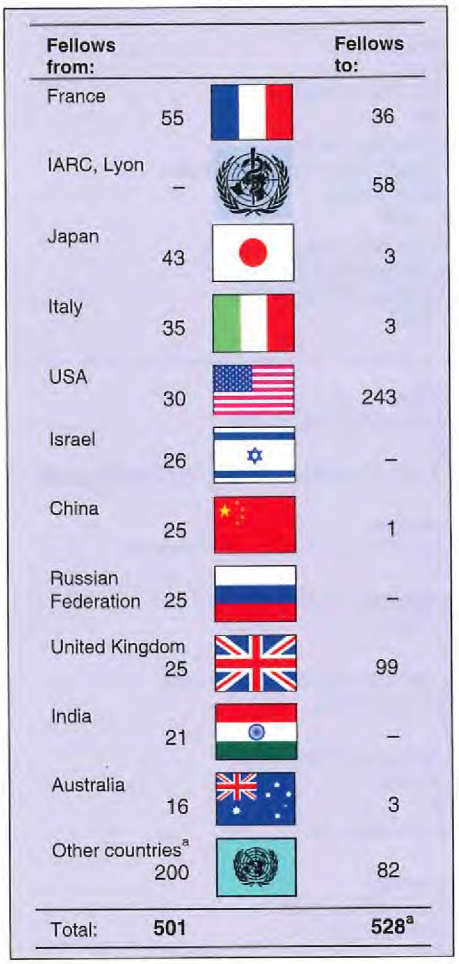


Figure 53. IARC fellows 1966–2001. Countries of origin and host countries

[a] Twenty-seven fellows had two host countries

Visiting Scientist Award

In 2000, this Award was given to Dr Patricia A. Buffler (School of Public Health, University of California, Berkeley, California, USA), who spent a year in the Unit of Environmental Cancer Epidemiology and in 2001 both to Dr H. Gilbert Welch (Veterans Administration Outcomes Research Group, Veterans Administration Medical Center, White River Junction, Vermont, USA), to spend ten months in the Unit of Descriptive Epidemiology, and to Dr Leslie T. Stayner (National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA), who is spending one year in the Unit of Carcinogen Identification and Evaluation.

Selection committee for postdoctoral fellowships at IARC

Z.-Q. Wang and E. El Akroud

The Postdoctoral Fellowships Selection Committee met twice during the biennium to select candidates for a fellowship at IARC, as well as the candidates for the Visiting Scientist Award. The members were: Dr P. Boffetta (2001), Dr E. Cardis (2000), Dr D. Goldgar (2000), Dr P. Hainaut (2001), Dr H. Ohgaki (2000, 2001), Dr E. Riboli (2000, 2001) and Dr Z.-Q. Wang (2000, 2001) (Chairman).
The committee met in March 2000 to review a total of 71 applications received, of which eight did not meet the eligibility requirements and four withdrew. Seven out of the 13 candidates recommended finally received an award, three in the field of epidemiology and four in laboratory sciences.
The committee met again in March 2001 to review a total of 55 applications received, 17 of which did not meet the eligibility requirements and two withdrew. Five out of the 12 candidates recommended received an award, two in the field of epidemiology and three in laboratory sciences.
Since its inception in 1998, this programme has proved to be effective in attracting young scientists of high quality. These fellows have contributed actively to IARC's research activities and have, in turn, received good training and experience, thus enhancing the prospects for their future scientific career.

Table 8. Distribution of research training fellowships awarded by discipline

Scientific discipline	No. of fellowships		
	2000	2001	1966–2001
Epidemiology and biostatistics	1	2	105
Cell biology, cell differentiation and cell genetics	2	–	118
Chemical carcinogenesis	3	–	70
Viral carcinogenesis	–	–	59
Biochemistry and molecular biology	3	6	93
Others	–	2	56
Total	9	10	501

Table 9. Fellowships awarded in 2000 and 2001

Name	Institute of origin	Host institute
2000		
ALM, A.K.	Lund University Department of Animal Physiology Lund, Sweden	Roswell Park Cancer Center Grace Cancer Drug Center Buffalo, NY, USA
ARNAUDEAU, C.Y.R.-M.	University of Stockholm Department of Genetic and Cellular Toxicology Stockholm, Sweden	Institut de Recherches sur le Cancer CNRS UPR 42, Laboratoire de Génétique Moléculaire Villejuif, France

Table 9 (contd)

Name	Institute of origin	Host institute
ELKIN, M.	Hadassah-Hebrew University Hospital Department of Oncology Jerusalem, Israel	National Institutes of Health National Institute of Dental Research Bethesda, MD, USA
HOBTA, A.I.	Kavetsky Institute for Experimental Pathology, Oncology and Radiobiology Department of Tumour Cell Biology Kiev, Ukraine	Bologna University Department of Biochemistry Bologna, Italy
JAFFE, A.	University of Pennsylvania Department of Genetics Philadelphia, PA, USA	University College London London, UK
KURTZ, J.-E.	Hopitaux Universitaires de Strasbourg Service d'Onco-Hématologie Strasbourg, France	Washington State University College of Pharmacy Pharmaceutical Sciences Department Pullman, WA, USA
MZAYEK, F.	Aleppo Directorate of Health Office of Training and Research Aleppo, Syria	Tulane University Medical Center School of Public Health and Tropical Medicine Department of Epidemiology New Orleans, LA, USA
SCARUFFI, P.	National Institute for Research on Cancer (ISR) Laboratory of Population Genetics Unit of Solid Tumour Biology Advanced Biotechnology Center Genoa, Italy	University of Pennsylvania Medical Center Molecular Biology Diagnostic Unit The Children's Hospital of Philadelphia Philadelphia, PA, USA
2001		
AOUACHRIA, A.-S.	Unit of Epidemiology and Preventive Medicine CHU Setif Setif, Algeria	Institut Louis Pasteur Unit of Epidemiology and Public Health Brussels, Belgium
BELLIDO, M.D.M.	Hospital de la Santa Creu I Sant Pau Department of Hematology Barcelona, Spain	Fred Hutchinson Cancer Research Center & Department of Medicine University of Washington Program in Genetics, Division of Clinical Research Seattle, WA, USA
BENTIRES-ALJ, M.	University of Liège, CHU Laboratory of Medical Chemistry & Medical Oncology Liège, Belgium	Beth Israel Deaconess Medical Center Cancer Biology Program Boston, MA, USA
DARDARI, R.	Institut Pasteur du Maroc Casablanca, Morocco	Centre de Recherche de l'Hôpital Saint-Justine Laboratoire d'Immunovirologie Montreal, Canada
FERNANDEZ DE MATTOS, S.	University of Barcelona School of Pharmacy Department of Biochemistry & Molecular Biology Barcelona, Spain	Imperial College School of Medicine at Hammersmith Campus CRC Laboratories Section of Cancer Cell Biology London, UK
GIGINEISHVILI, D.	Sarajishvili Institute of Neurology Tbilisi, Georgia	Johns Hopkins University School of Hygiene & Public Health Department of Epidemiology Baltimore, MD, USA
KUDO, Y.	Hiroshima University Faculty of Dentistry Department of Oral Pathology Hiroshima, Japan	New York University School of Medicine Department of Pathology New York, NY, USA
MOLIN, M.H.	Uppsala University Department of Medical Biochemistry & Microbiology Uppsala, Sweden	University of California, San Francisco Department of Microbiology & Immunology San Francisco, CA, USA
OKUDUCU, A.F.	Ege University Faculty of Medicine Department of Pathology Izmir, Turkey	University of Bonn Institute of Pathology Department of Molecular Pathology Bonn, Germany
SMIETANA, M.	Université Louis Pasteur Faculté de Pharmacie Laboratoire de Synthèse Bio-organique Illkirch-Graffenstaden, France	Stanford University Department of Chemistry Stanford, CA, USA

International Courses on Cancer Epidemiology

International courses on cancer epidemiology form the main series of courses run by IARC since the 1970s. They typically take place in areas with limited opportunities for training in cancer epidemiology, and usually provide the first exposure to modern epidemiological methods to participants, who include medical doctors (mainly oncologists), public health professionals and researchers.

Course on cancer epidemiology, with emphasis on environmental cancer

Budapest, Hungary, 6–17 March 2000

The course was organized in collaboration with the National Institute of Public Health and attended by 53 participants from 22 countries (33 from central and eastern Europe, 16 from western Europe and four from other regions). The instruction was given by two IARC staff, four local and four international faculty members. The first week concentrated on basic concepts of epidemiology and statistics, and the second on more advanced concepts. Lectures were complemented by computer-based practical sessions. Financial assistance from the US Environmental Protection Agency helped to pay for the travel and accommodation of 18 participants from central and eastern Europe. IARC provided support for three participants. The course directors were Paolo Boffetta and Paul Brennan from IARC.

Course on cancer epidemiology, principles and methods

Johannesburg, South Africa, 5–16 February 2001

The course was organized in collaboration with the Cancer Epidemiology Research Group in Johannesburg. It was attended by 38 participants, half of whom were from South Africa and half from 11 other African countries. Financial assistance from the SICAN association supported eight participants. The faculty inlcuded one member from IARC, three international members and two local members. The course covered the basic principles and methods of cancer epidemiology with a focus on the cancer problem in Africa. The second week included a workshop on the role of cancer registries in cancer control. The course director was Dr Isabel dos Santos Silva, of the London School of Hygiene and Tropical Medicine.

Advanced courses

International courses on molecular epidemiology

This course, held in collaboration with the Institute for Scientific Interchange Foundation (ISI) in Turin, is aimed at epidemiologists, molecular biologists, geneticists and pathologists who are or plan to become involved in interdisciplinary research in the field of cancer. It provides an overview of the state-of-the-art methods and approaches in molecular epidemiology.

The third international course on molecular epidemiology was held in Lyon, France, on 4–9 December 2000 and was attended by 42 participants from 22 countries. IARC provided financial support for nine participants. The faculty included 19 members from seven countries. The fourth course took place in Turin, Italy, on 3–8 December 2001, attended by 22 participants from 10 countries. The course directors were Marianne Berwick from New York, Paolo Boffetta from IARC and Paolo Vineis from Turin.

International course on infections and cancer

Veyrier-du-Lac, near Annecy, France, 22–28 April 2001

This course, second of a series started in 1998, presented the latest results on established links between cancer and different viruses as well as *Helicobacter pylori*, and also reviewed cancer-preventive opportunities. Emerging hypotheses on possible roles of other viral factors in human cancer were presented. Selected projects were discussed every day, allowing a close interaction between senior and junior scientists on specific research issues. The course welcomed 33 participants from 14 countries, mainly European, and was hosted and co-financed by the Fondation Mérieux. This provided support for the attendance of three participants from outside Europe. The course directors were Dr Silvia Franceschi, of IARC, and Dr Xavier Bosch, from the Catalan Institute of Oncology in Barcelona, Spain.

Courses on cancer registration and descriptive epidemiology

IARC summer school on cancer registration and applications in epidemiology

These courses have been organized annually by the Unit of Descriptive Epidemiology since 1996, primarily for staff of existing population-based cancer registries and those proposing to start cancer registration in their countries. The course begins with three weeks of intensive teaching in Lyon, with theory and practicals covering basic principles and practice of cancer registration (coding, data management using CanReg3 software, analysis and reporting) and epidemiological methods focusing on the applications of cancer registry data. This is followed by a week of observation and practical exposure in a cancer registry in Europe or Asia. So far, the six courses in English and two in French have hosted a total of 113 participants. The Alliance for Cervical Cancer Prevention (ACCP), the International Atomic Energy Agency (IAEA), ENCR, the Middle East Cancer Consortium (MECC), the United States National Cancer Institute, the International Union against Cancer (UICC) and WHO Regional Offices (AFRO, EMRO, SEARO, WPRO) and some national governments have supported the participation of candidates.

The fifth Summer School, held on 3–26 May, was attended by 17 participants from 15 countries, while the sixth, held on

7 May–1 June 2001, welcomed 21 participants from 18 countries.

Courses in Africa

Three training courses were held in Africa during the period, with the aim of improving the quality of cancer registries in the continent by teaching the registrars the principles and practices of cancer registration. The week-long courses included sessions on case-finding, abstracting, coding and the use of the CanReg software.

The first was held on 6–10 March 2000 in Bamako, Mali (in French) and was funded by the French Association pour la Recherche sur le Cancer (ARC). There were 13 participants from six countries (Figure 54). In 2001 two courses were held in English. In Ibadan, Nigeria (12–16 February), 16 students from the regional Nigerian cancer registries and two from the Gambian cancer registry received training. The course was financed by the African Regional Office of WHO. The UICC funded the second course, which took place on 23–27 September in Nairobi, Kenya, with 21 students from five countries.

Course for cancer registrars in Latin America

Lima, Peru, 16–26 October 2000 (in Spanish)

This course was organized in collaboration with the Cancer Registry of Lima, UICC and the Non-Communicable Diseases programme of PAHO. The aim was to re-launch cancer registration in the region and enhance standardization of methods and practices. The course focused on the practical activities of a registry, with emphasis on data abstraction, coding and quality checking. Nearly 30 participants from 15 countries of Central and South America attended the course.

ENCR courses

The European Network of Cancer Registries (ENCR) organized four courses in 2000 and two in 2001. Two courses on methods of population-based cancer registration were held in Sofia (Bulgaria) on 19–23 January 2000 and in Warsaw (Poland) on 19–23 September 2000. Participants at the Sofia course were mainly from central and eastern European countries; those in Warsaw were from nine more widely dispersed countries. Courses for EUROCIM users in Lyon on 15–17 March 2000 and in Sheffield, United Kingdom on 25–27 April 2001 covered the use of the EUROCIM software for statistical analysis of cancer registry data.

A statistical course on survival analysis methods for cancer registries took place in Lyon on 5–8 December 2000.

A course on coding ICD-O-3 was held in Copenhagen on 10–11 September 2001. This was the first in a series of local courses for trainers of cancer registry personnel for coding with ICD-O-3. It was mainly aimed at the registries in northern and central Europe.

Figure 54. Participants at the course on cancer registration in Bamako, Mali, March 2000

Other courses

IARC participates in the organization and running of courses which are primarily organized by other institutions.

European Educational Programme in Epidemiology

This three-week residential course, held annually in Florence, Italy, is co-sponsored by IARC, which provides logistic support for the secretariat, as well as by the WHO European Centre for Environment and Health, the European Commission, the International Epidemiological Association, the Health Authorities of Tuscany and the City of Florence. Two general modules present current developments in epidemiological study design and statistical analysis of epidemiological data. Special modules cover topics of clinical and public health relevance. Sessions include lectures, computer-based analyses, exercises and discussions.

The 13th course, held on 26 June–14 July 2000, was attended by 88 participants from 20 countries. The 14th course was held on 25 June–13 July 2001 and was attended by 94 participants from 18 countries. The course director is Rodolfo Saracci, from IARC and the National Research Council in Pisa, Italy.

Cancer genetics courses

These courses aim to provide training in genetics relevant to cancer prevention,

using an international approach and based on the experience of cancer genetic clinics. Their success is due to the high scientific standard of the morning lectures and afternoon workshops and the close interaction between the faculty and students.

The Fifth Gaslini–IARC–Menarini Course in Cancer Genetics and Pediatric Oncology, held in Sestri Levante, Italy, on 27 September–1 October 2000, attracted 70 students from 20 European and four other countries. The course directors were Riccardo Fodde (Leiden), Giovanni Romeo (Lyon) and Roberto Ravazzolo (Genoa).

The 6th IARC–Menarini Course in Cancer Genetics was held in Bertinoro di Romagna, Forlì, Italy, on 1–5 November 2001. It was attended by 55 students from 13 countries, and directed by Peter Devilee (Leiden), Pier-Luigi Lollini (Bologna) and Giovanni Romeo (Lyon).

NIVA Course on Molecular Epidemiology and Molecular Toxicology

Tallin, Estonia, 14–19 October 2001

IARC contributed to this course organized by the Nordic Institute for Advanced Training in Occupational Health, which was attended by 17 participants from six countries. 13 lecturers including four from IARC comprised the teaching faculty. The course directors were Paolo Boffetta and Kirsti Husgafvel-Pursiainen.

IARC Technical Transfer Awards

A promising participant is selected during each IARC course and invited to spend a period of several months in one of IARC's units. The stay usually leads to the establishment of a long-lasting collaboration between IARC and the home institute. From the cancer epidemiology course held in Khon Kaen, Thailand, in 1999, Dr Alongkone Phengsavanh, from the National University of Laos, was selected to work with the Unit of Descriptive Epidemiology. Two awardees selected at the molecular epidemiology course in Lyon in 2000, Dr Ariana Znaor (Croatian National Institute of Public Health, Zagreb, Croatia) and Dr Ana Jovicevic-Bekic (Institute for Oncology and Radiology of Serbia, Belgrade, Yugoslavia), both worked in the Unit of Environmental Cancer Epidemiology. Two awards were given in 2001: Dr Vikash Sewram, of the Medical Research Council (PROMEC), Tygerberg, South Africa, who attended the cancer epidemiology course in Johannesburg, received training in the Unit of Environmental Cancer Epidemiology, and Dr Hai-Rim Shin, from Dong-A University, Busan (Pusan), Republic of Korea, who was a participant at the course on infections and cancer, was hosted by the Unit of Field and Intervention Studies.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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Chair
Dr M. Aguet

Governing Council
Chair
Dr D. Dunstan

Director General, WHO
Dr G.H. Brundtland

Director
Dr P. Kleihues

Research Units

Carcinogen Identification and Evaluation

Dr J.M. Rice

Chemoprevention

Dr H. Vainio

Descriptive Epidemiology

Dr D.M. Parkin

Endogenous Cancer Risk Factors

Dr H. Ohshima

Environmental Cancer Epidemiology

Dr P. Boffetta

Epidemiology for Cancer Prevention

Dr A.J. Sasco

Field and Intervention Studies

Dr S. Franceschi

Gene-Environment Interactions

Dr Z.-Q. Wang

Genetic Epidemiology

Dr D.E. Goldgar

Genetic Cancer Susceptibility

Dr G. Romeo

Molecular Pathology

Dr H. Ohgaki

Nutrition and Cancer

Dr E. Riboli

Radiation and Cancer

Dr E. Cardis

Research Groups

DNA Repair

Dr J. Hall

Genome Analysis

Dr F. Canzian

Molecular Carcinogenesis

Dr P. Hainaut

Research Services

Communications

Dr N. Gaudin

Computer Services Group

M. Smans

Library

H. Miido

Administration and Finance

Director, Administration and Finance

V. Hay

Administrative Services

G. Guillerminet

Budget and Finance

R. Thomas

Personnel

R. Alloin

Personnel and Units

The scientific work of IARC is spread between Units and Research Groups that focus on particular areas of cancer research, while often collaborating closely on issues of common interest. The projects are conducted by long- and short-term staff members, as well as numerous visiting scientists from other institutions, including postdoctoral fellows who may spend one or two years at the Agency. Many students complete part or all of their studies for higher qualifications at IARC and contribute valuably to the research programmes. A wide range of support staff carry out the clerical, statistical, technical and secretarial work that forms an essential part of all research projects.

The lists that follow indicate the position of personnel at the end of the biennium, as of 31 December 2001. All short-term personnel are included who spent at least one month working at IARC.

Staff members who were no longer working at the Agency at the end of the biennium are indicated in italic type.

Office of the Director

Director, IARC
Dr P. Kleihues

Special adviser
Dr D. Evered, United Kingdom

Visiting scientists
Dr A.B. Miller, Canada (on secondment to the German Cancer Research Centre (DKFZ), Heidelberg, Germany)
Dr B.W. Stewart, Australia

Administrative assistant
Ms E. Rivière

Secretary
Ms C. Bassier

D. Evered, P. Kleihues, C. Bassier

E. Rivière

Carcinogen Identification and Evaluation

Chief of Unit
Dr J. Rice

Scientists
Dr R. Baan
Dr Y. Grosse
Dr D. McGregor
Ms C. Partensky
Dr K. Straif
Dr E. Suonio
Mr J. Wilbourn

Visiting scientists
Dr M.G. Bird, United States
Dr L. Stayner, United States

Technical assistance
Ms S. Egraz
Ms M. Lézère
Ms D. Mietton
Ms J. Mitchell

Secretaries
Ms E. Perez
Ms S. Reynaud

Rationale
Authoritative information about proven and possible human carcinogens is needed to assess the hazards posed by exposure to chemical, physical and biological factors. The sources of such exposures are varied; for example, the workplace (asbestos, solvents), the environment (ultraviolet radiation; viral, bacterial and parasitic infections) or individual lifestyles (alcohol drinking, tobacco smoking). Independent scientific evaluations of the carcinogenicity of such exposures can be used as a basis for information, regulation and legislation by the research community, national authorities and international organizations.

Objectives
The main work of the Unit is production of the prestigious IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, which has published authoritative reports on the hazards posed by more than 800 agents. The Unit collates the relevant data, coordinates and collaborates in their review by groups of independent external experts, and hosts meetings to agree the final conclusions. The critical, qualitative evaluations of carcinogenicity to humans that emerge are then published as monographs, and are respected for their integrity and accuracy. The Unit also prepares a directory of agents being tested for carcinogenicity (available on the web site), and edits a related series of IARC Scientific Publications related to mechanisms of carcinogenicity.

Multistage Carcinogenesis
In 2000, the Unit Chief, *Dr Hiroshi Yamasaki*, was seconded to Kwansei Gakuin University, Nishinomiya, Japan. The Unit was closed and the remaining staff members were temporarily attached to the Unit of Carcinogen Identification and Evaluation.

Scientist
Dr N. Mironov

Visiting scientists
Dr P.-P. Bringuier
Dr L. Giroldi
Dr F.-J. Hernandez-Blasquez
Ms J. Loncarek
Dr T. Yano
Dr Q.-F. Xiong
Dr M.-L. Zaidan-Dagli


IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Working Group, October 2001


C. Partensky

Chemoprevention

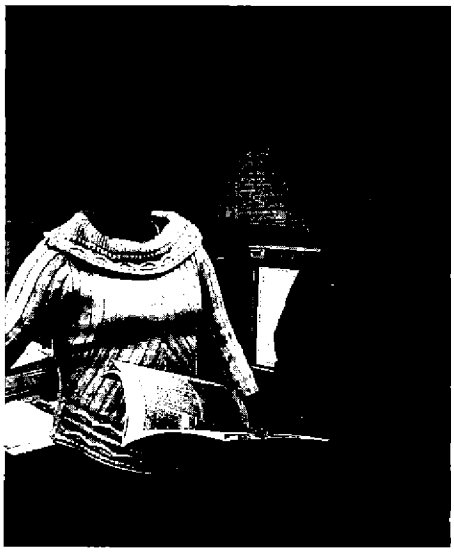
Chief of Unit
Dr H. Vainio

Scientist
Dr F. Bianchini

Visiting scientist
Dr R. Gallagher, Canada

Technical assistance
Ms C. Mogenet

Secretary
Ms J. Thévenoux


J. Thévenoux, F. Bianchini

Rationale

The prevention of cancer is one of the key objectives of IARC. The pro-active cancer-preventive strategies include:

1. Chemical, immunological, dietary and behavioural interventions that retard, block or reverse carcinogenic processes or reduce underlying risk factors.
2. Vaccination programmes against infective agents that predispose to cancer.
3. Screening programmes in targeted populations to identify patients with detectable precancerous lesions that are then treated.

The term chemoprevention refers to interventions with pharmaceuticals, vitamins, minerals or other chemicals (natural and synthetic) at any of the multiple stages of carcinogenesis to reduce cancer incidence. Chemoprevention is a relatively new field and the IARC established a Unit of Chemoprevention in May 1996. The publication series, IARC Handbooks of Cancer Prevention, evaluates scientific information on agents and interventions aimed at reducing cancer incidence and mortality.

Objectives

The main objectives of the Unit of Chemoprevention are to:

1. Convene working groups of international experts to prepare critical reviews and evaluations of cancer-preventive evidence and other relevant properties of a wide range of agents and strategies.
2. Publish and disseminate these evaluations widely to national and international authorities, public health specialists and cancer researchers.
3. Monitor scientific developments in the field of cancer prevention, to survey mechanistic advances and the availability of scientific tools for preventive purposes.


IARC Handbooks of Cancer Prevention, Working Group, February 2001

Descriptive Epidemiology

Chief of Unit
Dr D.M. Parkin

Scientists
Mr F. Bray
Mr J. Ferlay
Dr E. Kramárová
Dr P. Pisani
Dr R. Sankaranarayanan
Dr R. Sankila
Dr J. Tyczynski
Dr A. Vizcaino
Ms S. Whelan

Visiting scientists
Dr H. Botha, United Kingdom
Dr C. Burkhard, Switzerland
Dr J.-G. Chen, China
Dr W. Du, Singapore
Dr R. Lambert, France
Dr F. Montanaro, Italy
Dr A. Phengsavanh, Laos
Dr P. Pinheiro, Portugal
Dr U. Sen, India
Dr G. Welch, United States

Students
Ms S. Arrossi
Ms M. del Cielo Fernandez-Ortega
Ms A. Guilloux
Ms J.-C. Hung
Ms E. Kac
Ms A. Lee
Ms M.S. On
Ms E. Santana
Ms B. Yang

Technical assistance
Ms A. Bautista
Mr A. Cooke
Ms E. Démaret
Mr E. Lucas
Mr E. Masuyer
Mr N. Mitton
Ms K. Pitaksaringkarn
Mr A.V. Ramana Kumar
Ms T. Valdivieso Gonzales

Secretaries
Ms E. Bayle
Ms O. Bouvy
Ms C. Déchaux
Ms S. Dunderdale
Ms I. Haeve-Emery
Ms S. Haver-Legros
Ms Z. Merzoug
Ms S. Sibert-Dardenne

Gambia Hepatitis Intervention Study
Project leader
Dr D.M. Parkin

Registrar
Mr E. Bah

Scientist
Dr O. Lesi

Visiting scientist
Dr G. Kirk, United States

Technical assistance
Ms M. Mendy

Rationale

Descriptive epidemiology makes use of existing information systems to study the frequency of cancer – incidence, mortality, prevalence, survival – and its association with characteristics of individuals or their environment. The aim is to increase our understanding of the causes and effects of cancer so that we can intervene to reduce or eliminate exposures to risk factors, thereby minimizing the risk of being diagnosed with a cancer, and to reduce the consequences of a cancer diagnosis in terms of illness and risk of death.

Objectives

The Unit of Descriptive Epidemiology has the role of collating and making available information on the frequency of cancer in human populations around the world. Therefore one of its major roles involves developing and supporting organizations which record information on the occurrence of cancer, mainly population-based cancer registries, as well as making this information available to potential users in a comparable format. Collaboration is most active with registries in developing countries, where the problems caused by cancer are poorly defined, and includes field studies to elucidate the causes of cancers that are important locally. Cancer prevention activities – in particular, early detection and screening programmes and chemoprevention – are also evaluated.

The Unit also supervises the Gambia Hepatitis Intervention Study. This study was designed to assess the effectiveness of vaccination against HBV in preventing chronic infection and hepatocellular carcinoma.

R. Sankaranarayanan, A. Budukh (Barshi, India)

DNA Repair

Group Leader
Dr J. Hall

Scientist
Dr S. Angèle-Boivin

Visiting scientists
Dr M. Fernet, France
Dr S. Gutiérrez Enríquez, Ecuador

Students
Ms P. Auriemma
Mr S. Borel
Mr N. Moullan
Ms G. Prost

Technical assistance
Ms B. Chapot
Ms M. Vuillaume

Secretary
Ms M. Wrisez

Rationale

The characterization of the rare, radiation-sensitive cancer-prone diseases ataxia telangiectasia (AT) and Nijmegen breakage syndrome (NBS) has demonstrated that genetic predisposition increases the risk of developing cancer after exposure to ionizing radiation. It has been estimated that 1% of the general population are heterozygous carriers of the *ATM* gene, with such individuals and *NBS* heterozygotes having a higher risk of developing cancer. Molecular analyses of these disorders will provide valuable insights into the physiological function of these two gene products and their role in the cellular response to ionizing radiation. The involvement of these genes in sporadic cancers is being assessed and in particular the role of ATM as a risk factor in non-familial breast cancer.

Objectives

One of the objectives of our research is to determine genotype/phenotype relationships in AT patients. The mutation profile of the *ATM* gene in children with this rare disease is being determined and cell lines established from the peripheral blood lymphocytes of the affected individuals are being used to investigate the response to DNA damage produced by ionizing radiation *in vitro*. As epidemiological studies have shown that AT heterozygotes have an increased risk of developing cancers, in particular breast cancer, studies are under way to evaluate the role of the *ATM* gene in non-familial breast cancer. A prominent external sign of AT is telangiectasias in the eyeballs. Telangiectasias are found as a complication in patients treated by radiotherapy for age-related macular degeneration. Studies are in progress to assess whether alterations in the *ATM* gene are the underlying causes of these telangiectasias.


N. Moullan


J. Hall

Endogenous Cancer Risk Factors

Chief of Unit
Dr H. Ohshima

Scientists
Dr C. Malaveille
Dr B. Pignatelli

Visiting scientists
Dr B. Bancel, France
Dr M. Saleem Bhat, India
Dr K. Fukunaga, Japan
Dr R. Fukunaga, Japan
Dr C.-Q. Li, China
Dr M. Masuda, Japan
Dr H.F. Mower, United States
Dr T. Nakano, Japan
Dr T. Suzuki, Japan
Dr M. Tatemichi, Japan

Students
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Mr J. Blond
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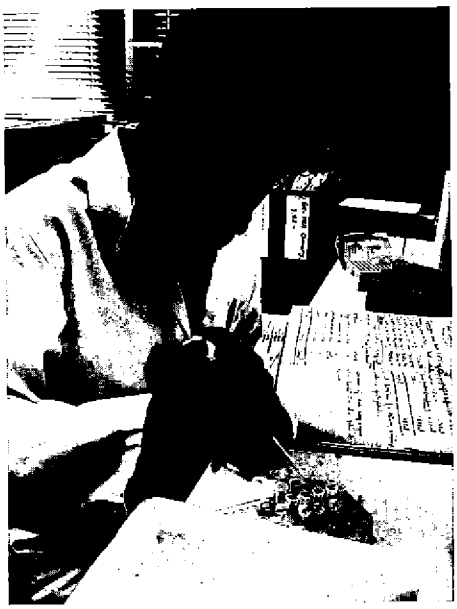
Ms L. Chazotte-Aubert
Ms A. Coche
Ms S. Cuenin

Technical assistance
Ms I. Gilibert
Ms A. Hautefeuille

Secretary
Ms P. Collard


M. Saleem Bhat

Rationale
Chronic inflammations caused by infection with viruses, bacteria or parasites increase the risk of certain human cancers; e.g. of the liver (hepatitis B virus), cervix (human papillomavirus), stomach (*Helicobacter pylori*) and bladder (schistosomes). Infected tissues can generate endogenous risk factors that may contribute to the development of cancer, such as reactive oxygen and nitrogen species that induce oxidative stress and may injure cells and damage DNA.


K. Fukunaga, R. Fukunaga

Objectives
The Unit studies the expression and regulation of key enzymes involved in oxidative stress, enzymes that generate free radicals, or protect against the tissue damage they induce. It also studies the DNA and protein damage induced by endogenous free radicals.

Environmental Cancer Epidemiology

Chief of Unit
Dr P. Boffetta

Scientist
Dr P. Brennan

Visiting scientists
Dr P. Buffler, United States
Dr R. Carel, Israel
Dr E. De Stefani, Uruguay
Dr A. Jovicevic-Bekic, Yugoslavia
Dr J. Korte, United States
Dr W. Lee, Republic of Korea
Dr S. Lewis, United Kingdom
Dr A. Ojajärvi, Finland
Dr T. Partanen, Finland
Dr A. Pitard, France
Dr A. Znaor, Croatia

Students
Mr I. Burstyn
Ms A. Crispo
Ms P. Cruise
Ms E. Decullier
Ms J.-C. Hung
Mr F. Hustache
Ms C. Longechamp
Ms E. Louis-Aimé
Ms A. 't Mannetje
Ms C. Stocco
Ms M. Tessari
Ms N. Travier

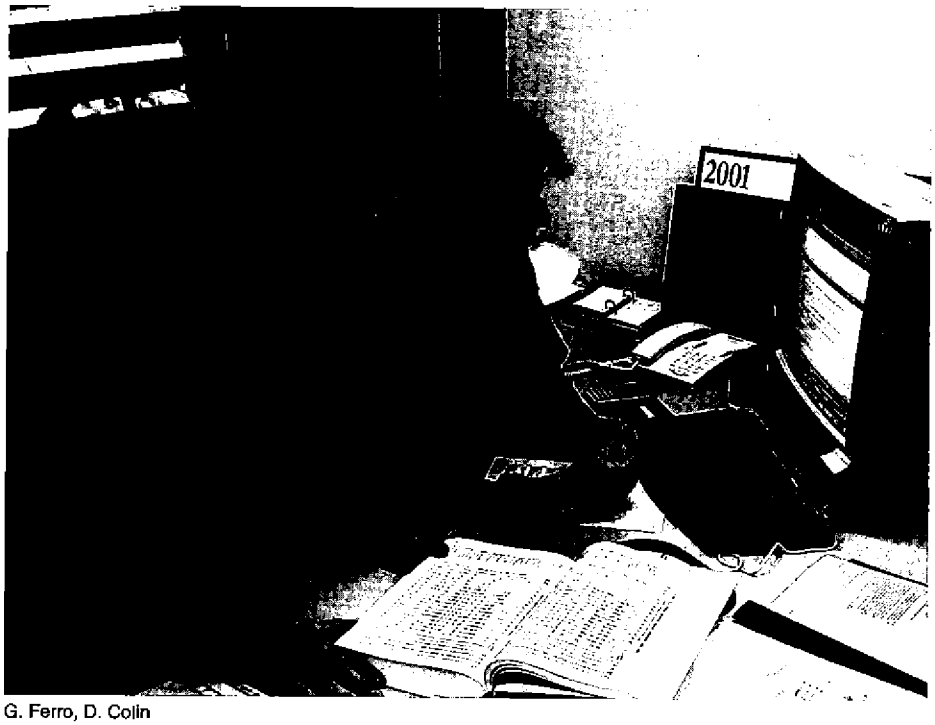
Technical assistance
Dr C. Cohet (courses)
Mr D. Colin
Ms M. Davis (courses)
Mr G. Ferro
Ms V. Gaborieau
Ms M. Garroni

Secretaries
Ms S. Fayolle
Ms M. Geesink

V. Gaborieau, J.-C. Hung

Rationale

Although several environmental risk factors for cancer have been identified, it is difficult to study the effects of many suspected carcinogens, particularly when low levels of exposure are involved. Several solutions have been proposed. International projects that are implemented in several centres can study the relatively large populations needed to investigate small risks. In epidemiological studies, use of reliable biomarkers of dose and of early effects yields better assessments of exposure and outcome. In addition, markers of genetic susceptibility to environmental agents allow identification of individuals who are at particularly high risk.



G. Ferro, D. Colin

Objectives

The Unit investigates environmental factors involved in cancer in human populations and their interaction with genetic factors, with the aim of contributing to primary prevention of cancer. These objectives are achieved through collaborative international epidemiological studies, which integrate molecular biology and genetic methods in a multidisciplinary approach.

Epidemiology for Cancer Prevention

Chief of Unit
Dr A.J. Sasco
(on secondment from INSERM)

Visiting scientists
Ms C.I. Cann, United States
Dr E. France, United States
Dr L. Laforest, France
Dr R. Little, United States
Dr R. Merrill, United States
Dr A. Mohr, France
Dr P. Renaudier, France
Dr Y. Rodvall, Sweden
Dr S. Yu, China

Students
Mr J. Bertiller
Mr H. Besson
Mr S. Brar
Dr F. Carriot
Ms S. Franklyn
Ms C. Hagnere
Ms D. D'Harcourt
Ms A. Husse
Ms M. Marsot
Dr S. Michard
Ms A. Pochelon
Ms E. Presles
Ms A. Prudhomme
Mr A. Sennelart
Ms L. Van Cotthem

Technical assistance
Ms V. Benhaïm-Luzon

Secretary
Ms M. Renaud

Rationale
Epidemiology aims to elucidate the etiology of diseases and to identify and quantify the factors that cause or prevent human cancer. Our current knowledge is already sufficient to allow certain preventive strategies to be implemented. Such strategies concern both primary prevention of cancer, through avoiding recognized carcinogens or intervening in the carcinogenic process in particular by pharmacoprevention, and secondary prevention or screening.


J. Bertiller, H. Besson

Objectives
Control of tobacco and tobacco-related diseases would dramatically reduce the burden of cancer worldwide. The highest priority is preventing tobacco use, among children and adolescents, and among women and in developing countries. For other cancers such as breast cancer – which kills more women than any other cancer – we need to know more about prevention and risk factors, such as the influence of hormones and environmental exposures. The Unit conducts etiological studies with particular emphasis on the role of hormonal determinants of cancer in women and newborn children, and evaluative studies measuring the impact of health education and legislation on smoking and other health-related behaviours.


A.J. Sasco, V. Benhaïm-Luzon, R. Merrill

Field and Intervention Studies

Chief of Unit
Dr S. Franceschi

Scientists
Dr C. Bosetti
Mr M. Plummer
Dr J. Smith
Dr S. Vaccarella
Dr E. Weiderpass

Visiting scientists
Dr N. Muñoz, Colombia
Dr R. Talamini, Italy

Students
Ms M.-L. Charpail
Mr G. Clifford
Mr B. Houot
Ms S Hussain

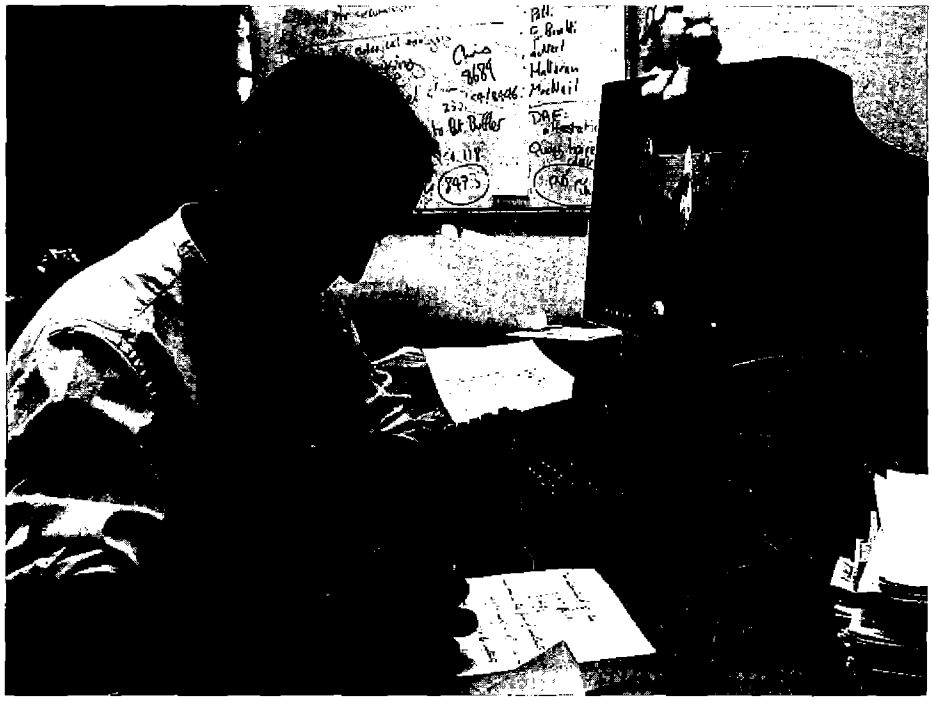
Technical assistance
Ms A. Arslan
Mr Y. Guy
Ms C. Lavé

Secretary
Ms H. Lorenzen

Rationale
Chronic infections have long been suspected to be associated with certain human cancers, but it is only recently that epidemiological and laboratory studies have provided a firm basis for these associations. It is now estimated that approximately 15% of all human cancers are associated with chronic infections. Most of these, such as cancer of the uterine cervix, stomach and liver are highly prevalent in developing countries, where the possibilities of treatment and prevention are poor. Production of safe, effective and cheap vaccines offers great potential for preventing such cancers.

Objectives
The Unit has set up field studies to investigate the role of human papillomavirus in cancers of the cervix and oral cavity, *Helicobacter pylori* in stomach cancer and the hepatitis B and C viruses in liver cancer. It also implements intervention studies to assess the prospects for primary prevention of stomach and cervical cancers through the use of chemopreventive agents and vaccines.

D. Hammouda (Algers, Algeria), A. Arslan



M. Plummer

Gene–Environment Interactions

Chief of Unit
Dr Z.-Q. Wang

Scientists
Dr A. Barbin
Dr Z. Herceg
Dr V. Krutovskikh
Dr B.S. Sylla
Dr W.-M. Tong
Dr E. Van Dyck

Visiting scientists
Dr F. Dal Piaz, Italy
Dr I. Demuth, Germany
Dr M. Dubina, Russian Federation
Dr V. Dumon, France
Dr S. Lee, Republic of Korea
Dr M. Lleonart, Spain
Dr J.-L. Luo, China
Dr G.B. Sajithlal, India
Dr G. Schmid, Austria
Dr B. Secretan, Switzerland
Dr R. Wang, China
Dr Y.-G. Yang, China

Students
Ms C. Andrieu
Ms J. Auclair
Mr P. Bertolino
Mr P. Bleyzac
Mr U. Cortes
Mr P.-O. Frappart
Ms S. Hamimes
Mr H. Li
Ms E. Moudilou
Ms V. Petrilli
Ms V. Pouchkine
Mr B. Salaun
Ms E. Speina
Mr X. Zhang

Technical assistance
Ms G. Brun
Mr C. Cuenin
Ms L. Garren
Ms C. Granier
Ms J. Michelon
Ms C. Piccoli

Secretary
Ms A.-M. Maillol

S. Lee, V. Krutovskikh

V. Petrilli

Rationale

Tumour development involves many genetic and epigenetic changes. Loss of cellular checkpoints and genomic integrity, resulting from genetic defects and exposure to environmental carcinogens, plays an important role. However, the mechanisms by which specific molecules, operative in chromatin functions, cell–cell communication and signal transduction initiate these pathogenic processes are not well understood. Elucidating the function of genes and their relation to cancer susceptibility and the role of environmental carcinogens in causing specific genetic changes are important areas of research.

Objectives

1. To elucidate the molecular mechanisms of genes responsible for DNA damage response, signal transduction and cell–cell communication, in maintaining genomic stability, cell-cycle control and neoplastic transformation.
2. To study cancer susceptibility and the relationship between particular genetic mutations and exposure to carcinogenic or genotoxic agents.
3. To establish and apply models for human cancer and molecular epidemiological studies.

Genetic Cancer Susceptibility

Chief of Unit
Dr G. Romeo

Scientists
Dr R. Corvi
Dr A. De Grandi
Dr L. Yin

Visiting scientists
Dr U. Al-Alem, Yemen
Dr V. Amarger, France
Dr C. Beu Volpato, Brazil
Dr P. Mehlen, France
Dr A. Metspalu, Estonia
Dr K. Stankov, Yugoslavia

Students
Ms E. Bessy
Ms A. Charpy
Ms C. Coutanson
Ms V. Ferrand
Ms N. Forey
Ms C. Gabus
Mr S. Lhomme
Ms L. Jonard
Ms F. Lesueur
Ms J. Liang
Dr M. Martinez-Alfaro
Mr J. McKay
Mr J.J. Médard
Mr A. Pastore
Ms K. Thiebault
Mr L. Toschi
Ms L. Wang

Technical assistance
Mr C. Lafaye
Ms M. F. Lavoue
Ms S. Pauly

Secretary
Ms A. Trochard

Rationale
Interaction of inherited and environmental factors (in particular, viruses and exposure to radiation) plays an important role in tumorigenesis. For example, infection with Epstein–Barr virus has unusually severe effects in people with X-linked lymphoproliferative disease (XLP), a rare inherited immunodeficiency syndrome, and has been associated with Burkitt lymphoma, nasopharyngeal carcinoma and Hodgkin disease. Likewise, incidence of papillary thyroid carcinoma (PTC), the commonest form of thyroid cancer, is increasing in populations exposed to radiation in the wake of the Chernobyl accident.

Objectives
The Unit aims to study genetic factors that predispose to human cancer, in particular, those involved in PTC and XLP. Somatic rearrangements of the *RET* protooncogene have been associated with PTC and the structure and role of *RET* in thyroid tumours have been studied extensively. Linkage analysis in families with recurrent PTC will determine what genes may be involved. A genetic and physical map of the XLP region has been constructed, and isolation and characterization of the relevant gene are in progress. Its role in XLP and its interaction with Epstein–Barr virus will be studied.


M. Martinez-Alfaro


J.J. Médard

Genetic Epidemiology

Chief of Unit
Dr D. Goldgar

Scientists
Dr M. Corbex
Dr O. Sinilnikova
Dr C. Szabo

Visiting scientists
Dr D. Hugues, Ireland
Dr M. de Los Angeles Rios, Cuba
Dr F. Vogl, Germany

Students
Ms S. Chopin
Ms S. Ginolhac-Heintz
Ms M. Leone

Technical assistance
Ms C. Audoynaud-Cour
Ms L. Barjhoux
Ms C. Bonnardel
Ms N. Martel
Mr F. Odefrey
Ms H. Renard
Mr O. Yaqoubi

Secretary
Ms Y. Granjard


O. Sinilnikova, C. Bonnardel

Rationale
It has long been recognized that familial factors play a significant role in the development of many common cancers. This observed familial clustering may stem from inherited defects in specific genes, from shared environmental exposures among family members, or from interaction between specific genetic and environmental factors. By identifying specific genetic predisposition to common cancers and by discovering how these genetic effects interact with known environmental risk factors, it should be possible to identify individuals who are particularly at high risk for developing cancer when exposed to specific carcinogens.


M. Leone

Objectives
The goals of the Unit of Genetic Epidemiology are:
1. to assess the magnitude of the role played by familial factors in the development of cancers at selected sites, through analysis of family history data;
2. to identify specific cancer predisposition genes through linkage analysis of high-risk families, through association or case–control studies with known polymorphisms, and through mutational analysis of specific candidate genes;
3. to estimate the age- and site-specific risks of cancer conferred by mutations and/or polymorphic variation in these genes, and examine how these risks are modified by known environmental factors;
4. to assess the contribution of variation in specific cancer predisposition genes to cancer incidence in the developing world.
To accomplish these goals, the unit also develops statistical tools for mapping and analysing complex traits.

Genome Analysis

Group Leader
Dr F. Canzian

Visiting scientists
Dr S. Landi, Italy
Dr S. Zienolddiny, Norway

Students
Mr D.G. Cox
Ms F. Gemignani
Ms C. Jost
Ms A. Llewellyn
Mr R. Llewellyn
Ms C. Pallara
Ms C. Peinado
Ms C. Perra
Ms H. Saulep
Mr F. Vivant

Technical assistance
Ms C. Boillot

Secretary
Ms A. Trochard

Rationale
Several mechanisms of genetic susceptibility to cancer act through rare germline mutations with high penetrance, conferring a very high risk of developing cancer and resulting in familial clustering of cases. The next frontier in cancer genetics is to find genes with high-prevalence alleles that confer a slight increase or decrease of cancer risk. Such genetic variants are likely to have large attributable risks, and therefore a strong impact in terms of public health.

Objectives
The main objective of the Group is to discover new genetic variants related to susceptibility to human cancers. The Group uses a multidisciplinary approach integrating genetics, molecular biology, bioinformatics and epidemiology. It aims at setting up a streamlined process going from discovery of new polymorphisms in candidate genes to the evaluation of their role in cancer etiology. To this end, it performs case–control studies within the framework of large population-based projects, in the first place the European Prospective Investigation into Cancer and Nutrition (EPIC), coordinated by the Unit of Nutrition and Cancer. The Group is also developing a technological platform to perform high-throughput genetic analysis and provides a service of genotyping and DNA mutation searching for the other units and groups within IARC.

D.G. Cox

Molecular Carcinogenesis

Group Leader
Dr P. Hainaut

Visiting scientists
Dr C. Caron de Fromentel, France
Dr K. Dimas, Greece
Dr E. Gormally, France
Dr O. Lesi, Nigeria
Dr K. Mann, United States
Dr D. Maurici, Italy
Dr S. North-Chassande, France
Dr M. Olivier, France
Dr D. Peixoto Guimaraes, Brazil
Dr I. Persson, Sweden
Dr A. Sepehr, Iran
Dr P. Tanière, France

Students
Ms N. Collidor
Ms S. Courtois
Ms E. Derepierre
Ms S. Evans
Ms M. Lauwen
Ms S. Michel
Mr. O. Pluquet
Ms S. Seemann
Ms H. Shi
Ms K. Szymanska
Ms E. Taranchon
Ms M. Volpato

Technical assistance
Ms G. Martel-Planche
Mr L. Ripert

Secretary
Ms M. Wrisez


H. Shi

Rationale
Cancer progression implies many coordinated changes in the genetic programme that drives the behaviour of single cells. Some of these changes are pre-determined by genetic predisposition. Others are acquired as the result of mutations caused by endogenous or exogenous risk factors. These changes primarily affect not only the function of the proteins encoded by the altered genes, but also the whole cellular circuitry controlling cell growth, replicative potential, survival and response to stress. One of the key genes involved in this process is the tumour-suppressor gene *TP53*, which is the most commonly mutated gene in human cancer.


K. Szymanska

Objectives
The group investigates the interplay between genetic and epigenetic changes during the development of human cancers. Most studies focus on the function and mutations of the *TP53* gene. Current projects address the molecular mechanisms of p53 protein activation in response to stress and the functional consequences of *TP53* mutations in human cancer. The group also maintains and develops a database of *TP53* mutations in human cancers worldwide. In parallel, multi-disciplinary approaches are developed to analyse the sequence of molecular events involved in the etiopathogenesis of oesophageal cancers and of hepatocellular carcinomas, two of the most important cancer types in developing countries.

Molecular Pathology

Chief of Unit
Dr H. Ohgaki

Scientist
Dr H. Huang

Visiting scientists
Dr N. Baeza, France
Dr S. Colella, Italy
Dr Y. Edamoto, Japan
Dr A. Hara, Japan
Dr S. Horstmann, Germany
Dr J. Masuoka, Japan
Dr M. Nakamura, Japan
Dr Y. Okamoto, Japan
Dr A. Sankila, Finland
Dr T. Watanabe, Japan
Dr H. Yokoo, Japan
Dr M. Yokoo, Japan

Students
Ms S. Benherri
Mr R. Reis

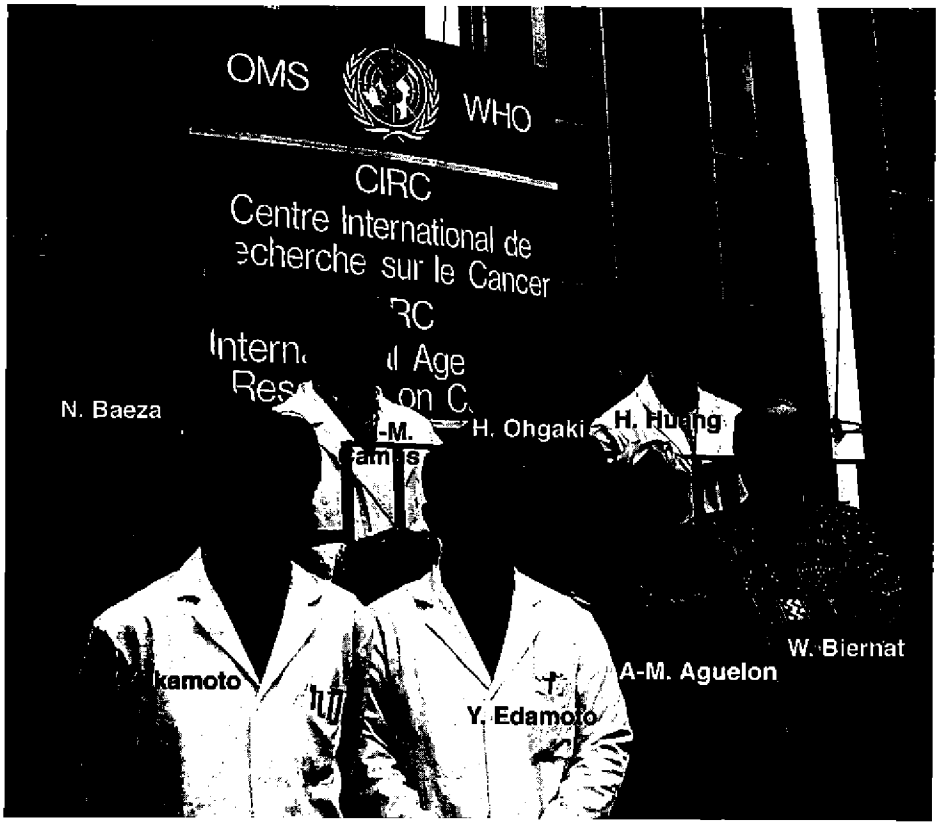
Technical assistance
Ms A.-M. Camus-Randon
Ms A.-M. Aguelon-Pegouries

Secretary
Ms A. Rivoire

Rationale
Carcinogenesis is a multistep process which may involve activation of oncogenes, inactivation of tumour-suppressor genes and overexpression of genes encoding growth factors. The type and timing of these genetic alterations appears to be both tissue-specific and cell-type-specific.

Objectives
The Unit of Molecular Pathology focuses on molecular mechanisms involved in the development of human brain tumours, with particular emphasis on the progression of glioma. To assess the role of genes that are associated with transformation of human brain tumours, mice that carry these genes under the control of astrocyte-specific promoters are generated. These transgenic animals also offer the opportunity to study the role of interactions between chemical carcinogens and inherited genetic alterations in tumour progression.

Y. Okamoto, Y. Edamoto



Nutrition and Cancer

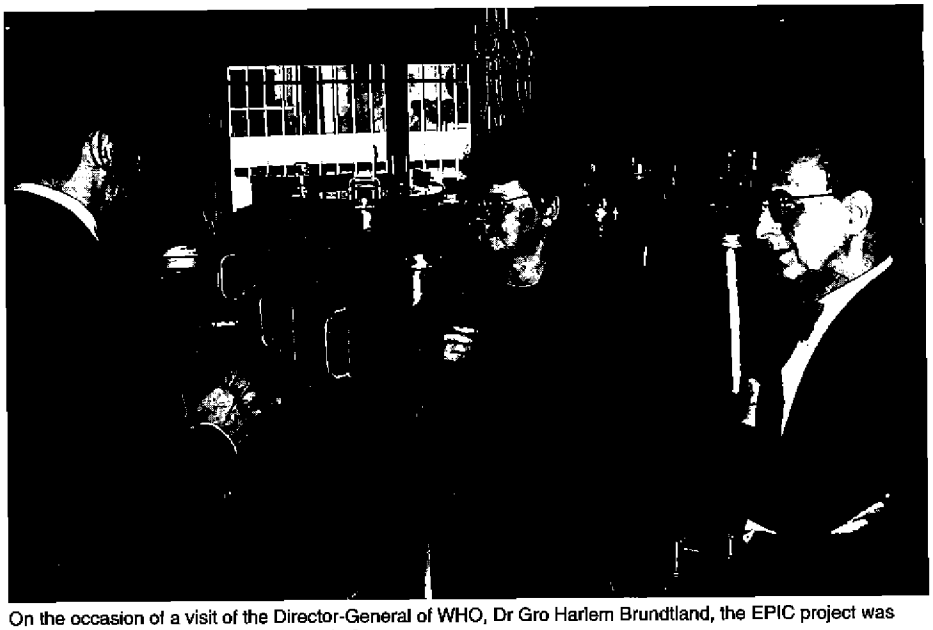
Chief of Unit
Dr E. Riboli

Scientists
Ms R. Arndt-Charrondière
Mr M. Fahey
Dr P. Ferrari
Dr M. Friesen
Dr R. Kaaks
Dr A. Lukanova
Dr T. Norat
Dr S. Rinaldi
Ms N. Slimani

Visiting scientists
Dr A. Ciampi, Canada
Dr K. Hunt, United States
Dr M. Kurzer, United States
Dr T. Lai, Estonia
Dr L. Le Marchand, United States
Dr E. Lund, Norway
Dr F. Pellegrini, Italy
Dr R. Saracci, Italy
Dr M. Van Bakel, Netherlands

Students
Mr J. Clech
Ms M. Elahi
Mr L. Zucchi

J. Bouzac, C. Lallemand



On the occasion of a visit of the Director-General of WHO, Dr Gro Harlem Brundtland, the EPIC project was presented by Drs Elio Riboli and Rodolfo Saracci

Technical assistance
Ms D. Achaintre
Ms C. Biessy
Ms J. Bouzac
Ms C. Casagrande
Ms S. David
Mr B. Hémon
Mr C. Lallemand
Ms S. Michel
Mr J. Vignat
Ms B. Vozar

Secretaries
Ms J. Dehedin
Ms O. Drutel
Ms S. Somerville

Rationale

Diet and nutrition are important in the development of some of the most common cancers, notably those of the digestive and respiratory tracts, breast, endometrium and prostate. Epidemiological studies show that while eating more fruits and vegetables may reduce risks of cancer of the digestive and respiratory tracts, eating meat and salt-preserved foods may increase the likelihood of developing colorectal and stomach cancer. Other diet-related factors, such as the amount of energy consumed and expended, certain anthropometric characteristics, such as fat, body mass and abdominal obesity, and their relationship to hormonal patterns may also be important, particularly for cancers of the breast, endometrium, prostate and colon.

Objectives

The Unit investigates the role of diet-related and lifestyle factors in cancer, by a multidisciplinary approach that involves large population-based prospective studies in which biological samples are collected and analysed for biomarkers of diet, metabolic processes and genetic susceptibility.

A network of large prospective studies has been developed. The main project is the European Prospective Investigation into Cancer and Nutrition (EPIC) based on over half a million volunteers in ten European countries. Through the collection of dietary, liefestyle and anthropometric data as well as the collection and storage of blood samples, EPIC integrates the nutritional, lifestyle, metabolic and genetic dimensions of cancer research.

Radiation and Cancer

Chief of Unit
Dr E. Cardis

Scientists
Dr L. Ardoino
Dr A. Kesminiene
Dr M. Pearce
Dr I. Thierry-Chef

Visiting scientists
Dr A. Cook, New Zealand
Ms L. Montestrucq, France
Dr D. Richardson, United States
Dr L. Richardson, Canada

Students
Ms M. Kilkenny
Mr E. Maceika

Technical assistance
Ms E. Amoros
Ms E. Combalot
Ms N. Encrenaz
Ms S. Marcadas
Ms A. Monnet
Ms H. Tardy
Ms V. Tenet

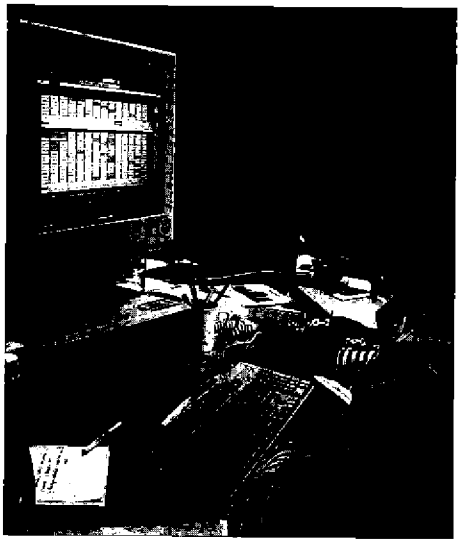
Secretaries
Ms B. Andrieux
Ms C. Laout

Rationale

Few data are available on the risk associated with low-dose ionizing radiation exposure, the effects of different types of radiation and, in particular, the risks associated with the prolonged exposure of concern for the general population. The influence of genetic and environmental factors on the risk of radiation-induced cancers is also largely unknown.

Radiations and electromagnetic fields which do not have enough energy to cause ionization in tissues may cause adverse health consequences in other ways. Although solar ultraviolet radiation has been established as a human carcinogen, the evidence for other parts of the electromagnetic spectrum (in particular radiofrequency radiation emitted by mobile telephones and extremely low-frequency fields emitted by electricity transmission lines and electrical appliances) is not conclusive.

Because of the ubiquity of human exposure to electromagnetic fields and because of widespread concern in the general population, there is an urgent need for targeted epidemiological studies of particular types of exposure.



L. Montestrucq, N. Encrenaz

Objectives

The Unit studies the carcinogenic effects of radiation, in particular, low doses of ionizing radiation, in relation to the type of radiation, patterns of exposure, and host and environmental factors. The aim of this work is twofold: to strengthen the scientific bases of radiation protection (ionizing and non-ionizing), and to increase our understanding of biological mechanisms of carcinogenesis.

A. Kesminiene (second from right), visiting the Chernobyl nuclear power plant with trainee interviewers for a case–control study of cancer among accident 'liquidators' (see page 32)

Computer Services Group

Head of Group
Mr M. Smans

Systems manager
Mr P. Damiecki

Technical assistance
Ms B. Kajo

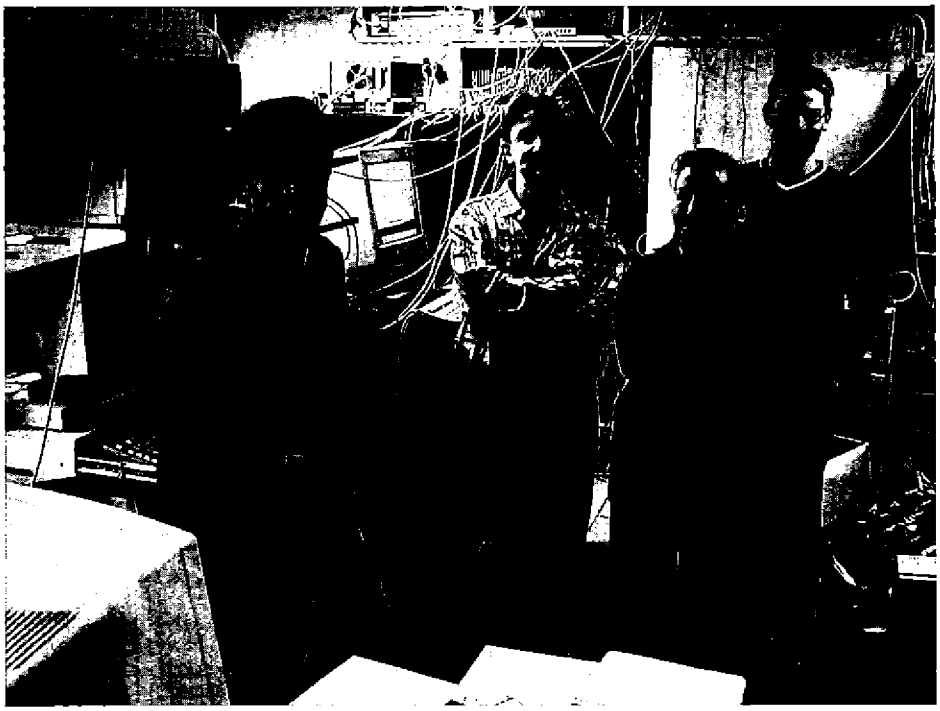
Trainees
Mr C. Jack
Mr P. Marquez

The Computer Services Group manages the framework of central computing at IARC. This includes provision of central services for statistical analysis, database storage and access, file management and communications services, as well as the management of the local area network (LAN) that allows both scientific and administrative users to connect to these services. In the current biennium, the LAN has been enhanced, in terms of both number of connections and total bandwith. The inauguration of the new Latarjet Building triggered even more improvements with the installation of a fibre optic connection to link the three IARC buildings.

A new connection to the Internet is now fully operational at 512 kb per second, using a relatively new technology based on radio transmission.

A new mail server, separate from the earlier VAX cluster, has been installed, providing more storage space and faster mail routing.

Although the total number of workstations (PCs, Macintoshes etc.) seems to be stabilizing, more servers are being installed, centrally or in the research units, and the management of this area is requiring more resources.



M. Smans, P. Damiecki, B. Kajo, C. Jack

Communications

Chief of Unit
Dr N. Gaudin

Senior editor
Dr J. Cheney

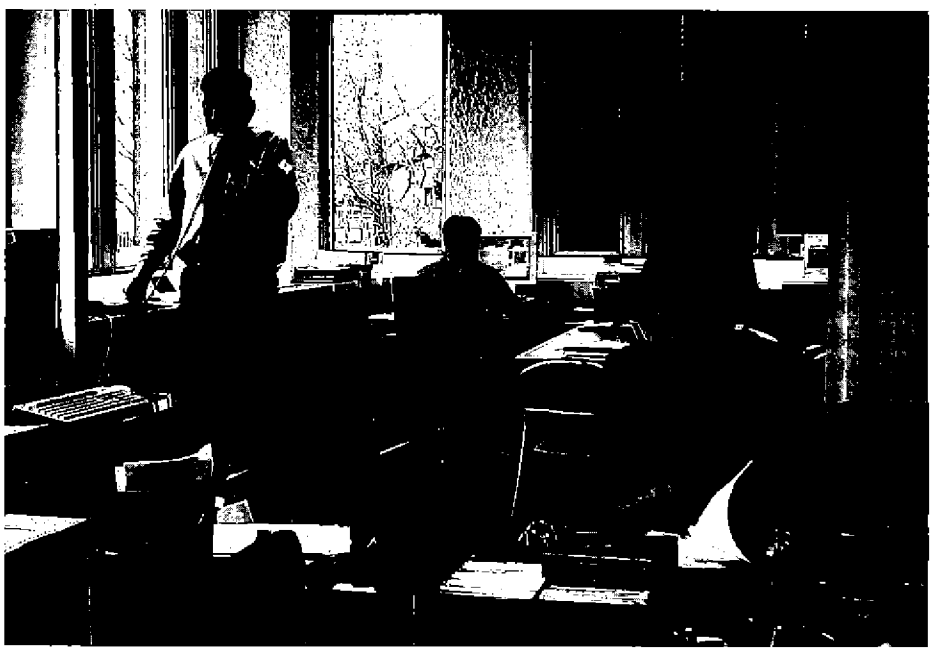
Visiting scientists
Dr P.L Di Patre, Italy
Dr F. Soylemezglu, Turkey
Dr W. Biernat, Poland
Dr H. Mattock, United Kingdom
Dr N. Napalkov, Russian Federation

Assistants (IARCPress)
Ms S. Cotterell
Ms D. Flint (Washington office)
Ms F. Romagnan
Ms S. Söring
Ms S. Thomas
Ms K. Wilson (Washington office)

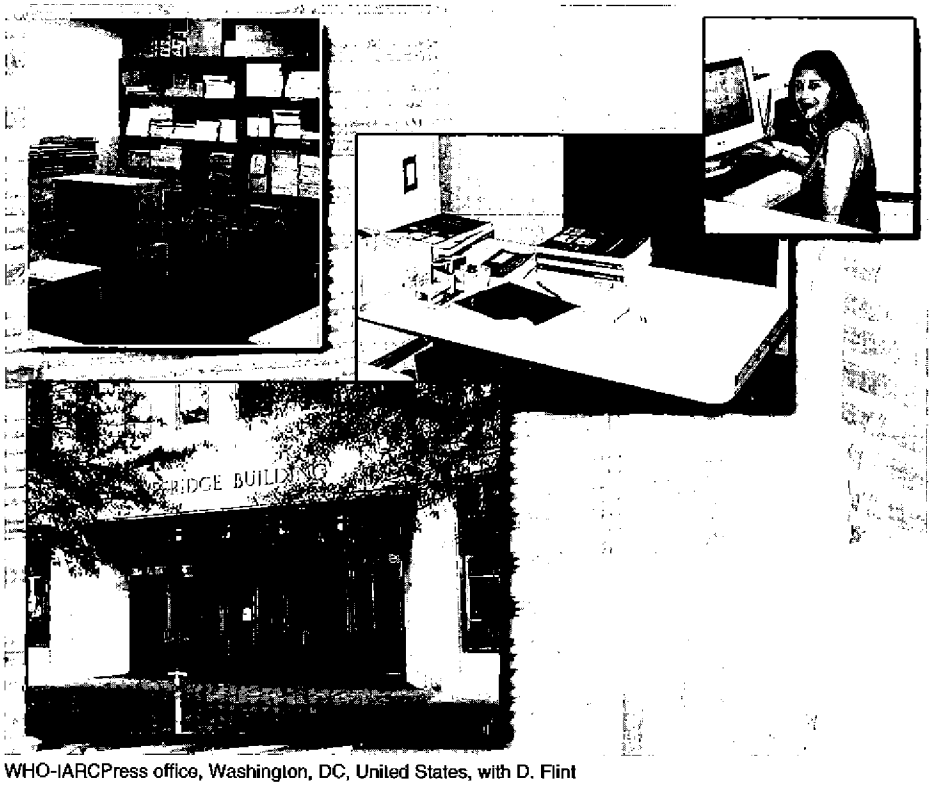
Technical assistance
Mr J. Croibier
Ms C. Goebels
Mr F. Kroenert
Ms S. Lee
Ms M. Mainaud
Mr G. Mollon

Trainee
Ms A. Ohara

Secretaries
Ms B. Geoffre
Ms A.-C. Moret



The IARCPress office, Lyon: N. Gaudin, A. Ohara, S. Cotterell



WHO-IARCPress office, Washington, DC, United States, with D. Flint

The Communications Unit has responsibility for the presentation of a homogeneous image of all aspects of IARC work to the scientific community, the media and the general public, as well as providing a service to the scientific units in all matters related to information. It thus assists the scientific units in dissemination of the results from their research, by providing advice and editorial help for publication of articles in international scientific journals and through its own publications under the IARCPress imprint. The IARCPress has sales and distribution offices in both Lyon and Washington, DC. The Unit also maintains the Agency's Internet and Intranet sites, and provides a service for translation of documents from English to French and a photographic service supporting all of the research units.

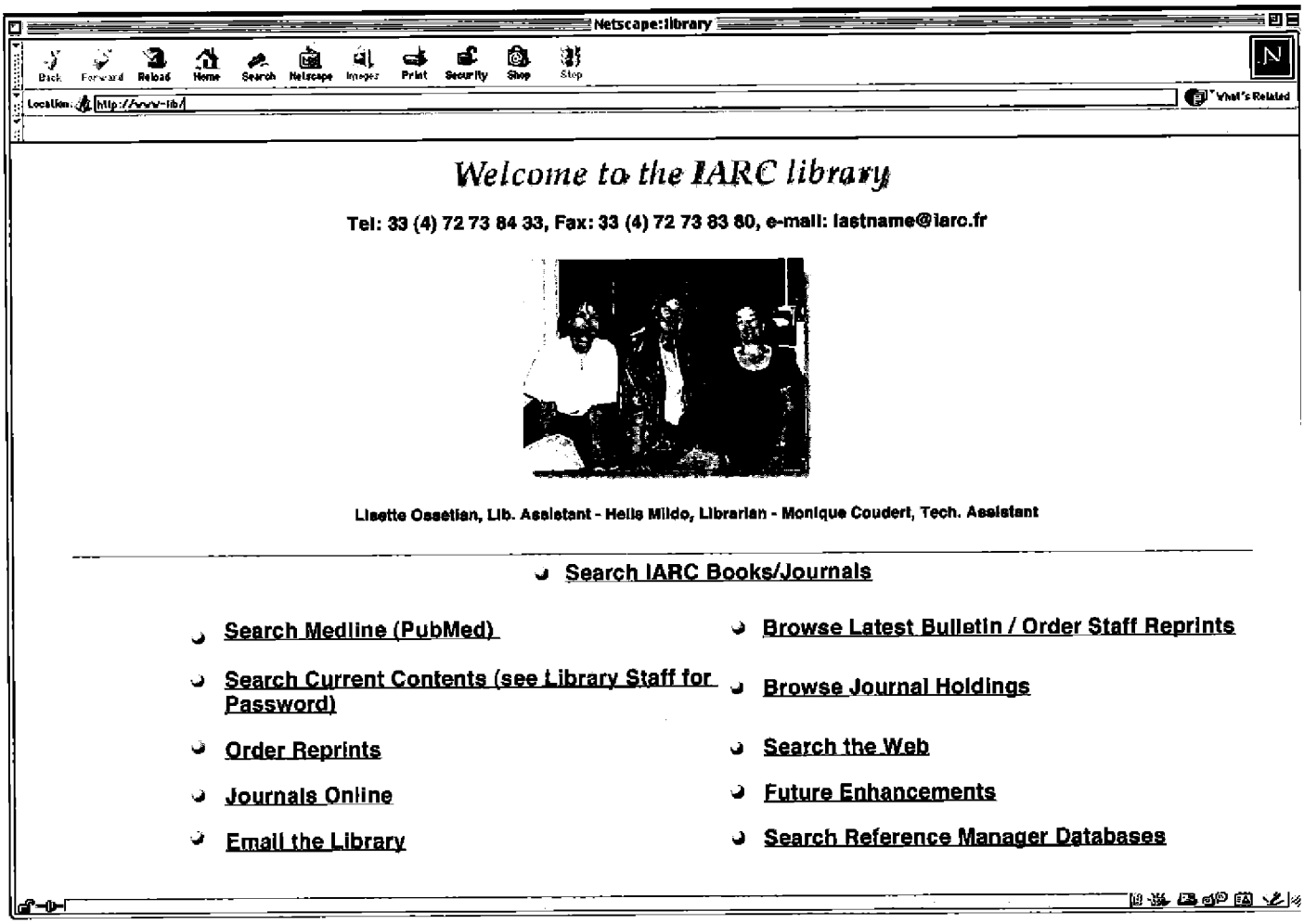
Library

Librarian
Ms H. Miido

Technical assistance
Ms M. Coudert
Ms L. Ossetian

The IARC library works closely with the library at WHO headquarters to identify resources and joint activities that can be used to satisfy the information needs of IARC scientists. Agreements signed between the United Nations Libraries Consortium and commercial entities apply also to IARC, such as the one providing access to one publisher's electronic journals for a fraction of the commercial cost. Technological advances which improve and enhance user access to library applications are identified and implemented with the help of the Computing Services Group.

On-line library services are accessed through the Library home page (see below). New features which have been added include accessing reprints of articles published by IARC scientists through the IARCPub database and searching WHO documents with tags which indicate those documents available in the IARC Library. Planned further enhancements include accessing biomedical information sources through a portal. Traditional library services continue to be offered through the Library home page, including the ability to search for books and journals using author/title/subject terms; to search Medline through the US National Library of Medicine web browser; to search Current Contents; to order reprints of articles not in the IARC library; to browse the latest Library Bulletin and order staff reprints; and to browse the journal holdings list.



IARC Library home page

Common Laboratory Services

Animal facility

Responsible scientist
Dr Z.-Q. Wang

Veterinary consultant
Dr L. Zenner

Technical assistance
Mr J. Cardia-Lima
Ms M.-P. Cros
Mr R. Dray
Ms D. Galendo
Mr J. Garcia
Mr D. Lyonnet
Mr E. Moudilou
Mr D. Petrilli
Ms C.T. Tchangwo
Mr F. Zeroual

The IARC animal facility provides technical support for a range of studies of tumorigenesis. The technical staff 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. All manipulations are carried out according to the specific IARC guidelines for manipulation of animals.

Genetically modified animals provide a unique system to study interactions of specific environmental factors and genetic information in mammals and have become a powerful tool for understanding mechanisms of cancer development. In addition, these mutant mice are indispensable models for studying the functions of newly identified genes that confer 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 IARC scientists.

Instrumentation and facilities in the animal house have recently been upgraded to comply with the European Union guidelines. Records are kept of all experimental studies performed in the animal house, especially in coordination with the histopathology laboratory, in accordance with good laboratory practice. The animals are used by all of the laboratory-based research units and programmes of IARC.

N. Lyandrat, Histopathology Laboratory

Histopathology laboratory

Responsible scientist
Dr H. Ohgaki

Technical assistance
Ms M. Laval
Ms N. Lyandrat

Trainees
Ms C. Carreira
Ms S. Roche

The histology laboratory processes all histological materials from experimental animals in the Agency, as well as human biopsy materials for genetic analyses sent from many collaborating universities and hospitals worldwide. The laboratory also carries out immunohistochemical analyses.

Glass-washing service

Responsible scientist
Dr H. Ohshima

Technical assistance
Mr F. Batomen
Ms G. Dubard
Ms M. Essertel
Ms N. Farina
Ms M. Maranhao
Ms G. Tchoua

Washing of glass laboratory equipment is centralized in order to ensure a reliable standard of cleanliness and to avoid duplication of effort.

Administration and Finance

Director
Ms V. Hay

Administrative assistants
Ms M.-H. Charrier
Ms V. Vocanson

Budget and finance

Budget and finance officer
Mr R. Thomas

Finance officers
Mr A. Mitra
Ms D. Pantua
Mr M. Samuel
Mr A. Tismo

Administrative assistants
Mr C. Augros
Ms W. Fevre-Hlaholuk

Ms D. Marcou
Ms R.A. Papworth

Assistant (accounting)
Ms M. Herin

Clerks
Ms F. Florentin
Mr D. Hornez
Ms D. Lombardo
Ms M. Ongaro
Mr. F. Rousset
Ms A. Seguret
Mr N. Srinivassane

Trainee
Mr P. Binet

R. Alloin, R. Thomas, V. Hay, G. Guillerminet

Timely financial information is provided to the scientific staff to enable them to submit realistic and accurate applications for funding; information is gathered on costs, trends are assessed and budgetary projections made. The programme budget for each biennium is prepared. The financial implementation of the programme budget is monitored and reported upon periodically. The Agency's resources are managed within acceptable risk parameters so as to maximize their potential. The advice of the auditors is sought when necessary and their recommendations are complied with. Travel arrangements are reviewed to get the best value for money, with periodic analyses made.

Human resources

Personnel officer
Ms R. Alloin
Ms A. Escoffier
Mr G. Mortier

Assistant (fellowships)
Ms E. El Akroud

Clerk
Ms I. Poncet

Social advisers
Mr H. Paraton
Ms M.A. Viot-Coster

The Personnel Office provides services in the field of human resources and staff development to meet the requirements of the Agency's programmes, to ensure the efficient recruitment of staff, administering of benefits and entitlements and related services. This involves identifying highly qualified candidates with appropriate skills and competences; post classification; selection and recruitment; periodic performance appraisals; contract administration through efficient, effective and fair application of the staff rules and personnel policies, processes and advice; handling of appeals; terminations and staff relations. The office also manages the administration of fellowships and short-term training for staff in house.

Administrative services

Administrative services officer
Mr G. Guillerminet

Administrative assistant
Ms A. Meneghel

Support staff
Mr M. Barbieux
Mr M. Bazin
Mr J.-P. Bonnefond
Mr J.-F. Durand-Gratian
Mr W. Goudard
Ms M. Greenland
Mr M. Javin
Ms R. Kibrisliyan
Ms F. Lelong
Ms M. Marsal
Mr C. Mestrallet
Ms L. Monnerat
Ms J. Popoff
Mr G. Tholly
Ms G. Walter

Trainees
Mr N. Andan
Mr E. Mitride

M. Javin, R. Kibrisliyan

Staff are provided with office accommodation, procurement, logistics and communications services of high quality. Postal, telephone and photocopying services are provided, where possible using carefully negotiated contracts and partnerships.

Registry services are provided to all the Agency's units including dispatch of outgoing mail, but efforts are being made to move from a physical routing of correspondence to electronic transmission, tracking and storage.

The Agency's buildings and installations are managed, maintained and kept in good repair. Essential services including electricity, water, air conditioning/heating and lifts are provided in the most cost-effective manner following negotiation with suppliers. All aspects of safety are kept permanently under review.

Meetings of the Governing Council and the Scientific Council, as well as conferences and meetings hosted by the Agency or occasionally other organizations are supported. A range of services is provided including electronic, audio and visual aids; précis writing; and simultaneous interpretation.

J.-P. Bonnefond

J.-F. Durand-Gratian

IARC Governing and Scientific Councils

IARC's work is overseen by two governing bodies, the Governing Council and the Scientific Council.

Governing Council
The Council consists of delegates from the 16 Participating States which direct and support the Agency. The Director-General of WHO is an *ex officio* voting member of the Governing Council. The Council oversees the scientific programme of the Agency and its execution. It elects the Director and determines the biennial budget. The Council meets once a year in Lyon, usually in the week before the World Health Assembly in Geneva. The Chairperson of the Governing Council prepares the meeting together with the secretariat and advises the Director throughout the year.

Scientific Council
The Scientific Council reviews the scientific activities of the Agency and advises the Director on research strategies, especially in setting priorities for future projects. The Scientific Council's reports to the Governing Council form the scientific basis for Governing Council policy, in particular when considering the budget. Members of the Scientific Council are elected by the Governing Council on the basis of their scientific expertise in areas relevant to the Agency's activities.

Budget
For the biennium 2000-2001, the IARC Governing Council voted a regular budget of US $36.3 million. Of this, 75% went directly to research programmes. In addition to the regular budget, the Agency receives extra-budgetary funds, mainly through research grants, and to a lesser extent through donations. In the 1998-99 biennium, extra-budgetary funds constituted approximately 25% of the Agency's overall budget. With the withdrawal of Argentina and Brazil with effect from 1 January 2001, the operating budget of the Agency was reduced to $34.6 million.

PARTICIPATING STATES AND REPRESENTATIVES AT THE FORTY-FIRST SESSION OF THE IARC GOVERNING COUNCIL

11–12 May 2000

Switzerland
Dr T. Zeltner (*Chairman*)
Office Fédéral de la Santé Publique, Bern

Dr R. Dürler
Office Fédéral de la Santé Publique, Bern

Argentina
No representative

Australia
Dr R.A. Smallwood
Department of Health and Aged Care, Canberra

Mr R. Eckhardt
Department of Health and Aged Care, Canberra

Belgium
Mrs Anne-Marie Sacré-Bastin
Ministère fédéral des Affaires Sociales, de la Santé Publique et de l'Environnement, Brussels

Brazil
Dr J. Kogut
Brazilian National Cancer Institute (INCA), Rio de Janeiro

Canada
Dr J. Larivière
Health Canada, Ottawa, Ontario

Denmark
Mr I.B. Knudsen
Danish Veterinary & Food Administration Søborg

Finland
Dr Pirjo Pietinen
National Public Health Institute, Helsinki

France
Dr W. Dab
Ministère de l'Emploi et de la Solidarité, Paris

Mr J.-C. Tallard-Fleury
Direction des Nations Unies et des Organisations internationales, Paris

Germany
Mr H. Voigtländer
Federal Ministry for Health, Bonn

Italy
Dr G. Benagiano
Istituto Superiore di Sanita, Rome

Japan
Dr N. Sakai
Ministry of Health and Welfare, Tokyo

Mr T. Yamamoto
Ministry of Health and Welfare, Tokyo

Netherlands
Dr J.-W. Hartgerink
Ministry of Health, Welfare and Sport, The Hague

Ms Monique Middelhoff
Ministry of Health, Welfare and Sport, The Hague

Norway
Dr Berit Morland
National Centre for Health Technology, Oslo

Dr L.E. Hanssen
Norwegian Board of Health, Oslo

Sweden
Dr O. Stendahl
Swedish Medical Research Council, Stockholm

United Kingdom of Great Britain and Northern Ireland
Dr Diana Dunstan
Medical Research Council, London

Dr D. Smith
Medical Research Council, London

United States of America
Dr G.J. Keusch
National Institutes of Health, Bethesda, MD

Ms Ann Blackwood
US Department of State, Washington, DC

Dr J. Harford
National Cancer Institute, Bethesda, MD

World Health Organization
Dr Gro Harlem Brundtland
Director-General

Dr A. Asamoa-Baah
Senior Policy Adviser to the Director-General

Dr A. Alwan
Director, Management of Noncommunicable Diseases

Dr C. Sepulveda
Coordinator, Programme on Cancer Control

Mr G. Burci
Senior Legal Officer

Observers
Dr Catherine Bonaïti-Pellié
Incoming Vice-Chairman, Scientific Council

Dr J. Hopper
Outgoing Chairman, Scientific Council

External Audit
Mr B. Matthee
Office of External Audit, World Health Organization

FORTY-SECOND SESSION OF THE IARC GOVERNING COUNCIL

10–11 May 2001

United Kingdom of Great Britain and Northern Ireland
Dr Diana Dunstan (Chairperson)
Medical Research Council, London

Dr D. Smith
Medical Research Council, London

Australia
Dr J. Mathews
National Centre for Disease Control, Canberra

Mr R. Eckhardt
Department of Health and Aged Care, Canberra

Mr T. Kingdon
Department of Health and Aged Care, Canberra

Belgium
Mrs Anne-Marie Sacré-Bastin
Ministère Fédéral des Affaires Sociales, de la Santé Publique et de l'Environnement, Brussels

Canada
Dr J. Larivière
Health Canada, Ottawa, Ontario

Denmark
Mr I.B. Knudsen
Danish Veterinary & Food Administration Søborg

Finland
Dr Pirjo Pietinen
National Public Health Institute, Helsinki

France
Mr. J.-C. Tallard-Fleury
Direction des Nations Unies et des Organisations Internationales, Paris

Dr Catherine Grillot-Courvalin
Ministère de l'Emploi et de la Solidarité, Paris

Germany
Mr H. Voigtländer
Federal Ministry of Health, Bonn

Italy
Dr G. Costanzo
Directorate-General for International Relations and Community Policies
Rome

Japan
Dr T. Shimoda
Ministry of Health, Labour and Welfare, Tokyo

Mr T. Fujimori
Ministry of Health, Labour and Welfare, Tokyo

Dr M. Sakoi
Ministry of Health, Labour and Welfare, Tokyo

Netherlands
Dr D. Kromhout
National Institute for Public Health and the Environment, Bilthoven

Ms Monique Middelhoff
Ministry of Health, Welfare and Sport, The Hague

Norway
Dr L.E. Hanssen
Norwegian Board of Health, Oslo

Dr Berit Mørland
National Centre for Health Technology, Blindern, Oslo

Sweden
Dr Harriet Wallberg-Henriksson
Swedish Research Council – Medicine, Stockholm

Switzerland
Dr T. Zeltner
Office Fédéral de la Santé Publique, Bern

Dr R. Dürler
Office Fédéral de la Santé Publique, Bern

United States of America
Dr J. Harford
National Cancer Institute, Bethesda, MD

Ms Ann Blackwood
US Department of State, Washington, DC

Dr Sharon Hrynkow
National Institutes of Health, Bethesda, MD

World Health Organization
Dr Gro Harlem Brundtland
Director-General

Dr A. Alwan
Director, Management of Non-communicable Diseases

Mr G. Burci
Senior Legal Officer

Mrs F. Mourain-Schut
Office of Legal Counsel

Dr C. Sepulveda
Coordinator, Programme on Cancer Control

Observers
Dr M. Aguet
Incoming Chairman, Scientific Council

Dr Catherine Bonaïti-Pellié
Outgoing Chairman, Scientific Council

Dr L. Denis
UICC Representative

External Audits
Mr G. Randall
Executive Manager, Office of the Auditor-General, Pretoria, South Africa

Ms J. Englund
Office of the External Auditor, World Health Organization

MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS THIRTY-SIXTH SESSION

7–9 February 2000

Dr J. Hopper (*Chairman*)
Australian NHMRC Twin Registry
University of Melbourne
Carlton, VIC, Australia

Dr N.E. Day (*Vice-Chairman*)
Strangeways Research Laboratory
University of Cambridge, United Kingdom

Dr P. Band (*Rapporteur*)
Environmental Health Directorate
Health Canada
Longueuil, Québec, Canada

Dr L. Aaltonen
University of Helsinki, Finland

Dr M. Aguet
Institut Suisse de Recherches Expérimentales sur le Cancer
Epalinges-sur-Lausanne, Switzerland

Dr F. Berrino
National Institute of Cancer
Milan, Italy

Dr Catherine Bonaïti-Pellié
Institut Gustave Roussy
Villejuif, France

Dr D. Bootsma
Erasmus University Rotterdam
Rotterdam, The Netherlands

Dr Anne-Lise Børresen-Dale
Institute for Cancer Research
Norwegian Radium Hospital
Oslo, Norway

Dr J.F. Fraumeni
National Cancer Institute
Bethesda, MD, USA

Dr K. Hemminki
Center for Nutrition and Toxicology
Karolinska Institute
Huddinge, Sweden

Dr S. Hirohashi
National Cancer Center Research Institute
Tokyo, Japan

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Office of Technical Specialized Agencies
US Department of State
Washington, DC, USA

World Health Organization
Dr Jie Chen
Executive Director, Non-Communicable Diseases

Dr R. Bengoa
Director, Non-communicable Disease Management

UICC
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Institut Suisse de Recherches Expérimentales sur le Cancer
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MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS THIRTY-SEVENTH SESSION

5–7 February 2001

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Villejuif, France

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University of Helsinki, Finland

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Epalinges-sur-Lausanne, Switzerland

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Health Canada, Québec, Canada

Dr F. Berrino
National Institute of Cancer
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Dr D. Bootsma
Erasmus University Rotterdam, The Netherlands

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Norwegian Radium Hospital
Oslo, Norway

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University of Wales College of Medicine
Cardiff, United Kingdom

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Cancer Control Research Institute
Carlton South, Vic., Australia

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Karolinska Institute
Huddinge, Sweden

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Dr P. Herrlich
University of Karlsruhe, Germany

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Medical Research Council
London, United Kingdom

Dr J. Larivière (Outgoing Vice-Chairman)
Health and Welfare Canada
Ottawa, Ontario, Canada

World Health Organization
Dr A. Alwan
Director, Management of Non-communicable Diseases

Dr C. Sepulveda
Coordinator, Programme on Cancer Control

UICC
Dr H. zur Hausen
German Cancer Research Centre
Heidelberg, Germany

Meetings and workshops organized by IARC

Ambillikai, India
8–13 January 2001
Course on colposcopy and treament of cervical precancers using LEEP

25–29 July 2001
Cervical cancer screening (VIA and VILI) and treatment course

Bamako, Mali
6–10 March 2000
Course on cancer registration techniques

4–8 September 2001
Cervical cancer screening course (VIA)

Barcelona, Spain
9–10 March 2000
EPIC working group on *H. pylori*, dietary and genetic factors and gastric cancer risk

19 September 2000
Liaison committee of study of cancer risk among asphalt workers

19–20 September 2000
Study of cancer risk among European asphalt workers

17–18 November 2000
Epilymph study group on non-Hodgkin lymphoma in Europe

Barshi, India
1–5 January 2001
Course on colposcopy and management of cervical precancers

Brazzaville, Congo
31 July–4 August 2001
Cervical cancer screening course (VIA)

Budapest, Hungary
6–17 March 2000
International course on cancer epidemiology with emphasis on environmental health

Calcutta, India
16–20 January 2001
Course on early detection of cervical cancer with colposcopy and treatment of cervical precancers

Conakry, Guinea
12–16 June 2000
Course on cervical cancer screening by visual inspection with acetic acid (VIA) and with Lugol's iodine (VILI)

16–19 September 2001
Cours de formation des formateurs en matière de traitement par résection à l'anse diathermique et cryothérapie

Copenhagen, Denmark
23 August 2001
Study of cancer risk among European asphalt workers

10–11 September 2001
ENCR course on coding ICD-O-3 for trainers of cancer registry staff

Goiânia, Brazil
28–29 August 2000
Study of larynx and oral cavity cancer in South America

Havana, Cuba
3–5 October 2001
Annual scientific meeting, International Association of Cancer Registries

Heidelberg, Germany
27–29 February 2000
Use of biomarkers in chemoprevention of cancer

24–25 May 2000
EPIC working group on lung cancer

Ibadan, Nigeria
12–16 February 2001
Course on cancer registration techniques

Jaipur, India
18–27 March 2001
Course on VIA, VILI, colposcopy and treatment of cervical cancer screening

Khon Kaen, Thailand
8–10 November 2000
Annual scientific meeting, International Association of Cancer Registries

Lima, Peru
16–26 October 2000
Course for cancer registrars (in Spanish)

London, United Kingdom
14–15 June 2001
Study of occupation, environment and cancer in central and eastern Europe

Lucknow, India
30–31 October 2000
Study of lung and laryngeal cancer in Asia

Lyon
10–11 January 2000
ENCR Steering Committee

17–18 January 2000
Epilymph study group on non-Hodgkin lymphoma in Europe

20–21 January 2000
Dosimetry for the case–control study of thyroid cancer among young people in Belarus and the Russian Federation

27–28 January 2000
EPIC-HEART project coordination

9–11 February 2000
Editorial meeting, third edition of the International Classification of Diseases for Oncology

15–18 February 2000
Exposure assessment for international case–control study of adult brain, head and neck tumours

15–22 February 2000
Monographs working group on some industrial chemicals (Volume 77)

24–25 February 2000
International BRCA 1/2 carrier cohort study

6 March 2000
GEN-AIR project

15–17 March 2000
ENCR EUROCIM course

21–22 March 2000
ENCR working group on auditing of cancer registries

23–24 March 2000
Dosimetry for the case–control study of liquidators in Belarus and the Russian Federation

27–28 March 2000
Dosimetry for case–control study of thyroid cancer among young people in Belarus and the Russian Federation

27–29 March 2000
EPIC steering committee

10–11 April 2000
Epidemiology subcommittee for international case–control study of adult brain, head and neck tumours

11–14 April 2000
Exposure assessment in study of cancer risk among workers in the pulp and paper industry

11–18 April 2000
Handbooks of Cancer Prevention working group on sunscreens (Volume 5)

27–28 April 2000
Fellowships Selection Committee

8–9 May 2000
Scientific Committee, Automated Childhood Cancer Registration system

22–23 May 2000
European nutrient database for nutritional epidemiology

23 May 2000
French contribution to Epilymph study

26–27 May 2000
Iodine deficiency in case–control study of thyroid cancer among young people in Belarus and the Russian Federation

29–30 May 2000
EPIC working group on statistical methods for multi-centre cohort studies

5–7 June 2000
Training of interviewer trainers for the international case–control study of adult brain, head and neck tumours

6–9 June 2000
Editorial board, *Cancer in Africa*

13 June 2000
Liaison committee of the MMVF lung cancer case–control study

13–14 June 2000
ENCR Steering Committee

14–21 June 2000
Monographs working group on ionizing radiation, part 2: Some internally deposited radionuclides (Volume 78)

16 June 2000
Automated cancer registration

22–23 June 2000
Case–control study of thyroid cancer among young people in Belarus and the Russian Federation

21–22 August 2000
EPIC working group on colorectal cancer

21 August–8 September 2000
Cours sur l'enregistrement du cancer

1–2 September 2000
Study group on occupation, environment and cancer in central and eastern Europe

4–5 September 2000
Dosimetry for case–control study of thyroid cancer among young people in Belarus and the Russian Federation

14 September 2000
Entretiens de Montchat

14–15 September 2000
ENCR working group on methods of detection

18 September–6 October 2000
Cours de formation des formateurs en matière de dépistage du cancer du col utérin

20–22 September 2000
Editorial board, *Cancer Incidence in Five Continents*, Volume VIII

28–29 September 2000
Iodine deficiency in case–control study of thyroid cancer among young people in Belarus and Russia

29 September 2000
Follow-up of IARC multicentre study of laryngeal cancer in southern Europe

4–6 October 2000
EPIC working group on dietary patterns

5–10 October 2000
Dosimetry for case–control study of thyroid cancer among young people in Belarus and the Russian Federation

9 October 2000
GEN-AIR project

10–17 October 2000
Monographs working group on some thyrotropic chemicals (Volume 79)

15–18 October 2000
Dosimetry for case–control study of liquidators in Belarus and the Russian Federation

13–14 November 2000
Genetic animal model as a tool for genetics and cancer research

16–17 November 2000
International BRCA1/2 carrier cohort study

18 November 2000
Groupe de Coordination pour l'Epidémiologie et l'Enregistrement du Cancer dans les Pays de Langue Latine

4–9 December 2000
Third IARC/ISI (Institute for Scientific Interchange) molecular epidemiology course

5–8 December 2000
ENCR course on survival analysis methods for cancer registries

11–12 December 2000
Exposure assessment for the INTERPHONE study

13–14 December 2000
Epidemiology subcommittee for the INTERPHONE study

12 January 2001
Cancer risk among meatworkers

15–16 January 2001
ENCR Steering Committee

15–19 January 2001
Fifth meeting of coders in study of occupation, environment and lung cancer in central and eastern Europe

22–24 January 2001
Editorial board, *Cancer in Africa*

22–24 January 2001
EPIC steering committee

25–26 January 2001
Dosimetry for case–control study of thyroid cancer in young people in Belarus and the Russian Federation

8 February 2001
Molecular epidemiology of early leukaemia

8–10 February 2001
European nutrient database for nutritional epidemiology

8–9 February 2001
Dosimetry for international collaborative study of cancer risk among radiation workers in the nuclear industry

13–20 February 2001
Handbooks of Cancer Prevention working group on weight control and physical activity (Volume 6)

22–23 February 2001
Feasibility of studies on depleted uranium and other substances

27 February 2001
GEN-AIR project

9 March 2001
Key issues in the design of HPV vaccine trials in Asia

22 March 2001
Colloque Franco-Italien: la recherche sur le genome humain en France et en Italie

2–5 April 2001
Editorial board, *Cancer Incidence in Five Continents*, Vol.VIII

5–6 April 2001
Fellowships Selection Committee

17–18 April 2001
International BRCA 1/2 carrier cohort study: Statistical analysis

17–20 April 2001
Chromosomal aberrations and risk of cancer in Central Europe

20–21 April 2001
Cytogenetic biomarkers and human cancer risk

7–25 May 2001
Summer course on cancer registration and applications in epidemiology

14 May 2001
Statistical issues in the EPIC study

14–16 May 2001
ACCIS 2nd Scientific Council meeting

14–18 May 2001
Epilymph-Europe coders workshop

15 May 2001
Key issues in the design of HPV vaccine trials in India

15–16 May 2001
EPIC steering committee

17 May 2001
EPIC working group on phytoestrogens

7–9 June 2001
INTERPHONE meetings on exposure assessment; fieldwork co-ordination and full study group

18 June 2001
Geochemistry for iodine deficiency thyroid case–control study in young people in Belarus and the Russian Federation

18 June 2001
Liaison committee of study of cancer risk among asphalt workers

18–26 June 2001
Monographs working group on static and extremely low frequency electromagnetic fields (Volume 80)

19–21 June 2001
On-going and future studies of environmental factors and cancer in India, coordinated by IARC and NCI

21 June 2001
EC Advisory Committee on Cancer Prevention

21–24 June 2001
European Conference on Nutrition and Cancer

27 June 2001
Diagnostic tests for *Helicobacter pylori* and human papillomavirus

28–29 June 2001
Epidemiology subcommittee, international collaborative study of cancer risk among radiation workers in the nuclear industry

29 June 2001
ENCR working group on the automated cancer registration project

5–6 July 2001
Dosimetry for case–control study of liquidators in Belarus and the Russian Federation

5–7 September 2001
Editorial board, *Cancer Incidence in Five Continents*, Vol.VIII

10–11 September 2001
ENCR Steering Committee

13–14 September 2001
Study group on larynx and oral cavity cancer in South America

24–25 September 2001
International BRCA 1/2 carrier cohort study

8–9 October 2001
Dosimetry for case–control study of thyroid cancer in young people in Belarus and the Russian Federation

9–16 October 2001
Monographs working group on man-made vitreous fibres (Volume 81)

12 October 2001
TDMA/Epidemiology liaison committee for mortality study in European titanium dioxide manufacturers

5–6 November 2001
Dosimetry for case–control study of liquidators in Belarus and the Russian Federation

8–9 November 2001
Epidemiology subcommittee for the INTERPHONE study

9 November 2001
Cancer metastasis models

14–17 November 2001
Mechanistic considerations in the molecular epidemiology of cancer

22–23 November 2001
Analysis group of the mortality study in European titanium dioxide manufacturers

26–27 November 2001
Exposure assessment subcommittee for the INTERPHONE study

28–29 November
Refresher workshop for interviewer trainers in the INTERPHONE study

10–11 December 2001
International BRCA1/2 carrier cohort study—statistical analysis

10–12 December 2001
EPIC steering committee

12–13 December 2001
EPIC working group on prostate cancer

Nairobi, Kenya
23–27 April 2001
Course on cancer registration techniques

Obninsk, Russian Federation
17–18 December 2001
Pathology review panel for study of Chernobyl liquidators

Oslo, Norway
23–24 May 2000
MMVF lung cancer case–control study group

Paris, France
25 September 2001
IARC/UICC satellite joint workshop on information for cancer control planning and evaluation

Prague, Czech Republic
7–9 June 2000
Fourth meeting of coders in study of occupation, environment and lung cancer in central and eastern Europe

Rochegude, France
12 June 2001
Tobacco and cancer

Sestri Levante, Italy
1–5 November 2001
Gaslini–IARC course in cancer genetics

27 September–1 October 2000
Gaslini–IARC course in cancer genetics

Sofia, Bulgaria
19–23 January 2000
ENCR course on population-based cancer registration

Vancouver, Canada
14–18 December 2001
Refresher workshop for interviewer trainers in the INTERPHONE study

Veldhoven, Netherlands
14–15 December 2001
ENCR workshop for cancer registries on evaluation of clinical care

Venice, Italy
3–5 February 2000
Study group on occupation, environment and cancer in central and eastern Europe

27 October 2000
ENCR workshop on automated cancer registration

Vientiane, Laos
15–21 December 2000
Course on cervical cancer screening by visual inspection with acetic acid (VIA) and with Iugol's iodine (VILI)

Warsaw, Poland
19–23 September 2000
ENCR course on population-based cancer registration

Washington, United States
4 November 2001
Epilymph study group on non-Hodgkin lymphoma in Europe

Seminars presented at IARC

Dr K. Baverstock, Finland
Radiation induced genomic instability: is it relevant to cancer?
Dr J. Beckmann, Israel
Calpainopathy: from the disease to the gene to its function...
Dr X. Bosch, Spain
Infections, infectious agents, and human cancer: strategies for intervention
Dr H. Brenner, Germany
Use of period analysis for up-to-date monitoring of long term cancer survival rates: background and empirical evaluation
Dr A. Carnero, United Kingdom
Replicative senescence and mechanisms of cellular immortalization
Dr C. Caron de Fromentel, France
The p53 family and the response of hepatocytes to genotoxic stress
Dr Marina Cavazzana-Calvo, France
Gene therapy for X-linked immune deficiency
Dr W.-H. Chow, United States
The epidemiology of renal cell carcinoma
Mr M. Col, United Kingdom
Information and use of radioactive substances in research laboratories
Dr M. Corbex, France
Candidate gene approach of complex disorders: strategy and method to study frequent polymorphisms
Dr P. Coursaget, France
Detection of HPV antibodies in epidemiological studies
Dr C. Deng, United States
BRCA1 and tumorigenesis
Dr S. Diehl, United States
Gene–environment interactions and oral cancer susceptibility: a tale of two countries
Dr V. Diehl, Germany
New developments in the biology and treatment of Hodgkin's disease
Dr J. Dillner, Sweden
Infections, infectious agents, and human cancer: strategies for intervention
Evaluation of the role of infections in cancer using biological specimen banks
Dr R. Duda, United States
Female cancers: causes and opportunities for prevention
Dr R. Elespuru, United States
Development of an in vitro system for studying DNA damage and mutagenesis in the p53 gene
Dr H. Esumi, Japan
New aspects on implications of inflammation and infection in carcinogenesis
Dr S. Emami, France
Fundamental and clinical oncology: recent progress for prevention, diagnostic, prognosis and therapy
Ms L. Ferguson, New Zealand
Is dietary fibre an important chemopreventive agent?
Dr T. Fletcher, United Kingdom
Childhood leukaemia and benzene emissions: a geographical study in south-east England
Dr S. Franceschi, Italy
Infections, infectious agents, and human cancer: strategies for intervention
Dr S.M. Garland, Switzerland
HPV in Australia: a perspective from down under
Dr S.A. Glantz, United States
Secondhand smoke: it's more than cancer
Rapidly reducing deaths from tobacco: Lessons from California
Dr E. Goode, United Kingdom
Prostate cancer linkage analysis using clinical family stratifications
Dr A. de Grandi, Germany
Functional genomics in mice by a large-scale gene trap approach in embryonic stem cells
Dr C. Harris, United States
Molecular carcinogenesis and epidemiology of human cancer
Dr K. Hayashi, Japan
Democratic technology on SNP characterization
Dr M. Hegi, Switzerland
Gene expression profiling divides human gliomas into distinct subtypes
Dr K. Hemminki, Sweden
Genetic epidemiology of multistage carcinogenesis
Familial squamous cell carcinomas: immune deficiency?
Dr P.L. Herrera, Switzerland
Defining the cell lineages of the islets of Langerhans in transgenic mice
Dr R. Herrero, Costa Rica
Rationale and design of the Costa Rica HPV vaccine trial
Dr E.A. Holly, United States
Case–control study of non-Hodgkin's lymphoma in San Francisco
Dr H. Ischiropoulos, United States
Biological significance and clinical implications of nitric oxide-mediated protein modifications
Dr J.A.Z. Jankowski, United Kingdom
Tissue remodelling in a chronic inflammatory environment in Barrett's metaplasia
Drs V. Kipnis, D. Midthune and A. Shubar, United States
The use of biomarkers (doubly labelled water and urinary nitrogen) for validating and calibrating dietary intake measurements
Dr M. Lang, Sweden
Stabilization of labile mRNA.s during disturbed transcription
Multifunctional gene regulators: hnRNP:s. How is their activity regulated?
Dr C. La Vecchia, Italy
Epidemiology of bladder cancer with focus on hair dyes
Dr E. Lazaridis, United States
Molecular fingerprint of STAT3 regulated genes for early detection of human cancer: the future of microarray biometrics
Dr J. Lence, Cuba
Evidence for the effectiveness of screening in the control of cervical cancer
Dr H. Maeda, Japan
Cancer, NO and vascular permeability and beyond tumor growth
Dr C. Mahé, Uganda
Evidence for the effectiveness of screening in the control of cervical cancer
Dr R. Malekzadeh, Iran
Upper gastrointestinal malignancy in north Iran: on-going and future research plan
Dr G. Maskarinec, United States
Soy, isoflavones, estrogens, and breast cancer risk
Dr A. Merdes, United Kingdom
Microtubule organizing centres in interphase and mitosis: potential roles of PCM-1 and NuMA
Dr F. Meyskens, Jr, United States
Chemoprevention of human cancer: fact, fantasy and future

Dr S.S. Mirvish, United States
Recent studies on N-nitroso compounds in foods and biological materials and on an alkylating agent produced from the reaction of glycine with nitrite

Dr G. Morel, France
L'hormone de croissance (GH) : synthèse extra-hypophysaire et mécanisme d'action

Dr C. Morrison, United Kingdom
Genetic analysis of the role of ataxia telangiectasia mutated in DNA double strand break repair

Dr A. Mylvaganam, Australia
Edutainment: conveying cancer prevention messages through education and entertainment

Dr J. Nair, Germany
Omega-6 polyunsaturated fatty acids and lipid peroxidation induced DNA damage as risk factors in colon and breast cancer

Dr S. Nandi, United States
Can estrogen prevent breast cancer?

Dr D. Nelson, United States
The use of chromosomal aberrations for monitoring Chernobyl liquidators

Dr S. Neuhausen, United States
Genetic and lifestyle factors that modify risk for BRCA1 and BRCA2 mutation carriers

Dr Y. Nikiforov, United States
Mechanisms of RET/PTC rearrangements in radiation-induced thyroid cancer

Dr S. Nishimura, Japan
8-Hydroxyguanine; DNA adduct formed by oxygen radicals, its repair and implication in mutagenesis and carcinogenesis

Dr H. Nishino, Japan
Cancer prevention by food factors

Dr T.R. O'Connor, United States
DNA repair and human cells

Ms E. Ong, United States
Tobacco industry efforts subverting the International Agency for Research on Cancer's secondhand smoke study

Dr R. Palmer Beasley, United States
Towards the eradication of HBV

Dr E. Passegue, Austria
Tumor suppressive function of the transcription factor JunB

Dr J. Peto, United Kingdom
Natural history of cervical HPV infection and neoplasia

Dr R. Peto, United Kingdom
Halving premature death
Smoking, smoking cessation and lung cancer in the United Kingdom since 1950

Dr N. Probst, Switzerland
Aromatase and breast cancer susceptibility

Dr H. Raslova, France
Infectious potential of murine gammaherpesvirus (MHV-72) in nude mice and the enzymatic activity of MHV thymidine kinase

Dr J.-L. Ravanat, France
Measuring oxidized bases in cellular DNA: a challenging analytical problem

Dr A. Sala, Italy
B-myb, transcription control and cancer: PARPable advances

Dr G.I. Sanchez, Colombia
Considerations for the development of prophylactic DNA vaccines against HPV-16

Dr L. Simonato, Italy
Uncertainties in evaluating epidemiological evidence from large data-sets on cancer risk
Automated Cancer Registration Project

Dr P. Snijders, Netherlands
Concept of HPV-mediated carcinogenesis of the uterine cervix

Dr K. Steindorf, Germany
Physical activity, diet and colon cancer – results from a case-control study in Cracow, Poland

Dr K. Straif, Germany
Cancer risks among rubber workers

Dr K. Strong, Switzerland
Evaluation of cancer screening programs

Dr J. Suso Platero, United States
What makes a centromere?

Dr K. Tajima, Japan
Ethnoepidemiology of HTLV-1 and its related diseases: with special reference to the paleo-mongoloids dispersal from Asia to America

Dr G. Tallini, United States
Chromosomes, morphology and dysregulation of architectural transcription factors in mesenchymal neoplasms

Dr Y. Taya, Japan
Regulation of the function of p53 and RB proteins by phosphorylation

Dr M. Tommasino, Germany
Papillomaviruses as human carcinogens: a lesson learned from cervical cancer

Dr S. Troyanovsky, United States
Molecular mechanisms of cadherin-based adhesion

Dr H. Tsuda, Japan
Prevention of colon carcinogenesis by bovine lactoferrin in the rat

Dr E. Van Dyck, United Kingdom
Human Rad52 protein and the recombinational repair of double-strand breaks in DNA

Dr M. Vrijheid, United Kingdom
Health impacts of hazardous waste landfill sites

Dr E. Weiderpass, Sweden
Female cancers: causes and opportunities for prevention

Dr P. Wild, France
Planning the second phase of two-phase case–control studies

Dr J.S. Witt, United States
Prostate cancer genetic epidemiology studies (CaP genes): linkage, association and characterization

Dr L. Yang, China
Evidence for the effectiveness of screening in the control of cervical cancer

Dr D. Zagzag, United States,
Molecular mechanisms implicated in brain tumor angiogenesis

Dr D.A. Zighed, France
Knowledge discovery and data mining by induction graph: medical applications of the SIPINA approach

Publications by IARC staff

1. Agudo A, Ahrens W, Benhamou E, Benhamou S, Boffetta P, Darby SC, Forastiere F, Fortes C, Gaborieau V, Gonzalez CA, Jöckel K-H, Kreuzer M, Merletti F, Pohlabeln H, Richiardi L, Whitley E, Wichmann H-E, Zambon P, Simonato L (2000) Lung cancer and cigarette smoking in women: a multicencer case-control study in Europe. *Int. J. Cancer*, **88**, 820–827

2. Ahn B, Ohshima H (2001) Suppression of intestinal polyposis $Apc^{Min/+}$ mice by inhibiting nitric oxide production. *Cancer Res.*, **61**, 8357–8360

3. Angèle S, Hall J (2000) The ATM gene and breast cancer: is it really a risk factor? *Mutat. Res.*, **462**, 167–178

4. Angèle S, Tanière P, Hall J (2001) Que savons-nous de l'expression de la protéine ATM dans le tissu mammaire? *Bull. Cancer*, **88**, 671–675

5. Angèle S, Treilleux I, Tanière P, Martel-Planche G, Vuillaume M, Bailly C, Brémond A, Montesano R, Hall J (2000) Abnormal expression of the ATM and TP53 genes in sporadic breast carcinomas. *Clin. Cancer Res.*, **6**, 3536–3544

6. Anttila S, Lei XD, Elovaara E, Karjalainen A, Sun W, Vainio H, Hankinson O (2000) An uncommon phenotype of poor inducibility of CYP1A1 in human lung is not ascribable to polymorphisms in the AHR, ARNT, or CYP1A1 genes. *Pharmacogenetics*, **10**, 741–751

7. Apostoli P, Boffetta P (2000) Why a conference on lead toxicity? Introductory remarks to the Proceedings of the International Conference on Lead Exposure, Reproductive Toxicity, and Carcinogenicity, Gargnano, Italy, 7–9 June 1999. *Am. J. Ind. Med.*, **38**, 229–230

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11. Bah E, Parkin DM, Hall AJ, Jack AD, Whittle H (2001) Cancer in The Gambia: 1988–97. *Br. J. Cancer*, **84**, 1207–1214

12. Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, Ravichandran K, Ramdas K, Sankaranarayanan R, Muñoz N, Franceschi S (2002) Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. *Int. J. Cancer* (in press)

13. Balbi JC, Larrinaga MT, De Stefani E, Mendilaharsu M, Ronco AL, Boffetta P, Brennan P (2001) Foods and risk of bladder cancer: a case-control study in Uruguay. *Eur. J. Cancer Prev.*, **10**, 453–458

14. Banda LT, Parkin DM, Dzamalala CP, Liomba NG (2001) Cancer incidence in Blantyre, Malawi, 1994–1998. *Trop. Med. Int. Health*, **6**, 296–304

15. Barbin A (2000) Etheno-adduct forming chemicals: from mutagenicity testing to tumor mutation spectra. *Mutat. Res.*, **462**, 55–69

16. Baron JA, Farahmand BY, Weiderpass E, Michaelsson K, Alberts A, Persson I, Ljunghall S (2001) Cigarette smoking, alcohol consumption, and risk of hip fracture in women. *Arch. Intern. Med.*, **161**, 983–988

17. Baron JA, Weiderpass E, Newcomb PA, Stampfer M, Titus-Ernstoff L, Egan K, Greenberg RE (2001) Metabolic diseases and breast cancer risk. *Cancer Causes Control* (in press)

18. Bay JO, Uhrhammer N, Pernin D, Presneau N, Tchirkov A, Vuillaume M, Laplace V, Grancho M, Verrelle P, Hall J, Bignon YJ (2000) High incidence of cancer in a family segregating a mutation of the ATM gene: possible role of ATM heterozygosity in cancer. *Hum. Mutat.*, **14**, 485–492

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