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WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

BIENNIAL REPORT

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International Agency for Research on Cancer

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The United Kingdom of Great Britain and Northern Ireland

The United States of America

Introduction

This biennial report covers the period from January 2002 to December 2003 and provides detailed information on current and newly initiated projects. It reflects the wide range of IARC scientific activities, ranging from basic molecular biology and genetics to major studies on cancer prevention.

IARC scientists have an enviable record of publications in major scientific and medical journals, with 570 articles published or accepted for publication during the biennium under review, mostly in peer-reviewed journals. In addition, many chapters were included in books and IARC staff were editors of 18 books.

Cancer registration

IARC continues to provide extensive support for cancer registration activities by giving practical and financial help to countries lacking the necessary indigenous resources, by promoting the optimization and standardization of registration procedures and by offering courses for training of personnel. The IARC-generated CanReg software for computerized registration is now installed in over 120 registries throughout the world, with versions in languages such as Arabic, Chinese and Thai.

Cancer occurrence

The highlight of the descriptive epidemiology programme is the quinquennial publication of *Cancer Incidence in Five Continents*, of which the eighth volume appeared early in 2003. Some registries now have data series extending over 40 years. The sets of data from these volumes being assembled as an electronic publication will provide an incomparable resource for monitoring trends and progress in cancer control at the national and international levels.

Another unique recent publication from this programme is *Cancer in Africa*, which brings together information from all reported studies of cancer occurrence and etiology from the continent.

IARC Monographs

The IARC Monographs programme has revisited a number of agents for which there is new evidence. The reconsideration of tobacco smoking was a major undertaking in view of the volume of published literature, but confirmed the carcinogenicity of both passive and active smoking, extending the list of sites at which tobacco causes cancer to include nasal cavities and sinuses, oesophagus (adenocarcinoma), stomach, liver, kidney (renal-cell), cervix and myeloid leukaemia. Re-evaluations of agents have usually strengthened the evidence of their carcinogenicity to humans. For some exposures, lack of epidemiological evidence and/or the assumption that tumours in experimental animals were caused through mechanisms not operative in humans, have led to a downgrading to a lower hazard level. This has been criticized by activist groups, but the Agency is confident that these evaluations will stand the test of time.

Diet and nutrition

Uncertainties about the role of dietary factors in carcinogenesis remain considerable, but the first data on some 20 000 cancers among over 500 000 subjects in the EPIC cohorts, across 10 European countries, have mainly provided support for existing hypotheses, with regard to, for example, protective effects of higher consumption of fruit, vegetables and fibre against colorectal cancer and of fruit against lung and stomach cancer. In view of the increasing evidence of the importance of hormonal factors in the dysregulation of cellular development that leads to cancer, a new research group has been established, under the leadership of Dr Rudolf Kaaks, that is conducting mainly epidemiological studies of these effects. The main foci of these studies are insulin and related molecules and the steroid sex hormones, in relation to cancers of, for example, the breast, endometrium, ovary and prostate, for which known environmental carcinogens do not seem to be major etiological factors. During the biennium, the capacity for high-throughput genetic analyses has been greatly expanded. For several major cancer types, DNA polymorphisms of the genes involved in hormonal pathways are being explored.

Infectious agents

Viral agents are now believed to participate in the etiology of many cancers, and many epidemiological studies are in progress to refine our understanding of these. To enhance the in-house capacity for work with these agents, a new unit has been created, headed by Dr Massimo Tommasino, and a new high-containment P3 laboratory has been installed.

Two infectious agents now clearly established as causes of cancer are human papillomavirus as an essential factor in cervical cancer, and the bacterium *Helicobacter pylori*, which is involved in stomach carcinogenesis. Infections with both agents are much more common in human populations than the corresponding cancers, so detailed work is under way to define what co-factors (environmental, metabolic or genetic) lead certain infected tissues to progress to a malignant state. It appears that certain forms of some HPV proteins may be associated with persistence of the viral infection, with consequently increased risk of cancer. Inflammation and oxidative stress are also involved in the effects of *H. pylori* in relation to stomach cancer, and the mechanisms of the interactions between these effects are being analysed in detail.

Lung cancer

Although tobacco smokers run a high risk of cancer, as well as of many other diseases, many smokers somehow escape the harmful effects of their habit. This could be due to compensatory beneficial lifestyle aspects, such as high consumption of protective fruit and vegetables, or to genetic variations in the enzymes involved in the

activation and detoxification of the carcinogens known to be present in tobacco smoke. Epidemiological studies are exploring these issues, including detailed genetic analyses using newly developed microarray techniques to evaluate the roles of many different polymorphisms.

Breast cancer

Breast cancer has a clearly genetic component in its etiology. The two major genes identified to date (*BRCA1* and *BRCA2*) account a significant part of the heritable fraction of the disease. Work is in progress to assess the role of other genes such as *ATM* and others involved in the repair of DNA damage, as well as to identify hitherto unknown genes. In parallel, the significance of specific polymorphisms or mutations in the known breast cancer genes is being examined using new analytical and statistical techniques, to assess which variants are particularly deleterious. With the spread of genetic analysis in clinical evaluation, this work is becoming of direct relevance to patient care and counselling.

Carcinogenesis

A population-based study on more than 900 glioma cases revealed excellent survival of patients with pilocytic astrocytoma, but also very poor prognosis associated with glioblastoma: only about 1% were still alive three years after diagnosis. The only significant predictors of particularly poor prognosis were old age and loss of heterozygosity on the long arm of chromosome 10, whereas other genetic alterations had no influence on survival.

Genetic analysis of oesophageal carcinomas from Iran, a country with a very high burden of this disease, revealed a high prevalence of G:C to A:T transitions at CpG dinucleotides, strongly suggesting an endogenous origin, probably reflecting chronic inflammatory tissue damage. The habit of drinking very hot tea remains a possible etiologic factor.

Inflammation activates a variety of inflammatory cells, which induce and activate several oxidant-generating enzymes. These enzymes produce high concentrations of diverse free radicals and oxidants, which react with each other to generate other more potent reactive oxygen and nitrogen species such as peroxynitrite. These species can damage DNA, RNA, lipids, and proteins, leading to increased mutations and altered functions of enzymes and proteins, thereby contributing to the multistage carcinogenesis process.

Cancer prevention

Work on primary prevention of cancer, aiming at reducing the burden of disease by preventing the initial causes, is particularly focused on vaccination programmes against viral infections. The Gambia Hepatitis Intervention Study has now been running for more than 15 years. The principal activity of following up the vaccinated cohort is in a long-term routine phase through the national cancer registry, although improvements in registry coverage and in identification of cohort members are always being sought. Meanwhile, ancillary studies, for example of aflatoxin-related *TP53* mutations, continue to benefit from the infrastructure now in place for the main study.

A second vaccination project, still in the planning phase in collaboration with WHO, is designed to test the reduction in human papillomavirus infection, with the aim of diminishing the incidence of cervical cancer, one of the commonest cancers of women in developing countries. Another prong of the attack on this disease is the major project in 10 African and Asian countries, with the generous support of the Bill and Melinda Gates Foundation, for early detection of cervical lesions and their treatment, by methods adapted to use in countries with limited resources. Various detection techniques are being tested, in parallel with programmes to train health care personnel. Randomized trials in India and Nepal are comparing cryotherapy and loop electrosurgical excision procedures for removal of pre-invasive cervical cancer.

The *IARC Handbooks of Cancer Prevention* have evaluated the cancer-preventive effects of breast-cancer screening and of consumption of fruit and vegetables. The book on breast cancer screening has had a great impact on discussions in several IARC member states which are considering the introduction of population-based screening programmes.

IARCPress

The Agency's own book publication programme has continued to produce many important volumes, as demonstrated by the ever-increasing sales figures achieved by IARCPress. In the series WHO Classification of Tumours (WHO Blue Books), five volumes have been published and the sixth, on *Tumours of the Urinary System and Male Genital Organs*, went to press in December 2003. It is anticipated that the entire series of 10 volumes will be published by the end of 2004. These Blue Books now have an initial print run of 15 000 copies each. One exceptional project was the *World Cancer Report*, published in early 2003, which reviews the whole field of cancer, covering its occurrence, causes, mechanisms of carcinogenesis, treatment and prevention and national cancer control programmes. A first in the Agency's history, the book was well received, with 20 000 copies already printed and a French edition in preparation.

Fellowships and training

In the present biennium, 15 fellowships were awarded in each year to young scientists of exceptional merit, to pursue their research careers either at IARC or in other institutions, mainly in Europe or the United States. Eight training courses were held in the core programme, hosting over 300 participants, and in addition the Unit of Descriptive Epidemiology was particularly active in organizing courses on cancer registration and on coding and computer software, as well as several on various aspects of cancer epidemiology.

Staff and visitors

At the end of the biennium, a total of 326 people were working at the Agency, of whom 143 were fixed-term staff members, 72 short-term staff members, and the other 111 special training awardees, fellows, visiting scientists and trainees. While budgetary constraints have limited the recruitment of long-term staff, an increasing number of doctoral students and postdoctoral fellows contribute to the

work of the Agency. In addition, the Agency has become increasingly attractive for visiting scientists, who often bring new ideas and frequently initiate collaborations that continue long after their departure.

During 2002–2003, the IARC Visiting Scientist Awards were held by Dr John Witte, from the Department of Epidemiology and Biostatistics at Case Western Reserve University, Cleveland, Ohio, and Dr Tony Fletcher, from the Environmental Epidemiology Unit, Department of Public Health and Policy at the London School of Hygiene and Tropical Medicine.

Dr Paola Pisani, from the Unit of Descriptive Epidemiology, went on special leave for training purposes to Leeds University in the UK, and Mr Ebrima Bah (The Gambia) went on study leave to Tampere University in Finland.

In June 2002, Dr Giovanni Romeo, Chief of the Unit of Genetic Cancer Susceptibility, retired to become Professor of Genetics at the University of Bologna, Italy. To succeed him, the Agency recruited Dr Sean Tavtigian, who previously worked at Myriad Genetics in Salt Lake City, Utah, where he was part of the team that identified and sequenced the *BRCA1* gene.

Following the retirement of Ms Helis Miido in October 2002, Ms Sharon Grant, previously at McGill University, Montreal, Canada, was appointed head of the Library, which is now part of the Unit of Communications.

Dr Jerry Rice also retired in 2002 and was succeeded as Chief of the Unit of Carcinogen Identification and Evaluation by Dr Vincent Cogliano, previously at the United States Environmental Protection Agency, Washington, DC. In the same Unit, Dr Nikolai Mironov took early retirement in March 2002, and Mrs Christiane Partensky retired, after more than 30 years of service to the Monographs programme, at the end of January 2003.

Dr Paolo Boffetta, Chief of the Unit of Environmental Cancer Epidemiology accepted an offer from the German Cancer Research Centre (DKFZ) in Heidelberg, to become Chief Epidemiologist and Professor of Epidemiology at the University of Heidelberg.

Visit to IARC of the French Minister of Health, Professor Jean-François Mattei (centre) on 8 December 2003, with Dr Paul Kleihues (left) and Dr Gilbert Lenoir, the French delegate to the Governing Council (right)

Dr Harri Vainio, Chief of the Unit of Chemoprevention, left IARC in December 2003 to take up the position of director of the Finnish Institute of Occupational Health in Helsinki.

New professional staff members at IARC in 2002–2003 include: Dr Wael Al-Delaimy in the Unit of Nutrition and Cancer, Dr Deepika de Silva in the Unit of Genetic Cancer Susceptibility, Dr Isabelle Deltour in the Unit of Radiation and Cancer, Dr Yann Grosse in the Unit of Carcinogen Identification and Evaluation, Dr Zdenko Herceg and Dr Wei-Min Tong in the Unit of Gene–Environment Interactions, Dr Hervé Huang in the Unit of Molecular Pathology, Dr Cédric Mahé in the Unit of Descriptive Epidemiology and Dr Tomohiro Sawa in the Unit of Endogenous Cancer Risk Factors.

Two new Research Units were created in 2002. The Unit of Infection and Cancer is headed by Dr Massimo Tommasino, previously at the German Cancer Research Centre (DKFZ) in Heidelberg, who is continuing his work on mechanisms of HPV-associated carcinogenesis, particularly in the development of skin tumours. Dr Emmanuel Lazaridis, previously at the University of Tampa, Florida, USA, was appointed Chief of the Unit of Bioinformatics and Biostatistics.

In February 2002, a new research group was created: Hormones and Cancer, headed by Dr Rudolf Kaaks. In July 2002, Dr Pierre Hainaut was promoted to Chief of the Unit of Molecular Carcinogenesis.

On behalf of the Agency and its member states, I should like to express my gratitude and appreciation for the excellent work of the outgoing staff members, together with best wishes for their future activities.

Relations with the City of Lyon

After some intensive negotiating, the Convention with the City of Lyon regarding the lease of the tower building was renewed and signed by the Mayor, Mr Gérard Collomb, and the Director on the occasion of IARC Day in May 2002. This reflects the excellent relationship and the continuous support that the Agency has received from the City of Lyon, ever since its creation in 1965.

Visit of the French Minister of Health

In December 2003, Professor Jean-François Mattei, the French Minister of Health, visited the Agency and signed an agreement for an extra-budgetary donation of !1 000 000 from the French Government to extend the Agency's scientific programme. These funds will be mainly used for research on tobacco and cancer.

IARC Day

This traditional event is held in conjunction with the Governing Council

meeting and is important since it strengthens the Agency's interactions with the scientific, diplomatic and political communities of Lyon. The Professor Roger Sohier Lecture 2002 was delivered by Dr J. Koplan (previously Director, Centers for Disease Control, Atlanta, Georgia, USA), who impressively documented the dramatic changes in lifestyle in developed countries and their adverse effects on public health. Another highlight of IARC Day 2002 was the musical performance of Dr Gottfried Thiers, Chairman of the WHO Executive Board, who is an accomplished singer and was greatly applauded for his programme of classical songs.

IARC Day 2003 was the last for the outgoing Director, who presented the Sohier Lecture on Poverty, Affluence and the Global Burden of Cancer and who also acted as guest conductor of the IARC chamber orchestra.

Dr J.M. Martin-Moreno (Spain) with the Chairman of the Governing Council, Dr J. Larivière, at the admission of Spain as a Participating State of IARC on 15 May 2003

Scientific Council

Members of the Scientific Council are elected on the basis of their expertise in areas of cancer research relevant to the work of the Agency. In addition to critically reviewing the work of IARC scientists, they give valuable advice on future research strategies. Our sincere thanks go to the Chairmen and Vice-Chairmen of the Scientific Council, Dr M. Aguet (Switzerland), Dr L. Borysiewicz (United Kingdom) and Dr A.L. Børresen-Dale (Norway). At the same time, we wish to thank those members who left the Council during the past biennium: Dr L. Aaltonen (Finland), Dr M. Aguet (Switzerland), Dr D. Bootsma (The Netherlands), Dr J. Olsen (Denmark), Dr F. Berrino (Italy), Dr A.L. Børresen-Dale (Norway), Dr K. Hemminki (Sweden), and Dr H. Rabes (Germany). Newly elected to the Council were Dr H. Autrup (Denmark), Dr J. Jiricny (Switzerland), Dr F. van Leeuwen (The Netherlands), Dr P. Pietinen (Finland), Dr J.D. Potter (USA – re-elected), Dr W. Boecker (Germany), Dr E. Lund (Norway), Dr M. Pierotti (Italy), and Dr R. Toftgard (Sweden).

Dr Kleihues conducts the IARC chamber orchestra, in a performance of a Handel organ concerto with the solo part played on the piano by Dr Hiroko Ohgaki

Election of IARC Director

At the Governing Council meeting in May 2003, Dr Peter Boyle, Director of the Department of Epidemiology and Biostatistics at the European Institute of Oncology, Milan, Italy, was elected Director of IARC for the period 2004–2008. He will take office on 1 January 2004. Since his election, he has been in frequent contact with the current Director and the Administration to ensure a smooth and effective transition.

Spain joins the Agency

At the May 2003 meeting of the Governing Council, Spain was admitted as the 16th Participating State of the Agency. All delegates and IARC staff warmly welcomed this event, and look forward to increasing collaboration with the Spanish cancer research community.

Governing Council

At the Governing Council in 2003, the budget for the biennium 2004–2005 was approved with a 4.43% increase in the programme budget. This will enable IARC to maintain its current level of scientific activities and will enable the new Director to expand into some new research domains.

Interaction with WHO Headquarters

The relationships with WHO Headquarters have been further strengthened at both the technical and administrative levels. We wish to thank Dr Gro Harlem Brundtland, Director-General, WHO, for her continuous support and advice. The new Director-General of WHO, Dr J.-W. Lee, has shown a strong interest in the work of the Agency and plans a visit to Lyon early in 2004.

On behalf of the Agency and its staff, I would like to thank the Governing Council for its support during my term as Director over the past 10 years.

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 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.

Lung cancer incidence among males, 2000. Incidence per 100 000: <5.7, <95.5

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 is essential.

International Association of Cancer Registries (IACR)

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

IARC provides administrative facilities to the International Association of Cancer Registries (IACR). The IACR is a non-governmental organization in official relations with WHO, and in 2003 had 463 members in 123 countries, 80% of them cancer registries. Membership fees are used to fund Association activities, including support to members from developing countries to participate in the annual scientific meetings. 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.

Assistance is provided to the hosts of the annual scientific meeting. The secretariat collaborated with the Finnish Cancer Society to organize the 2002 meeting, held in Tampere in June. The overall theme was *Registries in Cancer Research* and the programme encompassed the health effects of the Chernobyl accident, evaluation of prevention strategies, biological and genetic data banks, survival and ethics. In 2003, the subject of *Cancer Registration and Surveillance around the World* was the focus of a meeting in Hawaii, including sessions on Pacific islanders and indigenous populations, physical activity, diet, migrants and cervical cancer with special reference to human papillomavirus and vaccines. Preparations are now being made for the 2004 meeting, to take place in Beijing, China.

The Association provided support for African registry members to attend a meeting of the African Organization for Research and Training in Cancer, held in Accra, Ghana, in October 2003. The African Regional Representative of IACR, Dr Henry Wabinga, took the opportunity to organize a meeting of the African group of IACR cancer registries.

A 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 Dr Chu Hoang Hanh from Hanoi, Viet Nam to take part in the 2003 IARC Summer School on Cancer Registration and Applications in Epidemiology.

The IACR web site (http://www.iacr.com.fr/) presents news of activities, publications, meetings and national and regional associations of registries. The IACR Newsletter, sent to all members and also available on the web site, gives news of activities and provides a forum for registries to present their work. Cancer registries send copies of their reports to IACR, which maintains a collection of over 2300 such publications on cancer incidence, mortality and survival worldwide, a bibliography of which was made available on the web site in 2003. 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, J.E. Tyczynski, F. Bray, E. Démaret, J. Ferlay, E. Riboli; in collaboration with L. Barlow, Stockholm, Sweden; U. Batzler, Stuttgart, Germany; D. Brewster, Edinburgh, UK; J.W.W. Coebergh, Eindhoven, Netherlands; J. Faivre, Dijon, France; I. Izarzugaza, Spain; H. Møller, London, UK; L. Simonato, Padua, Italy

Supported by the Public Health Directorate of the European Commission

The aims of the European Network of Cancer Registries (ENCR) are to improve the quality, comparability and availability of data from cancer registries in Europe, and to promote the use of these data in research and cancer control activities. The ENCR has 184 member registries in 43 European countries (97 member registries in countries of the European Union (EU)). A steering committee, comprising elected members and nominees of cancer registry associations, guides and advises the secretariat provided by IARC. An ENCR Scientific and General Meeting was held in Tampere (Finland) in 2002 to review ENCR activities and to present registries' research projects.

The ENCR Internet home page at http://www.encr.com.fr provides comprehensive information on the activities of the ENCR.

Automated cancer registration

A specific web site for automated cancer registration was launched in spring 2003 (http:150.92.82.173/encr), to provide information on the principles and benefits of automated registration, definitions, an interactive test site and related publications.

Establishing standards and definitions

Expert working groups review aspects of registration practice and propose standards for the European registries. Issues addressed in 2002 and 2003 were

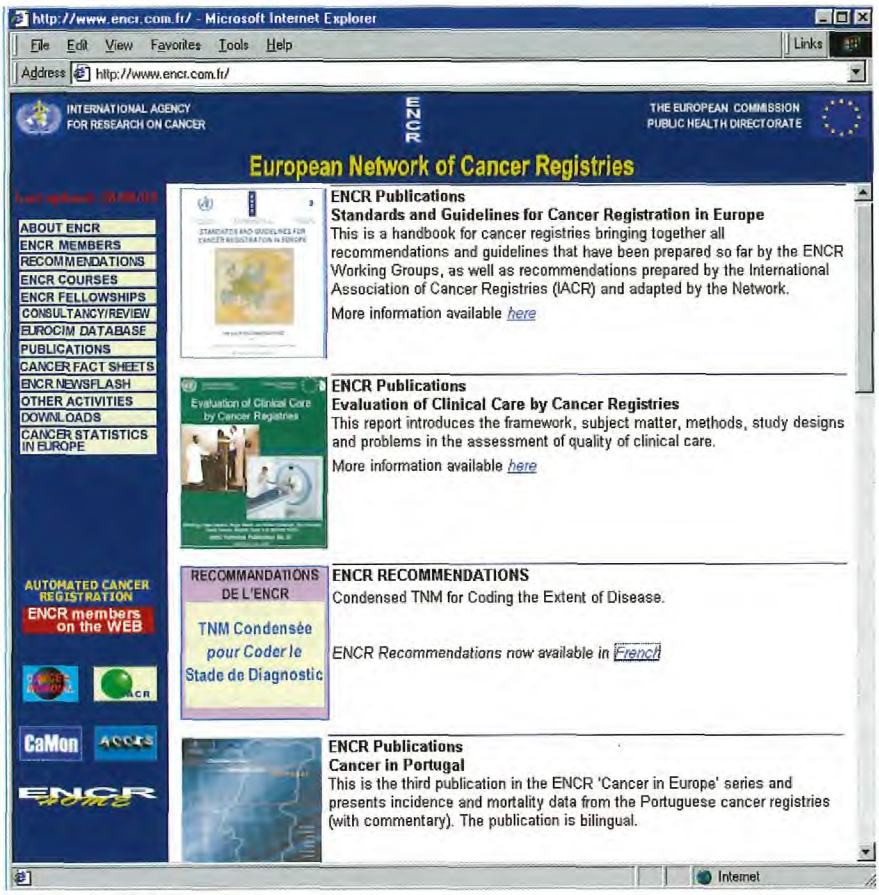


Figure 1. The ENCR home page

confidentiality in cancer registration (March 2002) and coding extent of disease (May 2002), and work on coding of bladder cancers and on completeness of registration was initiated. The working group on automated cancer registration met three times in 2002 and in 2003.

A handbook on *Standards and Guidelines for Cancer Registration in Europe* (IARC Technical Publication No. 40) [518] was published in 2003.

Training and fellowships

Cancer registration courses were held in Lyon, France in April 2002 and in Cluj, Romania in August 2003. Courses on statistical analysis methods are held annually; the topic in 2002 was geographical analysis, and in 2003 time trends analysis. Four courses on coding using ICD-O-3 were organized, in Germany, Norway, Spain and the United Kingdom. Courses on the use of the new EUROCIM software (version 4.0) were held in Spain and in Italy (see Section 7.3).

ENCR provides support to registry personnel to attend ENCR courses or to exchange skills through working visits to other registries. In 2002–03, 30 fellowships were awarded.

Consultancy and structured reviews

In 2002, an audit programme to provide in-depth reviews was introduced. Reviews took place in Hungary (National Paediatric Cancer Registry, Budapest), Poland (Holycross Cancer Registry, Kielce), Ireland (National Cancer Registry, Cork) and Germany (Regional Cancer Registry, Bremen).

Consultancy visits were made to Bosnia and Herzegovina (R. Sankila) and northern Cyprus (J.E. Tyczynski), with a view to establishing cancer registries.

Provision of information on cancer in Europe

Information on the burden of cancer in European populations is provided through traditional and, increasingly, electronic publications. Work included updating the EUROCIM databases and software, developing the new EUCAN dynamic database and software package and providing data for new projects (see Section 1.2). Work on the series "Cancer in Europe" continued, with the publication of an analysis of cancer incidence and mortality in Portugal (IARC Technical Publication No. 38) [372]. Analyses of time trends in melanoma, mesothelioma, breast cancer and lung cancer in Europe were published [75,81,134,314]. Three ENCR Cancer Fact Sheets were produced (on lung, breast, and bladder cancer in Europe).

Reliability and validity of registry data

International Classification of Diseases

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

IARC is responsible for producing the neoplasms chapter of the International Classification of Diseases (ICD) and the International Classification of Diseases for Oncology (ICD-O). The extensive revision of the haematological morphology rubrics in the third edition of ICD-O (ICD-O-3), published in 2000, led to inconsistencies in the international rules for the counting of multiple primary diagnoses. A working group was convened in 2003 and revised rules are to be published.

Histological groups for comparative studies

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

The ICD-O histology codes are grouped into classes for studies of etiology and survival. *Histological Groups for Comparative Studies* (Parkin *et al.*, 1998, IARC Technical Report No. 31) provided a description of recognized histological subtypes of selected cancers. In 2002 a

scheme for presenting histological data on one further site, cancer of the anus, and groupings for the tabulation of the major types of sarcoma and for mesotheliomas by site, were produced and published in Volume VIII of *Cancer Incidence in Five Continents*.

International Classification of Childhood Cancer

E. Šteliarová-Foucher, D.M. Parkin, N. Mitton; in collaboration with P. Kaatsch, Mainz, Germany; B. Lacour, Nancy, France; C.A. Stiller, Oxford, UK

Publication of the third edition of the ICD-O (see above) necessitated a revision to the existing International Classification of Childhood Cancer (ICCC). In order to preserve the capacity for comparison with older data, the new edition (ICCC-3) is, as before, classified into twelve main diagnostic groups: leukaemias, lymphomas, central nervous system tumours, neuroblastoma, retinoblastoma, renal tumours, hepatic tumours, bone tumours, soft-tissue sarcomas, germ-cell tumours, epithelial tumours and other and unspecified tumours. All these groups except retinoblastoma are further classified into more homogeneous diagnostic subgroups. The overall content of the different diagnostic groups is similar to that in the previous edition of ICCC, but newly recognized entities are included. The most important change is the inclusion of myelodysplastic syndrome and other myeloproliferative diseases, now considered to be malignant. Another new feature is the capacity to divide selected diagnostic subgroups into 2–11 subdivisions.

ICCC-3 was submitted for publication during 2003 and an automatic conversion program is in preparation.

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. Over the last two years, all users of version 3 have been upgraded to the Windows version, CanReg4 (Figures 2 and 3). This was accomplished by organizing regional courses in which the users' databases were transferred and converted to ICD-O-3 and appropriate training was given. Over 120 registries are now using the program in about 60 countries.

The data-entry module provides consistency checking for impossible/rare cases, searching for duplicate records and multiple primaries using probability matching and conversion from one classification system to another. Easy-to-use analysis options include frequency distributions, reports, incidence tables and an interface to EpiInfo.

CanReg4 allows full integration into a Windows-based network environment and extends the language-swapping capability to languages such as Arabic, Chinese, and Thai.

Special versions have been developed in collaboration with the Middle East Cancer Consortium and installed in the participating countries (Egypt, Jordan, Cyprus, Palestine). The project is partially funded by the Bill and Melinda Gates foundation through the Alliance for Cervical Cancer Prevention and Control.

IARCcrgTools

IARCcrgTools is a Windows®-based package providing various batch programs to convert data from ICD versions 9 or 10 or the first and second editions of ICD-O, to the ICD-O-3. Also included are programs for conversion from the second edition of ICD-O to ICD versions 9 and 10, and from ICD-O-3 to ICD version 10 and to the International Classification of Childhood Cancer (ICCC).

The IARC-CHECK and the IARC multiple primary check programs, which perform various validity and consistency checks, have been updated to use the ICD-O-3 codes. In particular, new histology/site validation rules have been defined. The IARCcrgTools package is distributed free from the Internet at the IACR web site (http://www.iacr.com.fr/iarccrgtools.htm) or on CD-ROM (on request).

Support to specific cancer registries

D.M. Parkin, P. Pisani, R. Sankaranarayanan, S.L. Whelan, A. Cooke, J.E. Tyczynski

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 IARC for training or discussion. A structured course in cancer registration and applications in epidemio-

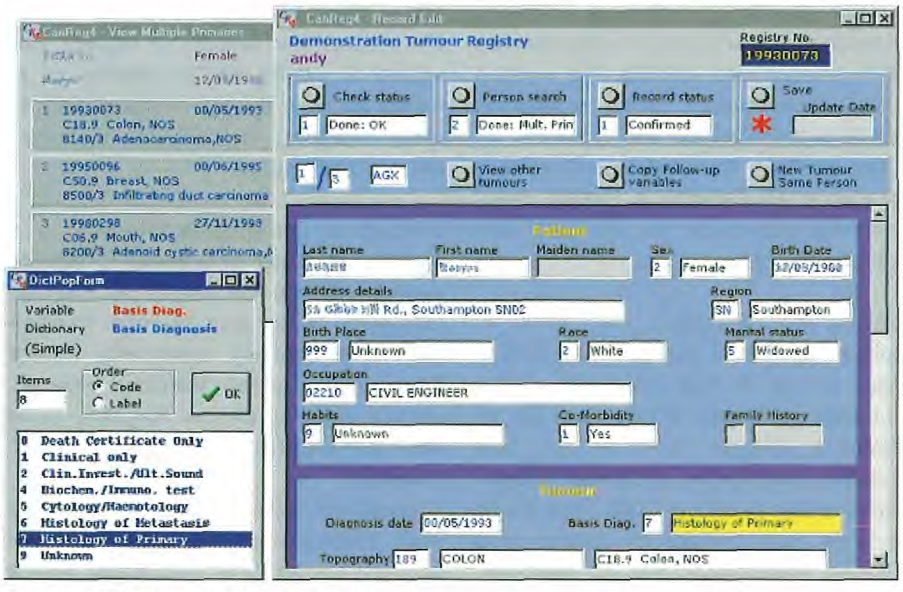


Figure 2. CanReg4; example of data-entry screen

logy is held every May in Lyon and 10 courses on coding and use of CanReg were held during the biennium (see Section 7.3). In May 2003, a course was held in Buenos Aires jointly with the country programme (VIGIA) of the World Bank, for new registries recently established in Argentina.

In September 2003, 26 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). Aid with analyses often leads to joint publications (see Section 1.2).

Close collaboration is maintained with regional offices of WHO with respect to cancer registry activities. IARC staff provided consultancies on cancer registration and cancer control in several countries.

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), Buenos Aires (R. Pradier) and Concordia (M.A. Price). A consultant visit was made on behalf of IARC to Mendoza and Bahia Blanca.

Bahrain (J. Al-Sayyad): Progress was reviewed during a visit in 2003.

Burkina Faso (B. Sakande and R.B. Soudré): Registration for the city of Ouagadougou commenced in 1998. A review visit by a staff member was made in March 2003.

Cambodia (P. Piseth Raingsey and Khuon Eng Mony): The registry was visited in 2002 and a consultant visit arranged in 2003, to assist the staff with abstraction and coding of data and with the use of CanReg.

China (Li Lian-di, Yang Ling, Zhang Si-wei): During the biennium, a special programme was established to enhance cancer registration and availability of cancer data from China. A visiting fellow from the National Office of Cancer Prevention and Control assisted with a review of existing data sources (both mortality and incidence) and carried out a survey of cancer registries nationwide, and training courses were held for registry staff, in collaboration with the National Office of Cancer Prevention and Control. A version of CanReg was developed using Chinese characters and a special training course was held (see Section 7.3).

Congo (C. Gombe-Mbalawa and S. Moubie): Support continues for the Brazzaville registry.

Côte d'Ivoire (A. Echimane): Support to the registry continues.

Cuba: The central registry in Havana (L. Fernandez and Y. Galan) is being decentralized to regional registries, and assistance is being provided in developing computer systems.

Gabon (E. Belembagao and P. Nsie-Obame): A consultant visit took place in March 2002, and recommendations were made for development of the national registry in two locations.

The Gambia (E. Bah): The cancer registry is an integral part of the Gambia Hepatitis Intervention Study (see Section 5.1) and the registry collaborates in the study of cancer survival (Section 1.4).

Guam (R.L. Haddock): Population coverage has been completed with the inclusion of information from private clinics. A consultant visited on behalf of IARC in June 2003.

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

Honduras: The registry supervisor in Tegucigalpa (J. Figueroa) took part in a training course in Lyon

India: Numerous registries participate actively in research projects on cervical cancer screening (Ambilikkai: J. Cherian and R. Rajkumar; Barshi: B. Nene, K. Jayant and A. Budukh; Kolkata (Calcutta): M. Siddiqi and U. Sen), cancer survival (Bhopal: S. Khanere and R. Dikshit; Mumbai (Bombay): B.B. Yeole; Chennai (Madras): V. Shanta and C. Swaminathan), oral cancer screening (Trivandrum: K. Nair and A. Mathew) (Section 5.3) and a cohort study focusing on the risks of tobacco use (Mumbai and Trivandrum) (Section 2.4). IARC staff act as advisers to the National Cancer Registry Project (A. Nandakumar) and to a WHO-sponsored project to develop a national cancer atlas for India (A. Nandakumar). Technical support was provided for development of pathology-based and population-based cancer registries in various regions of India.

Iran: The registry in Teheran (A. Mohagheghi and A. Mosavi) now covers the entire metropolitan population. New registries have been established by the Digestive Diseases Research Centre (R. Malekzadeh and A. Sadjadi) in the Caspian region, for studies on oesophageal cancer (Golestan) (see Section 3.1) and stomach cancer (Ardabil). There are plans to reactivate the cancer registry in Shiraz (M.J. Saalabian and J. Shamsnia).

Kenya: Progress at the recently established cancer registry in Eldoret (N. Buziba), western Kenya, was evaluated at a visit during 2002, and a staff member assisted with renewal of the computer system in 2003.

Lao People's Democratic Republic (B. Phouthone and P. Alongkone): A visit to evaluate the success of this registry project was made in 2002.

Malawi (C. Dzamalala and N.G. Liomba): Dr Dzamalala attended a training course on CanReg4 in Lyon in September 2002.

Mali (S. Bayo and S. Kané): The registry is actively collaborating in the studies of cervical cancer screening (see Section 5.3). A visit was made in March 2003 to evaluate progress.

Mauritania (M.H. Diop): A consultant visit was made in 2002 to discuss setting up a cancer registry. Dr Diop attended a training course in Lyon in 2002.

Mozambique (J. Ferro): A consultant visit on behalf of WHO in April 2003 recommended delay in the implementation of a regional registry until the issue of the scientific direction could be clarified.

Niger (H. Nouhou): Support to the registry continues.

Nigeria: The Ibadan registry (J.O. Thomas) 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 2.7). A consul-

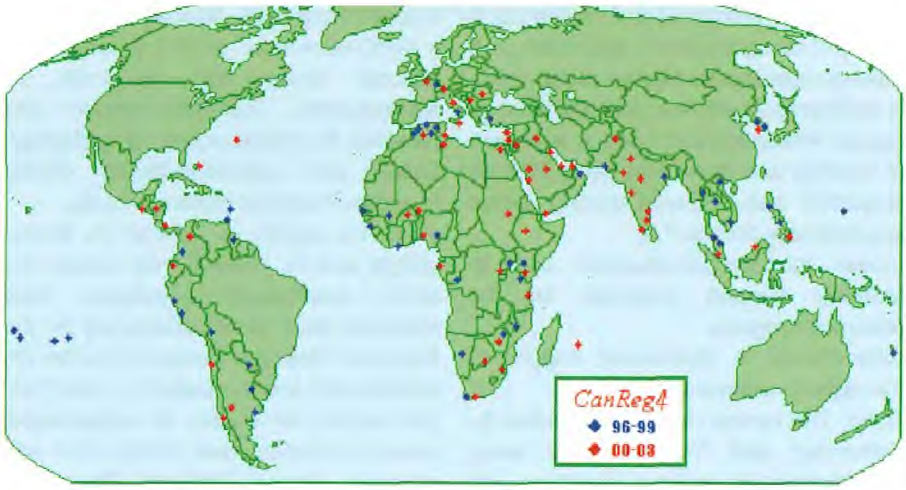


Figure 3. Locations of CanReg4 installations

tant visit was made in 2003, to advise how to support the development of registry projects in Ife-Ijesha (S. Ojo), Calabar (I.O. Ekanem) and Maiduguri (M.I. Khalil).

Oman (J. Al Lawati): Registry results for 1993–97 were published in volume VIII of *Cancer Incidence in Five Continents*. Progress was reviewed during a visit in 2003.

Pakistan: A population-based registry (Y. Bhurgri) covering the population of the southern part of Karachi is supported. A new registry is planned for the city of Lahore, with the support of the International Network for Cancer Treatment and Research (INCTR). A consultant visit was made during 2003.

The Philippines: The two registries in greater Manila (D. Esteban and A. Laudico) 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: Cancer registration (C. Chiotan, D. Coza and N. Ghilezan) is being developed through initiatives in the Ministry of Health and in several provinces. The regional cancer registry in Cluj-Napoca hosted a course in cancer registration and CanReg4 for the ENCR in August 2003 (see Section 7.3). The Ministry of Health plans to develop five regional cancer registries (with support of the ENCR and the European Commission's PHARE programme), to cover the whole population of Romania. A special version of the CanReg4 software has been prepared.

Saudi Arabia: The national registry (N. Al Hamdan) provides a resource centre for the other registries in the countries of the Gulf Cooperation Council. A visit was made in 2003 to discuss how to coordinate support to the latter group.

Senegal: One of the first population-based registries in Africa was located in Dakar. The situation seems favourable to its reactivation, which was discussed during a consultant visit, and the director of the project (J.-M. Dangou) attended the training course in Lyon in 2003.

South Africa: Currently, the only population-based registries are in the Transkei regions of the Eastern Cape, supported by the PROMEC programme of the South African Medical Research Council (four districts: N. Somdyala, W. Marasas and W. Gelderblom) and the University of Transkei (Umtata district, D. Mugwanya). A visit was made to make recommendations for future development.

Swaziland (S. Okonda): A visit was made to review progress with the national cancer registry in April 2002.

Tanzania: A registry in Moshi (E. Moshi) has operated since 1998, covering four surrounding districts of the north of Tanzania. A hospital-based cancer registry has been set up in the Ocean Road Cancer Institute (T. Ngoma and F. Temu-Mbaga), as a first step to population-based registration in the Dar es Salaam area. A staff member received training in Lyon.

Thailand: Five population-based registries (Lampang, Chiang Mai, Khon Kaen, Bangkok and Songkhla) (S. Deerasamee, P. Srivatanakul, S. Srisukho, S. Sontipong, S. Sriamporn, H. Sriplung and N. Martin) are collaborating in the preparation of a third monograph on cancer in Thailand. Khon Kaen registry provides follow-up for a population-based study (Section 3.3) and together with Chiang Mai participates in the studies of cancer survival (Section 1.4).

Turkey (M. Tuncer, C. Fidaner and S. Eser): Registration for Izmir province is now complete. The registry is providing a model for the development of a network of regional registries. A consultative visit was made in January 2003.

Uganda (H. Wabinga and S. Nambooze): The registry 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 2.7) and collaborates in the study of survival in Africa (Section 1.4). The registry also provides a resource for other collaborative studies with IARC (see Section 2.7).

Viet Nam: The registries in Hanoi (Pham Hoang Anh) and Ho Chi Minh City (Nguyen Chan Hung and Nguyen Manh Quoc) have been supported for some time, and are active in supporting the development of several new registries in the country. A visit to review needs for training and technical support was made in November 2003.

Yemen: The registry in Aden (A. Bawazir) continues to receive support and has prepared a first report of results for 1997–2001. A new registry is being started in Sana'a (N. Nagi), with the establishment of a cancer treatment centre.

Zimbabwe: The registry in Harare (M. Bassett, M. Borok, E. Chokunonga and B. Mauchaza) 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 2.7) and collaborates in the study of cancer survival (Section 1.4).

1.2 Geographical variation in cancer occurrence

Documenting the enormous range in incidence and mortality from diseases in different populations has been a powerful stimulus to research into the underlying causes. The presence or absence of environmental exposures, or differing susceptibility of the populations may contribute to the observed variations, to varying degrees. 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 can 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

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, USA

The eighth volume in the *Cancer Incidence in Five Continents* series, published in 2002, presents comprehensive data on cancer incidence for over 200 populations worldwide. The period covered is 1993–97, making information available on patterns and trends of cancer for over 40 years for the older-established cancer registries. The book follows the traditional format, with background chapters and descriptions of the areas and populations presented, as well as data on incidence by site and by histological type. The printed tables are, however, less numerous than previously, the detail of age-specific incidence now being presented as PDF files on an accompanying compact disc. This disc includes the entire database (as text files), with cases tabulated by population (registry), age group, sex and diagnosis (252 units defined by site and histology) that can be extracted for analysis. It also contains software to analyse and present these data in a tabulated or graphic format: the usual summary rates (crude, cumulative, world and European age-standardized) can be calculated over any chosen age range. The software also performs some elementary statistical tests, e.g., for homogeneity, trend and significance of the ratio of age-specific rates from two populations.

Cancer Incidence in Five Continents, Volumes I–VIII

D.M. Parkin, S.L. Whelan, J. Ferlay; in collaboration with N. Al-Hamdan, Riyadh, Saudi Arabia; H.H. Storm, Copenhagen, Denmark

The data from the eight volumes of *Cancer Incidence in Five Continents* are being prepared for publication in electronic format. At an editorial meeting held in April 2003, it was decided to prepare three databases. The first will provide the basic published data, so giving access to data from earlier volumes that are no longer readily available. A second database will present time-trend data for registries with three or more time-periods in the volumes. For these data, the denominators and the data will be updated and, where necessary, corrected and years will be re-grouped to correspond to standard five-year periods. The third database will provide annual incidence and mortality rates, and graphs based upon them. Registries contributing data to Volume VIII and registries with 15 years or more of recent data have been invited to send an updated database.

Cancer in Europe

Cancer Monitoring in Europe (CaMon)

F. Bray, E. Démaret, J. Ferlay, P. Pisani, D.M. Parkin; in collaboration with F. Berrino, Milan, Italy; L. Cherie-Challine, St Maurice, France; M. Colonna, Grenoble, France; M. Diaz, Paris, France; T. Hakulinen, Helsinki, Finland; Y. Le Cam, P. Mourouga, Paris, France; M. Guerra Yi, Havana, Cuba; C. Mathers, Geneva, Switzerland; A. Micheli, Milan, Italy; F. Pignatti, London, UK; G. de Pouvourville, Villejuif, France; M. Stenbeck, Stockholm, Sweden

Supported by the Health Monitoring Programme (Health and Consumer Protection Directorate-General) of the European Commission

The CaMon (Comprehensive Cancer Monitoring in Europe) project was set up with the objectives of (i) developing a cancer surveillance system for cancer occurrence and outcome (incidence, mortality, prevalence and survival), permitting situation analysis and monitoring of the cancer burden in the Member States of the EU and its applicant states; and (ii) disseminating such information within the EU and worldwide, and making it available for incorporation into the health-monitoring system of the European Commission.

The tasks included the compilation and maintenance of an updatable database of indicators of cancer burden and outcome for EU countries and applicant states. This was achieved by expanding the EUCAN database with estimates for other European countries, supplementing the incidence, mortality and prevalence data with recent estimates of survival from EUROCARE.

A workshop on time trends in November 2002 reviewed the methodological aspects of systematic time trend analyses (see below). A second workshop, in February 2003 (in collaboration with the French Cancer League), brought together methodologists, users and potential users of cancer prevalence data. It focused on the usefulness of prevalence, and on the problems encountered in defining, measuring and estimating this indicator.

Recent and future trends in lung cancer mortality (in relation to current smoking patterns) in the 15 EU Member States have been examined in detail [81]. The CaMon project has been described in relation to the role of the key indicators specific to cancer monitoring and the most recent estimates of the burden of the disease in the EU and Europe [78].

European cancer incidence and mortality databases

J. Ferlay, F. Bray, D.M. Parkin, J.E. Tyczynski

EUROCIM is a powerful software package allowing statistical analyses of cancer incidence and mortality data contributed by ENCR members (see Section 1.1). In addition to the set of standard statistical tools (age standardization, log linear model-fitting), the latest EUROCIM software (Version 4.1) contains a time trends analysis module that allows the user to fit age–period–cohort models to the registry incidence and mortality data (Figure 4). New databases (Version 2.4) containing data from over 140 European cancer registries covering the period 1953 to 2000 have been distributed to ENCR members via a secure FTP web site. New versions of EUROCIM are made available periodically, with further software enhancements, as well as the most recent cancer registry data. The software and database are managed and maintained at IARC, while an external contractor is responsible for the development of the program.

EUCAN is a Windows®-based package which provides access to the most up-to-date information on cancer incidence, mortality, prevalence and survival in the 15 Member States of the EU 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 conventional tabular format, graphically as line plots, bar or pie charts, or as maps. The presentations can be easily printed or exported to other packages. In addition, the countries and cancer sites can be grouped, allowing users flexibility in specifying their own requirements.

The EUCAN database is updated annually to incorporate the latest incidence and mortality data. The user can download new versions of the database directly from the ENCR Internet home page (http://www.encr.com.fr/). The latest estimates for 1998 were made available online in 2002. A new version of the software (EUCAN 2000) is under development (Figure 5). The user interface and the online help have been extensively revised to enhance ease of use. This new version takes into account the forthcoming inclusion of ten new Member States and three associated countries (Iceland, Norway and Switzerland) and provides estimates of cancer incidence, mortality and prevalence for the year 2000.

A simplified version of the EUCAN soft-

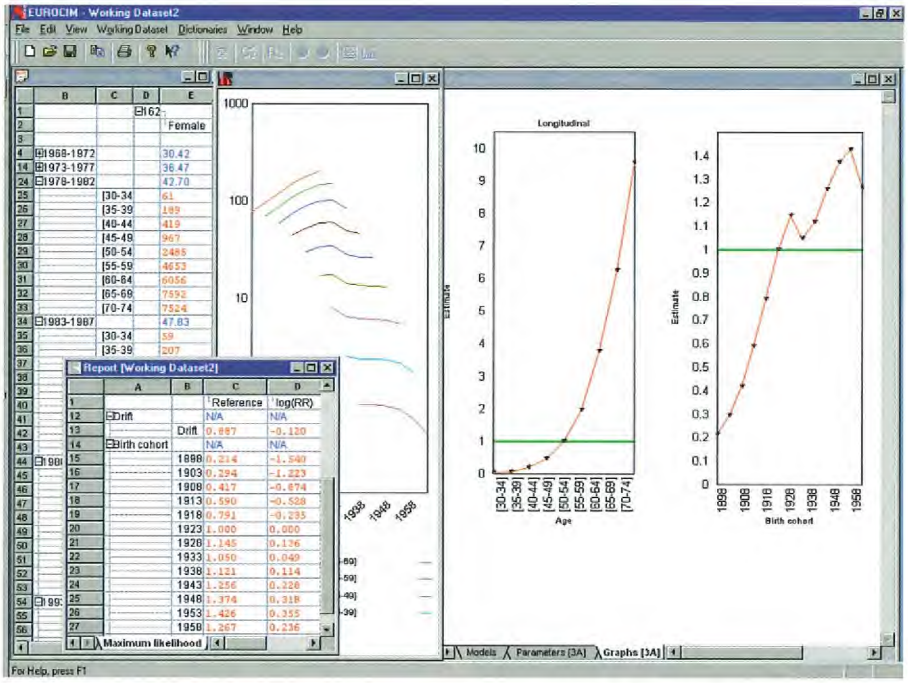


Figure 4. EUROCIM version 4: evaluating the effects of age, period and cohort on lung cancer rates over time

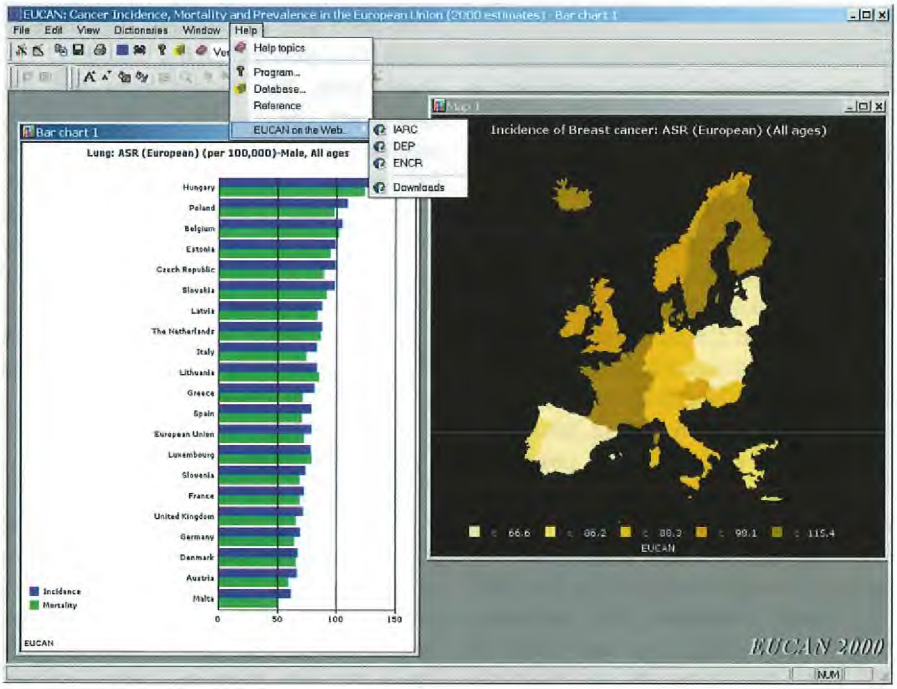


Figure 5. EUCAN screen display of lung cancer data

ware is available on the ENCR web site. EUCAN was published in the IARC electronic publication series as CancerBase No. 4 (see Section 7.1).

Analyses of time trends and projections of cancer incidence and mortality

F. Bray, A. Loos, G. Clifford, E. Démaret, J. Ferlay, S. Franceschi, P. Pisani, J.E. Tyczynski, P Vizcaino, E. Weiderpass, L. Yang, D.M. Parkin; in collaboration with A. Anttila, T. Dyba, T. Hakulinen, R. Sankila, Helsinki, Finland; M. Arbyn, Brussels, Belgium; H. Botha, Leicester, UK; L Bravo, Cali, Colombia S.S. Devesa, Bethesda, MD, USA; M. Hakama, Tampere, Finland; L. Li, Y. Chen, Beijing, China; P. McCarron, Belfast, UK; B. Møller, Oslo, Norway; F. Montonaro, Genoa, Italy; M Piñeros, Bogotá, Colombia; G. Ronco, Turin, Italy; A. Verdecchia, Rome, Italy; E. de Vries, Rotterdam, Netherlands; B.B. Yeole, Bombay, India

Europe

Within the framework of the CaMon project (see above), a comprehensive and systematic analysis of time trends of incidence and mortality of 23 cancers in Europe is being undertaken, with a central aim of supporting the planning of prevention strategies at the European level. The work started in November 2002 with a workshop of international experts to review the methodological aspects of systematic time trend analyses, discussing issues related to the availability, quality and comparability of cancer incidence and mortality data, the rationale of time trends and predictions of cancer, graphical displays, and the use of statistical models for age–period–cohort analyses and the short-term prediction of future cancer burden.

The analyses are being undertaken at IARC and distributed to a series of cancer-specific expert panels for interpretation and discussion. The working groups consist of cancer registry personnel, a coordinator who is an established authority on the relevant cancer, as well as the IARC staff responsible for the analysis. 89 cancer registry staff from 50 European cancer registries have joined one of the 23 working groups. The task of each working group is to collectively analyse, interpret and publish the incidence and mortality data. The secretariat at IARC has established suitable methodology for the systematic investigation of trends and provided analyses of the trends of each cancer using graphical and statistical approaches (JoinPoint regression, age–period–cohort modelling and short-term predictions). The results of these analyses are now being examined and interpreted by the respective working groups.

The project involves collaboration with other relevant groups. With the European Network for Cervical Cancer Screening (ECCSN), developments in cervical cancer screening programmes in Europe are being examined, to identify potential sources of inadequacies and establish an EU-wide comparable system for monitoring the effect of screening on trends. Figure 6 shows the observed and fitted incidence and mortality trends in the Czech Republic and Finland in two age groups (25–49 and 50 years and over) using the JoinPoint program.

Four projects have been completed by scientists from European cancer registries, who were invited to IARC to investigate temporal trends of cancer in Europe, in collaboration with IARC staff and ENCR member registries. The cancers under study, determined by the particular interests of the visiting scientists, included: (1) breast cancer, for which incidence is increasing but mortality decreasing; countries having national mammographic screening programmes were compared with those having no such programme; (2) malignant cutaneous melanoma, for which incidence and mortality have been rising, but have recently stabilized in western Europe and decreased in Scandinavia; (3) pleural mesothelioma, for which incidence rates are still increasing but are likely to decline in the near future; and (4) lung cancer, for

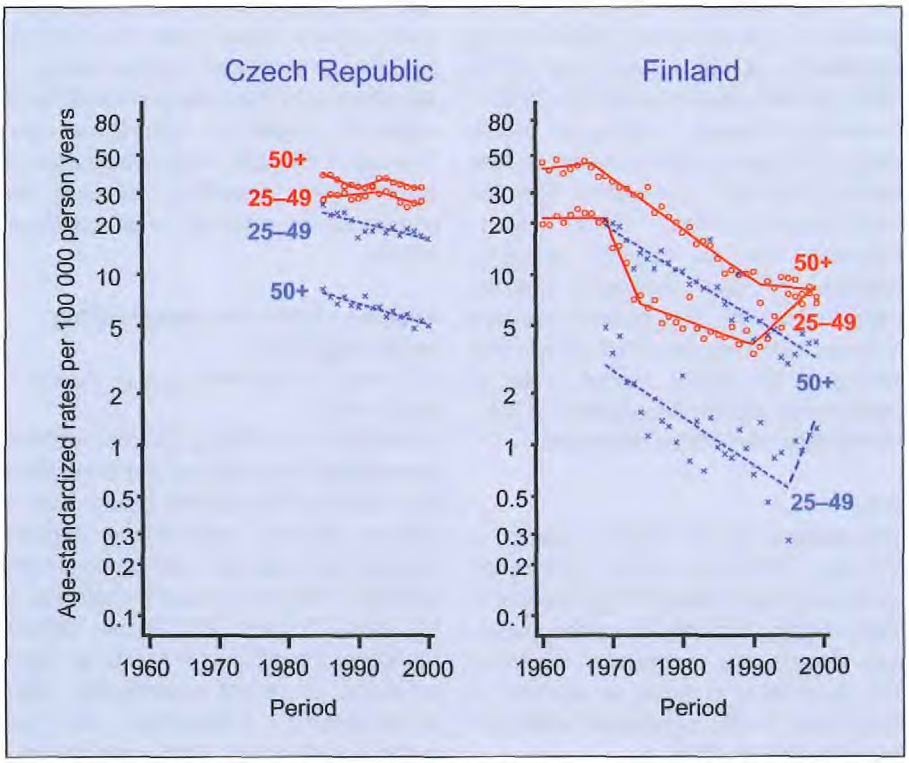


Figure 6. Cervical cancer incidence (o) and mortality (x) trends in younger and older women (20–49 and 50 years and over) in the Czech Republic and Finland (JoinPoint analysis)

which trends were analysed in relation to smoking prevalence.

China

Following a systematic review of sources of data on cancer mortality in China [562], a study of time trends was completed, using data from the surveillance system of the Chinese Centre for Health Information and Statistics for the period 1987–99 (Figure 7). Rates are increasing for, in particular, lung cancer and breast cancer, while for cancers of the oesophagus, stomach and cervix, mortality has declined [563]. These time trend data have been used to prepare national estimates of mortality, based on a representative survey of deaths in 1990–92, and to prepare short-term projections of national mortality for the year 2005 [561].

Colombia

An analysis of time trends for several of the cancers commonly observed in the population served by the cancer registry of Cali, Colombia, for the period 1962–98 has been completed. Included in the analysis is a detailed examination of the contribution of age, period and cohort effects on the incidence rates over time.

In addition, a study involving an examination of recent age and sex-specific time trends (1981–96) of mortality from the most common causes of cancer death in Colombia has considered underlying reasons for the temporal patterns; mortality from the most common cancers is rising, indicating the need for effective strategies for cancer control, while to monitor their impact, the provision of high-quality data needs to be addressed.

India

The database of the cancer registry in Mumbai (Bombay), India, established since the implementation of the register in 1963, is being updated, by entering individual records into a computer database. The purpose is to allow an analysis of time trends in this population, which will take place during 2004.

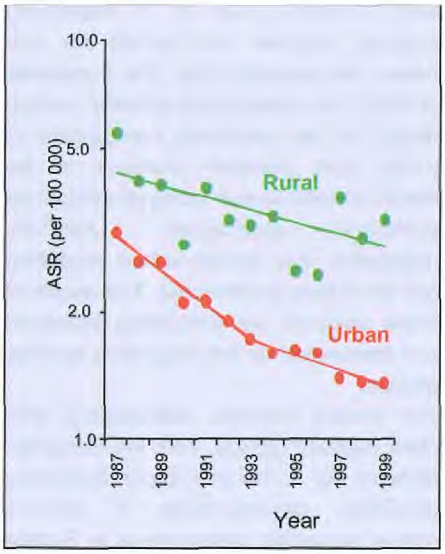


Figure 7. Cervix uteri cancer mortality rates during 1987–99 in China, using age-standardized rate (ASR) and age-specific rates by area

International trends in lung cancer

Worldwide geographical and temporal variations in lung cancer by histological type are being examined using high-quality cancer registry data. The analysis includes an evaluation of the results of adjustments for the varying proportions of cases of unspecified histological type. The role of changes in the composition of manufactured cigarettes, as well as prevalence of smoking, is of particular interest.

Analysis of data from collaborating cancer registries

D.M. Parkin, R. Sankaranarayanan, P. Vizcainio, F. Bray, P. Pisani

Investigators working in cancer registries are assisted in analysing and presenting their data. Priority is given to data-sets of special interest, representing hitherto unpublished material, and to combined analysis of data from several registries in the same country. For African cancer registries, the emphasis has been upon preparing up-to-date submissions, with accompanying commentary, for the publication *Cancer in Africa* (see below).

In Asia, results from the cancer registry in Kolkata (India) were published – the first data on cancer patterns in this populous region. An analysis of the incidence of cancer of the nasopharynx in the indigenous peoples of Sarawak (Malaysia) was completed; among these native Malays, the Bidayuh population was shown to have a particularly high risk for this cancer.

A review of the geography and temporal variation of cervix cancer in Latin America was completed [15]. Time trends of incidence in 1962–97 and mortality in 1984–2001 of the three most common cancers in each sex (prostate, stomach and lung cancer in males, and breast, cervix and stomach cancer in females) in Cali (Colombia) are now being analysed.

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 an analysis of time trends in incidence of carcinoma of the oesophagus and gastric cardia, by histological type, [540] and a similar study of lung cancer. A comparative study of time trends in gastric cancer incidence, mortality and survival in Japan (Osaka), Slovenia and the USA was completed [256].

Time trends in breast cancer incidence and mortality in Yorkshire (UK) have been analysed. Age-standardized mortality rates declined by 25% between 1982–84 and 1997–99, accompanied by an improvement in survival. Around 30% of the improvement in survival in cases under 65 years could be attributed to a more favourable stage at diagnosis, whereas this accounted for all of the 17% relative improvement in survival among older cases. A study to measure the contribution of death certificates to the completeness and quality of the data has been carried out in Manila (the Philippines) [513].

While demographic changes are increasing, the burden of cancer in Colombia, changes in the mortality rates are also apparent and are indicative of changes in the risk of cancer death. A

study of recent time trends (1981–96) in the most common causes of cancer death in Colombia by sex and age includes some interpretation of the underlying reasons for the temporal patterns observed.

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

Worldwide burden of cancer

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

The estimates of the incidence, mortality and prevalence of cancer at 25 sites have been updated to the year 2002. The estimates are made at country level, by sex and five broad age groups. They are based on the most recent incidence and mortality rates, together with population estimates for the year 2002. They are available using the GLOBOCAN 2000 software (published in the IARC electronic publication series as CancerBase No. 5), into which these new estimates may be downloaded from the CANCER*Mondial* Internet site. A simplified version with limited options is also available on the Internet (Section 7.1).

Cause-attributable cancer

P. Pisani, P. Boffetta, D.M. Parkin, E. Riboli, R. Saracci; in collaboration with H.-O. Adami, Stockholm, Sweden; D. Easton, N.E. Day, Cambridge, UK; K. Hemminki, Heidelberg, Germany; M. Kogevinas, Barcelona, Spain

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. We are 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, HIV and human T-cell lymphotropic virus (HTLV)-I), parasites (*Schistosoma* and liver flukes) or bacteria (*H. pylori*); the corresponding figure in developed areas is estimated to be 9%.

With the support of the Europe Against Cancer Programme, detailed calculations for the countries of the EU have been completed for several factors. 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 EU, 5% of all cancers were attributed to excess body weight (3% in men, 6% in women). Among female cancers, 11% are attributed 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.

The estimates are now being updated to include the new Member States of the EU.

Cancer in Africa

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

Until quite recently, knowledge of cancer patterns in Africa was based mainly on the work of pioneering clinicians and pathologists, who published clinical and pathological case series in the 1950s and 1960s. The new publication *Cancer in Africa* describes all past and present cancer registration activities in Africa, and presents the results. In addition to tables of incidence rates, the results from registries for which no realistic population at risk could be derived, or for which calculated rates were considered by the editors to be too misleading, are reproduced as tables showing numbers of cases, by age group and sex, with the percentage frequencies by site and sex. To accompany the country-by-country description of cancer profiles, some background material on each country is presented, together with a review of all published literature on the cancer profile in the country.

This comprehensive review of the epidemiology and prevention of 20 major cancers of importance on the African continent draws upon all significant studies on the African continent over the last 50 years. Special chapters consider cancer in children and cancers related to AIDS. A CD-ROM provided with the volume allows the user to analyse the data from the contributing registries.

Nasopharyngeal carcinoma in migrants to the United States

F. Bray; in collaboration with L. Mu, Shanghai, China

Nasopharyngeal carcinoma (NPC) has a distinct racial and geographical distribution, with both genetic and environmental risk factor components. Migrant studies provide an opportunity to gain insight into their relative etiological contributions. This study updates estimates of risk of NPC among migrants to the USA from high-risk areas and their offspring, relative the US-born population.

Data from the Surveillance, Epidemiology, and End Results (SEER) programme in the USA for the period 1973–99 were abstracted using the SEERStat software package, by race (white, black, American Indian/Alaskan, Chinese, and south-east Asian) and place of birth (United States, China, North Africa, south-east Asia). Nested logistic regression models were used to estimate the relative risk of NPC according to interactions between race, period of diagnosis and place of birth, adjusted for age and sex. 3422 histologically confirmed NPC cases and 1 902 889 other cancer controls were included in the study.

Among all subjects born in the USA, ethnic Chinese had the highest risk (relative to whites) for every birthplace, the relative risk ranging from about 25 in China-born to over 50 in south-east Asia-born. Moderately increased risks were observed among south-east Asians and American Indians/Alaskans, and a slight excess was also seen in blacks, all

relative to whites. Comparisons according to place of birth suggested that US-born descendants of migrants from China retain two thirds of the risk of NPC relative to their parents. However, the diminution in risk was more striking in south-east Asians, for whom the risk in descendants was only a quarter of that in first-generation migrants. The difference in risk diminution between Chinese and south-east Asians may be explained by (*a*) a higher genetic predisposition to NPC among Chinese; (*b*) certain risk factors related to Chinese lifestyle which are slow to change upon migration; or (*c*) a higher prevalence of certain EBV genotypes in Chinese and their migrants.

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. Several studies of radiation as a cause of childhood cancer are described in Section 2.6.

Automated Childhood Cancer Information System (ACCIS)

E. Šteliarová-Foucher, D.M. Parkin, N. Mitton, M.T. Valdivieso-Gonzales; in collaboration with F. Berrino, Milan, Italy; J.W.W. Coebergh, Eindhoven, Netherlands; P. Kaatsch, Mainz, Germany; B. Lacour, Nancy, France; C.A. Stiller, Oxford, UK

Supported by the European Commission

Cancer in childhood differs in many respects from cancer occurring in adults. The Automated Childhood Cancer Information System (ACCIS) is a project to collect, present, interpret and disseminate data on childhood cancer in Europe.

With the collaboration of some 80 population-based cancer registries, including a dozen specialized paediatric registries, data have been assembled on some 160 000 cases of cancer in children and adolescents (age-range 0–19 years), diagnosed across Europe since 1970, constituting the world's largest database of such information. In mid-2003, a new round of data collection was initiated to update the database, which will bring the coverage up to the year 2000. Incidence rates and survival can be calculated by sex, period of incidence, age-group, tumour type and method of diagnosis.

The ACCISpass 1.01 software has been released and distributed to all contributing registries. This permits access to the ACCIS database and calculates incidence and survival rates for selected subsets of records. A new version, permitting analyses for user-defined groups of patients, is in preparation.

On the web site of the ACCIS project (http://www-dep.iarc.fr/accis.htm), information on incidence and survival of children and adolescents in Europe is presented in over 100 tables. A software package providing more comprehensive data and analysis tools is under development.

The collected data are disseminated to all those interested, in order to encourage research into causes of childhood cancer and to evaluate progress in patient management on a population basis. Analysis and interpretation of the data is carried out by the ACCIS collaborators (see below).

Descriptive studies of cancer in childhood

E. Šteliarová-Foucher, D.M. Parkin, H.-M. Yang, N. Mitton; in collaboration with P. Kaatsch, Mainz, Germany; B. Lacour, Nancy, France; C.A. Stiller, Oxford, UK; and ACCIS collaborators

Within the framework of ACCIS (see above), a coordinated action for exploration of the ACCIS database and interpretation of results was launched in 2003. The aim is to process the large quantity of information contained in the

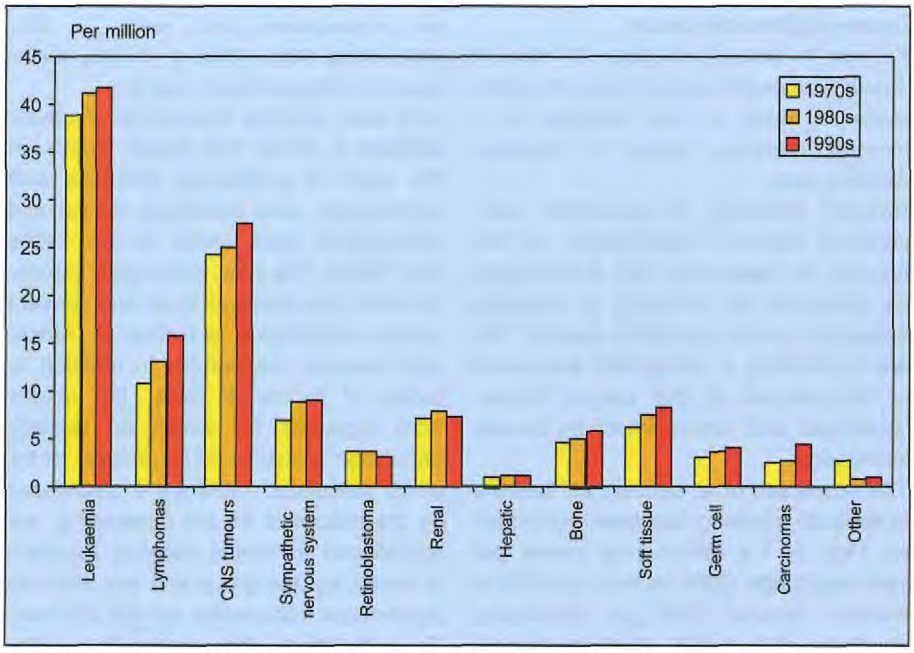


Figure 8. Age-standardized cancer incidence rates, Europe (ACCIS database), age 0–14 years

database and to disseminate the results to the scientific community. In collaboration with some thirty epidemiologists and clinicians, general issues of childhood cancer incidence and survival over the last thirty years, as well as selected tumour types, have been reviewed.

Incidence and survival of children in Zimbabwe has been studied in collaboration with Harare Cancer Registry. This is the first population-based description of cancer survival in Africa and the dismal level of survival (20% overall five-year survival) reflects the lack of support for the treatment of childhood cancer, but also the late presentation due to lack of awareness (the 33% five-year survival from retinoblastoma).

In a study of incidence of brain tumours in Costa Rican children for the period 1981–96, possible reasons for the low incidence rates were examined. The age-standardized rate of brain tumours was 15.3 per million, about half of that observed in developed countries. This may be explained by under-diagnosis, notably the lack of non-invasive diagnostic methods, in contrast to areas where magnetic resonance imaging is available for diagnosis.

A special chapter of the volume *Cancer in Africa* (see above) was devoted to epidemiology of childhood cancer.

The data published in the volumes of *International Incidence of Childhood Cancer* were used to analyse the pattern of leukaemia incidence and distribution across different population groups around the world. A peak of occurrence of lymphoid leukaemia in young children aged 2–3 years is associated, especially in the developed countries, with white ethnic origin and seems to be related to both the ethnic group and the socioeconomic level of the country (see Figure 9). Comparison of the data from the 1970s and 1980s, the periods covered in the two volumes, revealed a slight upward tendency in the incidence rates.

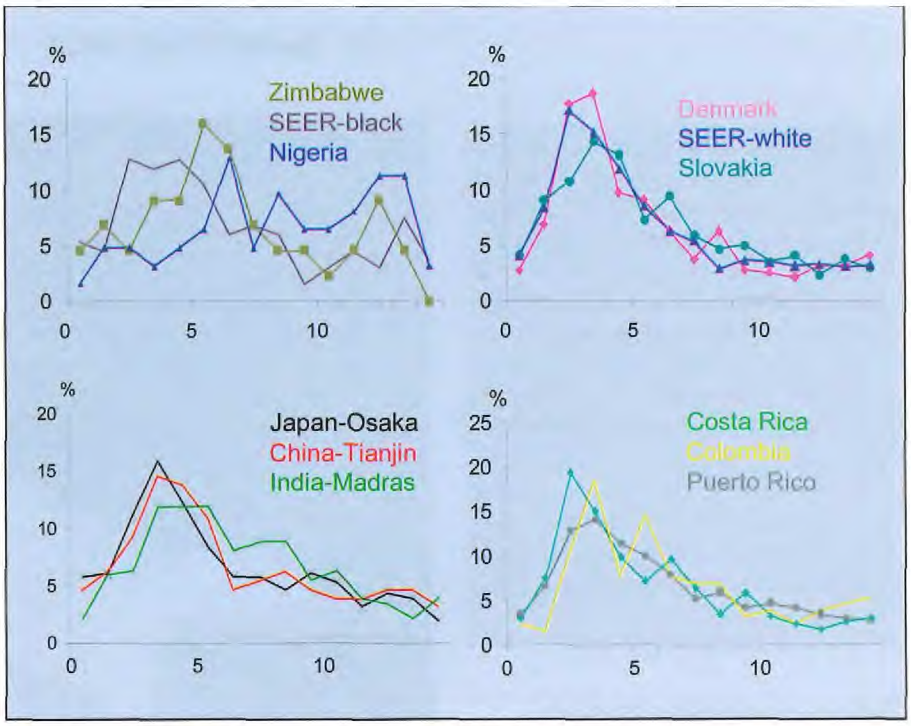


Figure 9. Lymphoid leukaemia occurrence in the 1980s: age distribution

Neonatal tumours

A.J. Sasco; *in collaboration with* S.W. Moore, Cape Town, South Africa; J. Plaschkes, A. Zimmermann, Bern, Switzerland; R.C. Rudigoz, Lyon, France; D. Satgé, Tulle, France

Neonatal tumours, including malignant ones, represent a unique opportunity to study the natural history of cancer and tumour development in general and may provide insights for cancer therapy opportunities. An international working group has been set up to review the epidemiology [316], prepare a concept paper and draw up specific plans to study these rare tumours, including etiological issues, taking advantage of the short period of exposures and molecular approaches to elucidate cellular and genetic mechanisms of proliferation, differentiation and regression. Links between fetal and tumour development clearly need to be better studied [430].

Besides cancers, 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 on date and hospital of birth indicate that slightly more girls than boys are affected and that angiomas are more frequent among children born to mothers who had problematic pregnancies and had taken drug treatment. The risk of angiomas is also higher among children born in families already affected by this disease.

1.4 Survival from cancer

Population-based estimates of survival among 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 and thus provide valuable leads for the planning and improvement of national and regional cancer control strategies. Only limited population-based data are available on cancer survival in developing countries.

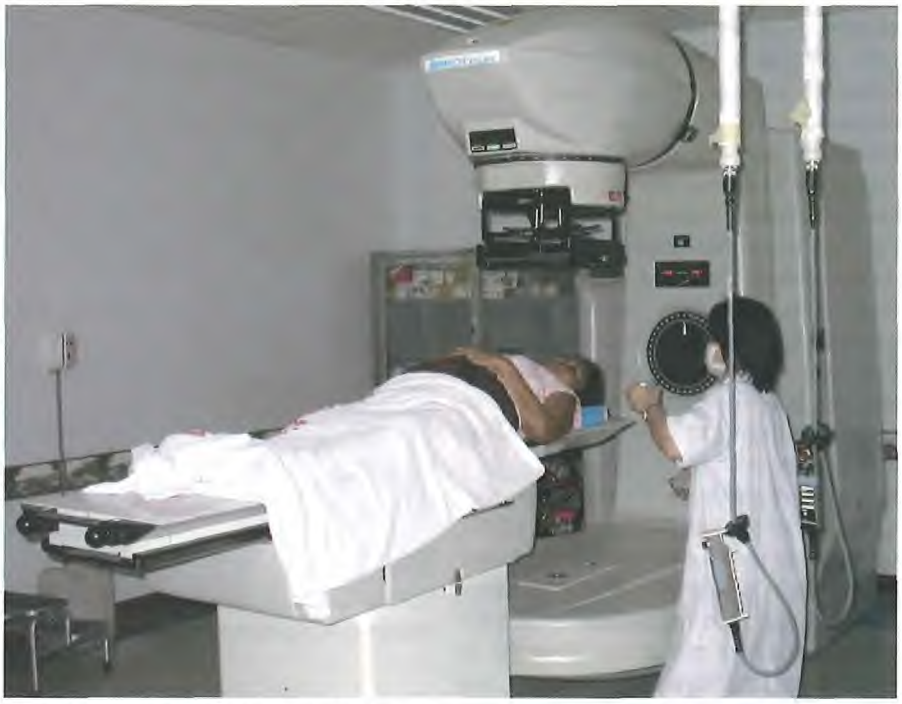


Figure 10. A patient in Thailand undergoing radiotherapy

Survival in developing countries

R. Sankaranarayanan, D.M. Parkin, R. Sankila, R. Kumar; in collaboration with: *Algeria*, M. Hamdi-Cherif, Sétif; *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; *Gambia*, E. Bah; *Germany*: H. Brenner, A. Gondos, Heidelberg; *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, R. Swaminathan, Chennai; P. Gangadharan, K. Jayalakshmi, Karunagapppalli; B.B. Yeole, L. Sunny, Mumbai; *Pakistan*, Y. Bhurgri, Karachi; *Philippines*, D. Esteban, Manila; *Singapore*, H. Lee, K. Chia; *Thailand*, V. Lornvidhaya, S. Srisukho, Chiang Mai; S. Sriamporn, S. Wiangnon, Khon Kaen; *Turkey*: S. Eser, Izmir; *Uganda*, H. Wabinga, S. Nambooze, Kampala; *UK*, R.J. Black, Edinburgh; *Zimbabwe*, L. Levy, M. Bassett, B. Mauchaza, E. Chokunonga, Harare

Population-based survival data provide an important indicator for evaluating the efficiency of cancer health services in a region. A collaboration has been established with population-based cancer registries to describe the overall and stage-specific survival experience of cancer patients registered during 1990–1999 in populations in China (Beijing, Qidong, Shanghai, Tianjin), Costa Rica, Colombia (Cali), Cuba, The Gambia, India (Ahmedabad, Bhopal, Chennai, Karunagappalli, Kolkata, Mumbai), Pakistan (Karachi), The Philippines (Manila, Rizal-DOH), Republic of Singapore, Thailand (Chiang Mai, Khon Kaen), Uganda (Kampala), Viet Nam (Ho Chi Minh City) and Zimbabwe (Harare). The registries use a variety of active and passive methods to obtain follow-up information on the vital status of incident cases and provide data on all incident cases for the period under study for all cancer sites (or selected sites in the case of certain registries). The data are subjected to uniform quality (proportion of cases with histological verification of diagnosis, proportion of cases registered based on a death certificate only) and validation checks.

Analysis of data for Singapore, Mumbai, Chiang Mai and Khon Kaen has been completed. Details of survival for selected cancers from these registries are given in Table 1. Results for selected cancer sites for Singapore, Mumbai and Kampala have been published [137,408,542,543]. Data analysis for Qidong and Shanghai (China), Chennai, Barshi, Karunagappalli and Bhopal (India), Harare (Zimbabwe) and Kampala (Uganda) is in progress. A monograph to present the findings is in preparation.

Table 1. Five-year relative survival (%) for selected cancers in India and Thailand

Registry	Colon	Rectum	Breast	Cervix	Ovary	Leukaemia	Lymphoma
Thailand							
Chiang Mai	31.6	30.4	62.8	60.7	48.7	13.7	30.0
Khon Kaen	43.5	43.5	63.9	56.8	61.4	NA	47.1
India							
Mumbai	34.3	30.4	46.8	47.8	25.0	16.0	37.7

NA, not available

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.

Aflatoxin exposure through *Aspergillus*-infested groundnuts

2.1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* are a series of consensus reports developed by international working groups of scientific experts. Since 1971 there have been 86 volumes evaluating the carcinogenic hazard of nearly 900 agents. These can be individual chemicals, groups of related chemicals, complex mixtures, occupational exposures, pharmaceutical treatments, cultural or lifestyle habits, physical agents or biological agents. Lists of evaluations, summaries of each evaluation, and the principles used in developing these evaluations, are available at http://monographs.iarc.fr.

Each Monograph considers the available evidence of carcinogenicity in humans, the evidence of carcinogenicity in experimental animals, and other data relevant to the evaluation of carcinogenicity and its mechanisms. An overall evaluation indicates the consensus determination about whether the agent poses a carcinogenic hazard to humans. The 889 agents and exposure conditions evaluated so far have been classified as follows:

Group 1	*Carcinogenic to humans*	*91 agents*
Group 2A	*Probably carcinogenic to humans*	*64 agents*
Group 2B	*Possibly carcinogenic to humans*	*238 agents*
Group 3	*Not classifiable as to carcinogenicity to humans*	*495 agents*
Group 4	*Probably not carcinogenic to humans*	*1 agent*

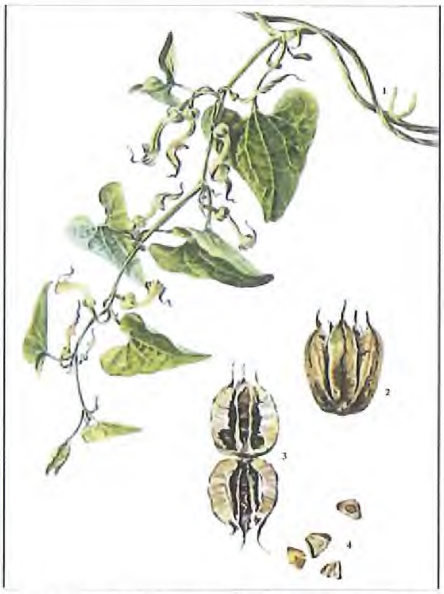


Figure 11. *Aristolochia contorta*, used for various therapeutic purposes in Chinese traditional medicine, contains aristolochic acids

V.J. Cogliano, R.A. Baan, K. Straif, Y. Grosse, B. Secretan, F. El Ghissassi, J.M. Rice, C. Partensky, L. Stayner, E. Suonio, E. Perez, S. Egraz, M. Lézère, J. Mitchell. Scientists from other IARC units have contributed to the Programme: P. Boffetta, P. Brennan, J. Cheney, R. Durusoy, S. Franceschi, M.D. Friesen, P. Hainaut, M. Hashibe, R. Hung, S. Lewis, A. 't Mannetje, N. Napalkov, H. Ohgaki, H. Ohshima, R. Sankaranarayanan, A.J. Sasco, V. Sewram, M. Shen, J. Smith, S.V. Tavtigian, J.E. Tyczynski, S. Vaccarella, H. Vainio

Working groups were convened to develop five new volumes (Nos. 82–86) during 2002–03. In addition, an Advisory Group consisting of scientists from national and international health agencies and research institutions was convened to advise on priorities for future evaluations. Such guidance ensures that future Monographs are relevant to the needs of IARC's Participating States and the public health community and that they also reflect the current state of scientific research.

Some traditional herbal medicines, some mycotoxins, naphthalene and styrene (Volume 82, February 2002)

A working group of 29 scientific experts from 15 countries evaluated the evidence of carcinogenicity for some traditional herbal medicines, some mycotoxins, naphthalene and styrene.

Traditional herbal medicines encompass an extremely diverse group of preparations that originate from many different cultures. In recent years, such products have become widely available in developed countries and are sometimes marketed for uses, for example weight loss regimens or enhancement of athletic performance, that were never contemplated in the traditional healing systems from which they emerged. In many countries, herbal medicines are not subject to rigorous standards with respect to manufacturing, efficacy, quality and safety.

Following an outbreak of rapidly progressing renal fibrosis in Belgium and elsewhere among women undergoing a body-weight loss regimen that involved a mixture of Asian herbs, a high prevalence of urothelial tumours of the renal pelvis, the ureter and the urinary bladder was correlated with consumption of the herbal mixture, which contained aristolochic acids. The working group evaluated herbal remedies containing plant species of the genus *Aristolochia* (Figure 11) as *carcinogenic to humans* (Group 1) and naturally occurring mixtures of aristolochic acids as *probably carcinogenic to humans* (Group 2A).

Herbs containing anthraquinone derivatives have been widely used as laxatives. In animal experiments, 1-hydroxyanthraquinone induced intestinal adenocarcinomas in rats, and the herb madder root (*Rubia tinctorum*), which contains 1,3-dihydroxy-2-hydroxymethylanthraquinone, caused slight increases in hepatocellular carcinomas and adenomas and carcinomas of the renal cortex in rats. The working group evaluated 1-hydroxyanthraquinone as *possibly carcinogenic to*

humans (Group 2B) and madder root as *not classifiable as to human carcinogenicity* (Group 3).

Riddelliine is a pyrrolizidine alkaloid found in several *Senecio* species, including *S. longilobus*, which is used as a herbal tea in the southwestern USA. Riddelliine induced hepatic haemangiosarcomas in male and female rats and in male mice, bronchiolo-alveolar adenomas and carcinomas in female mice, and hepatocellular carcinomas and/or adenomas and mononuclear cell leukaemia in male and female rats. The working group evaluated riddelliine as *possibly carcinogenic to humans* (Group 2B).

Some mycotoxins. Fumonisin B_1 is the most prevalent member of a family of toxins produced by several species of the fungal genus *Fusarium.* These fungi occur mainly in maize, which is infected before harvest, leading to human exposure at levels of micrograms to milligrams fumonisin B_1 per day. Purified fumonisin B_1 induced hepatocellular adenomas and carcinomas in female mice, cholangiofibrosis and hepatocellular carcinomas in male rats in one study, and renal tubule carcinomas in male rats in another. Disruption by fumonisin B_1 of sphingolipid, phospholipid and fatty acid metabolism appears to be an important aspect of the mode of toxic action of this compound, including its carcinogenicity in animals. This metabolic disruption has been observed in a many animal species after exposure to fumonisin B_1, and in a single human study. The working group evaluated fumonisin B_1 as *possibly carcinogenic to humans* (Group 2B).

In an update of the data on the carcinogenicity of aflatoxins, the Working Group reaffirmed the previous evaluation of naturally occurring aflatoxins as *carcinogenic to humans* (Group 1).

Naphthalene is a commercially important aromatic hydrocarbon produced from coal tar and petroleum. Human exposure can occur during its production, during its use as an industrial intermediate, from cigarette smoking, in creosote treatment of wood and during its use as a moth-repellent. No relevant data were available on the carcinogenicity of naphthalene to humans. In inhalation studies, naphthalene caused an increase in the incidence of bronchio-alveolar adenomas in female mice, and of neuroblastomas of the olfactory epithelium and adenomas of the nasal respiratory epithelium in male and female rats. These results led the working group to evaluate naphthalene as *possibly carcinogenic to humans* (Group 2B).

Styrene is used extensively in the manufacture of polystyrene resins and in co-polymers with acrylonitrile and 1,3-butadiene (reinforced plastics). Exposure of the general population to styrene occurs at levels of micrograms per day, due mainly to inhalation of polluted ambient air and cigarette smoke, and intake of food that has been in contact with styrene-containing polymers. Cohort studies in the production of styrene monomer and polymers, of glass-reinforced plastics and of styrene–butadiene rubber provided limited evidence of carcinogenicity in humans. There was also limited evidence of carcinogenicity in experimental animals, based on an increase in lung tumours in mice, but not in rats, after inhalation exposure. These tumours probably arise from *in situ* formation of styrene-7,8-oxide. The working group evaluated styrene as *possibly carcinogenic to humans* (Group 2B).

Tobacco smoke and involuntary smoking (Volume 83, June 2002)

Tobacco smoking is practised worldwide by over one thousand million people. While its prevalence has declined in many developed countries, it remains high in others and is increasing among females and in developing countries. Between one-fifth and two-thirds of men in most populations smoke. Rates of smoking among women vary more widely but rarely equal those of men.

The major cause of lung cancer (the most common fatal cancer in the world) is tobacco smoking, primarily of cigarettes. In populations with prolonged cigarette use, the proportion of lung cancer cases attributable to cigarette smoking has reached 90%. Stopping smoking at any age avoids the further increase in risk of lung cancer incurred by continued smoking; the younger the age at cessation, the greater the benefit.

Tobacco smoking and tobacco smoke. The working group evaluated tobacco smoking and tobacco smoke *as carcinogenic to humans* (Group 1). In the previous *IARC Monograph* on *Tobacco Smoking* (Volume 38, 1986), cancers of the lung, oral cavity, pharynx, larynx, oesophagus (squamous-cell carcinoma), pancreas, urinary bladder and renal pelvis were identified as caused by cigarette smoking. Many subsequent studies support these causal links. In addition, there is now sufficient evidence for a causal association between cigarette smoking and cancers of the nasal cavities and nasal sinuses, oesophagus (adenocarcinoma), stomach, liver, kidney (renal-cell carcinoma), uterine cervix and myeloid leukaemia (Table 2).

Cigar and/or pipe smoking is strongly related to cancers of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus, the magnitude of risk being similar to that from cigarette smoking. These risks increase with the amount of cigar and/or pipe smoking and with the combination of alcohol and tobacco consumption. Cigar and/or pipe smoking is causally associated with cancer of the lung and there is evidence that cigar and/or pipe smoking are also causally associated with cancers of the pancreas, stomach and urinary bladder.

Bidi smoking is the most common form of tobacco smoking in India and is also prevalent in other south-Asian countries; it is also an emerging problem in the USA. *Bidi* smoke was evaluated as carcinogenic in *IARC Monographs* Volume 38 and later studies have provided further evidence of causality, with strong associations with cancer at various sites: oral cavity (including subsites), pharynx, larynx, oesophagus, lung and stomach. Almost all studies show significant trends with duration of *bidi* smoking and number of *bidis* smoked.

The studies reviewed found evidence of synergy (that is, a combined effect that is more than additive) between smoking and several occupational causes of lung cancer (arsenic, asbestos and radon), and between smoking and alcohol consumption for cancers of the oral cavity, pharynx, larynx and oesophagus and between smoking and human papillomavirus (HPV) infection for cancer of the cervix. Data were inadequate to evaluate the evidence for synergy between smoking and other known causes of cancer (e.g., hepatitis B and alcohol for liver cancer).

Causal associations have been clearly established between active smoking and adverse reproductive outcomes and numerous non-neoplastic diseases, including chronic obstructive pulmonary disease and cardiovascular diseases.

Involuntary (or passive) smoking is exposure to secondhand (or "environmental") tobacco smoke, which is a mixture of exhaled mainstream smoke and sidestream smoke released from a smouldering cigarette or other smoking device (cigar, pipe, *bidi* etc.). Involuntary smoking involves inhaling carcinogens and other toxic components that are present in the tobacco smoke produced by active smoking.

Table 2. Sites of cancers evaluated as caused by tobacco smoke in the *IARC Monographs* programme

Organ	Relative risk
1986 evaluation (Vol. 38)	
Lung	20–30
Bladder and renal pelvis	5–6
Oral cavity	4–5
Pharynx	4–5
Larynx	4–5
Oesophagus (squamous cell)	4–5
Pancreas	3–4
Additional sites in 2002 evaluation (Vol. 83)	
Kidney	2–3
Stomach	2–3
Oesophagus (adenocarcinoma)	2–3
Liver	2–3
Nasal cavities and sinuses	2–3
Myeloid leukaemia	2–3
Uterine cervix	2

There is currently no evidence that smoking causes breast, prostate or endometrial cancer.

More than 50 studies of involuntary smoking and lung cancer risk in never-smokers, particularly spouses of smokers, have mostly shown an increased risk, especially for persons with higher exposures. Meta-analyses in which the relative risk estimates from individual studies were pooled together have shown a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand tobacco smoke from the spouse who smokes. The excess risk, of the order of 20% for women and 30% for men, remains after controlling for some potential sources of bias and confounding. The excess risk increases with higher exposure. Other meta-analyses of lung cancer in never-smokers exposed to secondhand tobacco smoke at their workplace have found a statistically significant increased risk of 16–19%. This evidence is sufficient to conclude that involuntary smoking is a cause of lung cancer in never-smokers. The magnitudes of the observed risks are reasonably consistent with predictions based on studies of active smoking in many populations. The working group evaluated involuntary smoking as *carcinogenic to humans* (Group 1).

In humans, concentrations of adducts of carcinogens to biological macromolecules, including haemoglobin adducts of aromatic amines and albumin adducts of polycyclic aromatic hydrocarbons, are higher in adult involuntary smokers and in the children of smoking mothers than in individuals not exposed to secondhand tobacco smoke. Protein adduct concentrations in fetal cord blood correlate with those in maternal blood but are lower. A few studies of DNA adduct levels in white blood cells of exposed and unexposed non-smokers have mostly failed to find clear differences. Urinary levels of metabolites of the tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, are consistently elevated in involuntary smokers, though only 1–5% as great as those in smokers. Data on uptake by non-smokers of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a lung carcinogen in rodents, support a causal link between exposure to secondhand tobacco smoke and development of lung cancer. There is sufficient evidence in experimental animals for the carcinogenicity of sidestream smoke condensates. The genotoxicity of sidestream smoke, 'environmental' tobacco smoke, sidestream smoke condensate or a mixture of sidestream and mainstream smoke condensates has been demonstrated in experimental systems *in vitro* and *in vivo*.

Involuntary smoking has been associated with a number of non-neoplastic diseases and adverse effects in never-smokers, including both children and adults. Epidemiological studies have demonstrated that exposure to secondhand tobacco smoke is causally associated with coronary heart disease. From the available meta-analyses, it has been estimated that involuntary smoking increases the risk of an acute coronary heart disease event by 25–35%. Adverse effects of involuntary smoking on the respiratory system have also been detected in children and in adults. Some effects on lung function have been detected, but their medical relevance is uncertain. Maternal cigarette smoking has repeatedly been associated with adverse effects on fetal growth; full-term infants born to women who smoke weigh about 200 g less than those born to non-smokers. A smaller adverse effect has been attributed to maternal passive smoking.

Some drinking-water disinfectants and contaminants, including arsenic

(Volume 84, October 2002)

A working group of 23 experts from 13 countries met in Lyon to evaluate the evidence for carcinogenicity of arsenic (mostly naturally occurring) as a contaminant of drinking-water, and of the water-disinfectant chloramine. The working group also evaluated or re-evaluated four chlorination by-products found in drinking-

water, namely chloral hydrate, di- and trichloroacetic acids, and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (also known as MX).

Arsenic and arsenic compounds were previously evaluated in Supplement 7 of the IARC Monographs (1987) as *carcinogenic to humans* (Group 1), on the basis of sufficient evidence for an increased risk for skin cancer among patients exposed to inorganic arsenic through medical treatment and an increased risk for lung cancer among workers involved in mining and smelting who inhaled inorganic arsenic. High-level exposure to arsenic in drinking-water occurs in some regions of China, South America, Bangladesh and West Bengal. After reviewing epidemiological studies, the Working Group evaluated arsenic in drinking-water (primarily inorganic, as arsenate and to a lesser extent arsenite) as *carcinogenic to humans* (Group 1), on the basis of sufficient evidence for an increased risk for cancer of the urinary bladder, lung and skin. Studies on inorganic arsenic in experimental animals provided limited evidence for its carcinogenicity, but evidence was considered sufficient for the carcinogenicity of dimethylarsinic acid (an organic form of arsenic) in experimental animals, on the basis of urinary bladder tumours in rats and lung tumours in mice after oral administration.

Chloramine is used increasingly in disinfection of drinking-water. In the absence of data on human cancer and on the basis of inadequate evidence for the carcinogenicity of monochloramine in experimental animals, chloramine was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3).

As in previous evaluations (Volume 63, 1995), chloral hydrate and trichloroacetic acid were evaluated as *not classifiable as to their carcinogenicity to humans* (Group 3) because of the lack of data on human cancer for these compounds and limited evidence for their carcinogenicity in experimental animals. Dichloroacetic acid, previously classified in Group 3 (Volume 63, 1995), was re-evaluated as *possibly carcinogenic to humans* (Group 2B) in the absence of data on human cancer, on the basis of sufficient evidence of its carcinogenicity in experimental animals. It caused hepatocellular adenomas and/or carcinomas when administered orally to mice and rats.

No data on human cancer were available for MX and there was limited evidence for its carcinogenicity in experimental animals, from a single bioassay in male and female rats in which benign and malignant thyroid and mammary tumours were induced. However, MX was evaluated as *possibly carcinogenic to humans* (Group 2B), taking account of the fact that it is a potent direct-acting mutagen in bacterial and mammalian cells, a chromosomal mutagen *in vitro* and *in vivo* and an inducer of thyroid gland tumours by mechanisms other than promotion of thyroid-stimulating hormone.

Betel-quid and areca-nut chewing and some areca-nut related nitrosamines
(Volume 85, June 2003)

A working group of 16 experts from seven countries re-evaluated the evidence of the carcinogenicity of betel-quid and areca-nut chewing and some areca-nut related nitrosamines. Betel-quid and areca-nut chewing are widely practised in many parts of Asia and in Asian-migrant communities elsewhere in the world. There are hundreds of millions of users worldwide (Figure 12).

The working group evaluated betel quid with tobacco as *carcinogenic to humans* (Group 1) on the basis of sufficient evidence of increased risk of cancer of the oral cavity, pharynx and oesophagus from epidemiological studies of human cancer, mainly from India and Pakistan. Studies on betel quid with tobacco and areca nut with tobacco in experimental animals now also provide sufficient evidence of carcinogenicity.

The working group evaluated betel quid without tobacco as *carcinogenic to humans* (Group 1), on the basis of sufficient evidence of increased risk of oral cancer. Recent epidemiological studies from India and Pakistan and studies in Taiwan (China), where tobacco is not added to betel quid, allowed the effect of betel quid with and without tobacco to be disentangled. Studies on betel quid without tobacco and areca nut without tobacco in experimental animals now also provide sufficient evidence of carcinogenicity.

Areca nut, a common ingredient of betel quid and many different chewing preparations, including those available commercially, has been observed to cause oral submucous fibrosis (a pre-cancerous condition that can progress to malignant oral cancer). The working group evaluated areca nut as *carcinogenic to humans* (Group 1), on the basis of sufficient evidence of carcinogenicity in experimental animals, induction of oral submucous fibrosis in humans and strong mechanistic evidence.

Four areca-nut-related nitrosamines were evaluated in Supplement 7 of the IARC Monographs (1987). In experimental animals, there was sufficient evidence of the carcinogenicity of 3-(methylnitrosamino)-propionitrile (MNPN) and inadequate evidence of the carcinogenicity of *N*-nitrosoguvacoline (NGL). No data were available to assess the carcinogenicity of *N*-nitrosoguvacine (NGC) or 3-(methylnitrosamino)propionaldehyde (MNPA). No data on humans were available. There is now limited evidence of the carcinogenicity of MNPA. As in the previous evaluations, MNPN was evaluated as *possibly carcinogenic to humans* (Group 2B), and the other three areca-nut related nitrosamines were evaluated as *not classifiable as to human carcinogenicity* (Group 3).

Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide (Volume 86) (7–14 October 2003)

A working group of 17 experts from 10 countries met in Lyon to evaluate the evidence of carcinogenicity of metallic cobalt particles with or without tungsten carbide, to which workers in the hard-metal industry are exposed, and of cobalt sulfate and other soluble cobalt (II) salts. It also evaluated three other

Figure 12. Betel quid components for sale in a Phnom Penh market (courtesy of Professor Peter A. Reichart)

particulate compounds: gallium arsenide and indium phosphide, which are used extensively in the microelectronics industry; and vanadium pentoxide, a contaminant at facilities refining and processing vanadium-rich ores and in various workplaces that use oil-fired boilers and furnaces.

Cobalt and cobalt compounds were previously evaluated in Volume 52 of the IARC *Monographs* (1991) as *possibly carcinogenic to humans* (Group 2B), with *inadequate evidence* of carcinogenicity in humans, and, in particular, *sufficient evidence* for the carcinogenicity of cobalt metal powder in experimental animal on the basis of an increased incidence of sarcomas at injection sites, though no inhalation studies of the metal were reported. Since that evaluation, an animal carcinogenesis bioassay of inhaled cobalt sulfate heptahydrate reported an increase in bronchiolo-alveolar neoplasms in exposed male and female mice and rats. In addition, several epidemiological studies addressed cancer risks among workers exposed to dusts containing cobalt with or without tungsten carbide in hard metal production facilities. Those conducted in France provided evidence of an increased lung cancer risk related to exposure to hard-metal dust containing cobalt and tungsten carbide, taking into account potential confounding by smoking and other occupational carcinogens. Hence, cobalt metal with tungsten carbide was evaluated as *probably carcinogenic to humans* (Group 2A) on the basis of *limited evidence* in humans for increased risk of lung cancer and *sufficient evidence* in experimental animals for the carcinogenicity of cobalt sulfate and of cobalt metal powder. The evidence of carcinogenicity for exposure to cobalt in the absence of tungsten carbide was considered *inadequate*, so that with *sufficient evidence* in experimental animals for the carcinogenicity of cobalt sulfate and of cobalt metal powder, the overall evaluation of cobalt metal without tungsten carbide was *possibly carcinogenic to humans* (Group 2B). Cobalt sulfate and other soluble cobalt (II) salts were evaluated as *possibly carcinogenic to humans* (Group 2B).

Gallium arsenide was evaluated as *carcinogenic to humans* (Group 1). For gallium arsenide itself, no data on human cancer were available and the evidence of carcinogenicity in experimental animals was considered *limited* based on increased incidence of bronchiolo-alveolar neoplasms observed in female rats in one study. However, once in the body, gallium arsenide releases a small amount of its arsenic moiety, which behaves as inorganic arsenic, already evaluated as *carcinogenic to humans* in Volume 84 (in press) and Supplement 7 (1987) of the *IARC Monographs*. The gallium moiety may be responsible for the pulmonary neoplasms observed in rats, in view of the apparent resistance of this species to the carcinogenic potential of arsenic.

Indium phosphide was evaluated as *probably carcinogenic to humans* (Group 2A). In one inhalation study, exposure to very low concentrations of indium phosphide caused very high incidences of bronchiolo-alveolar neoplasms (mostly carcinomas) in male and female rats and mice, and increased incidences of adrenal gland phaeochromocytomas in male and female rats and of hepatocellular neoplasms in male and female mice. These results not only provided *sufficient evidence* for the carcinogenicity of indium phosphide in experimental animals, but also a strong rationale for the working group to reach the overall evaluation, solely on the basis of this inhalation study.

Vanadium pentoxide was evaluated as *possibly carcinogenic to humans* (Group 2B). In one inhalation study, an increased incidence of bronchiolo-alveolar neoplasms was observed in male and female mice and male rats. The overall evaluation was reached on the basis of *sufficient evidence* as to the carcinogenicity of vanadium pentoxide in experimental animals, in the absence of data on human cancer.

Advisory group on priorities for future evaluations in *IARC Monographs* (February 2003)

An advisory group of 12 scientists from 10 countries met in Lyon to develop a list of priorities for future evaluations of

carcinogenicity. Before the meeting, nominations were solicited from scientists at major national cancer research centres and other national and international organizations. Nominations were also solicited through the Internet. The advisory group identified more than 20 chemical agents, mixtures, or exposures as high priority for future evaluation or re-evaluation. These will be considered for *IARC Monographs* to be prepared during the period 2004–09.

The advisory group also considered a number of questions concerning working procedures, public health issues and future developments in the *IARC Monographs* programme. Their discussions and recommendations are summarized in IARC Internal Report No. 03/001.

Mechanisms of carcinogenesis: contributions of molecular epidemiology

Molecular epidemiology is the study of the distribution and determinants of disease in human populations using techniques of molecular biology and epidemiology; it has become an important discipline in cancer research. Early contributions of molecular epidemiology came from application of markers of exposure, such as measurements of adducts in blood and urine, in population-based studies. The investigation of aflatoxin exposure markers in cohorts at high risk of liver cancer is a classic example. Over the years, molecular cancer epidemiology has evolved towards the development, validation and application of markers of susceptibility and, more recently, markers of mechanisms of cancer development. Previous IARC Scientific Publications have addressed aspects of molecular epidemiology such as the development and application of biomarkers to cancer epidemiology (Toniolo *et al.*, eds, IARC Scientific Publications No. 142, Lyon, IARC, 1997) and the use of genetic polymorphisms as markers of cancer susceptibility (Vineis *et al.*, eds, IARC Scientific Publications No. 148, Lyon, IARC, 1999).

A workshop in Lyon on "Mechanistic Considerations in the Molecular Epidemiology of Cancer", organized jointly by IARC and the University of Vermont (November 2001) was devoted to providing guidelines for use of molecular techniques in cancer epidemiology, in particular with respect to the study of mechanisms of carcinogenesis. Molecular cancer epidemiology is often defined in terms of biomarkers, which are found internally within biological systems as indicators of exposure, of effects or of susceptibility to disease. However, the traditional distinction between biomarkers of exposure, effect and susceptibility is no longer necessary. For example, DNA adducts are markers that integrate exposure, effect and susceptibility. A new IARC Scientific Publication (edited by P. Buffler, J. Rice, M. Bird and P. Boffetta) is in preparation based on the contributions to the workshop.

Management of mycotoxins in foods and feeds for improving public health

J.M. Rice; in collaboration with M. Castegnaro, St Jean Chambre, France; S.H. Henry, D.L. Park, College Park, MD, USA; J.D. Miller, Ottawa, Canada; S. Page (WHO), Geneva, Switzerland; M. Pineiro (FAO), Rome, Italy; J.I. Pitt, North Ryde, Australia; R.T. Riley, Athens, GA, USA; C.P. Wild, Leeds, UK

A group of 15 scientists from 14 countries convened on 21–23 November 2002 in Lyon to prepare the outline for an IARC Scientific Publication on methods and strategies to prevent, limit and control infection of foods and feeds by mycotoxin-producing fungi. Several participants were from regions where mycotoxin contamination of staple food is a serious concern. Also present were representatives from the WHO (Geneva) and from the Food and Agriculture Organization (FAO, Rome).

This meeting was a result of a recommendation by the working group that convened in February 2002 to prepare *IARC Monographs* Volume 82 (*Some Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*), for the publication of a separate, comprehensive document on strategies for remediation of mycotoxin-infested crops. It was agreed that the document should:

(a) Focus on five types of mycotoxin (aflatoxins, ochratoxin A, fumonisins, deoxynivalenol and ergot) that are generally considered to be most important on a worldwide basis.

(b) Review the species of fungi known to produce these toxins, with clear emphasis on those that affect crops of commercial importance.

(c) Provide physical, chemical, analytical and toxicological data on the mycotoxins.

(d) Discuss the major and minor crops affected by these toxins, as well as crops unlikely to be affected, and the times (pre- or post-harvest) when crops become contaminated.

(e) Outline strategies that may be used to limit the production of toxins before or immediately after harvest of the major crops, including during transport and storage.

(f) Discuss methods to reduce existing toxins in crops by improved farm management practice (crop rotation, weed control and irrigation, row spacing, etc.); cleaning; analysis and segregation; colour and UV sorting; roasting (for peanuts); and chemical means, notably ammoniation to produce animal feed.

The publication will also review specific questions, past experience and particular needs in relation to contamination of crops with mycotoxins encountered in developing countries (case studies).

An editorial board meeting was held on 13–15 November 2003 in Lyon to review draft chapters, identify gaps and plan the remaining work towards publication.

2.2 Occupational exposures

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, multicentre 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 former socialist countries and in developing countries. These studies are based on the case–control approach, and are reported in the sections on cancer sites (Sections 3.3 and 3.6–3.10).

Workers employed in man-made vitreous fibre production

P. Boffetta, K. Soldan, G. Ferro, H Ohgaki; in collaboration with A. Andersen, Oslo, Norway; J. Chang-Claude, Heidelberg, Germany; B. Guldhammer Skov, Gentofte, Denmark; J. Hansen, Copenhagen, Denmark; F.D. Pooley, Cardiff, UK

A historical cohort study has been conducted since 1977 in 13 factories producing man-made vitreous fibres (MMVF) in seven European countries. Following a case–control study of lung cancer that evaluated the occupational exposures of MMVF production workers using exposures estimated from questionnaires and expert assessment [238], lung-tissue specimens from cases (where available) were retrospectively retrieved. Fibre recovery and analysis by transmission electron microscopy (TEM) was conducted to determine fibre type, dimensions and numbers per gram of dry lung tissue. MMVF were detected in all 17 cases analysed and asbestos fibres in 16. No difference or trend in tissue concentration of MMVF was observed across the estimated exposure categories. Regression models using estimated exposure variables as independent variables did not predict lung-fibre concentration. The odds ratio (OR) for MMVF per gram dry lung was 0.5 (95% confidence interval (CI) 0.1–2.4) for the second, and 3.5 (0.6–18.9) for the third quartile of index of average exposure to MMVF in industry, compared with the least exposed quartile (no cases from the highest quartile were analysed).

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

A multicentre international cohort study is being conducted to examine 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. Personnel employed in plants producing pulp, paper and paper products, and in mills involved in recycling, are included. The study has been completed in Brazil, Denmark, Finland, France, Italy, Japan, New Zealand, Norway, Poland, South Africa, Spain, Sweden, the United Kingdom and the United States. An industrial hygiene study has produced time-, mill- and department-specific estimates of exposure to 27 chemicals and groups of chemicals [233]. An analysis of exposure to asbestos has shown that, contrary to expectation, asbestos-related cancer does occur in this industry [105]. Additional analyses of exposure to inorganic dust, chlorinated compounds and other agents are being carried out.

Workers employed in the asphalt industry

P. Boffetta, G. Ferro; in collaboration with W. Ahrens, R. Frentzel-Beyme, Bremen, Germany; I. Burstyn, Edmonton, Canada; D. Heederik, H. Kromhout, Utrecht, Netherlands; B. Jarvholm, Umeå, Sweden; T. Kauppinen, P. Heikkilä, Helsinki, Finland; S. Langard, B. Randem, Oslo, Norway; T. Partanen, San José, Costa Rica; J. Shaham, Raanana, Israel; I. Stücker, Paris, France; O. Svane, J. Hansen, C. Johansen, Copenhagen, Denmark

Cancer risk associated with exposure to asphalt fumes is particularly difficult to study because of the complex and variable nature of asphalt, the occurrence of co-exposures (motor engine exhaust, tobacco smoking) and the nature of the workforce (seasonal employment, instability, low skill) (Figure 13). Previous epidemiological studies have suggested increased risks of cancer of the lung and other organs, but could not 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, based on an extensive collection of published and unpublished data on occupational exposure of asphalt workers and on company questionnaires, resulted in job-based estimates of exposure to bitumen fumes and other agents present in the working environment [95]. Detailed results of the cancer mortality follow-up [53, 54] showed an

increased risk of lung cancer as compared to national reference populations, and a dose–response relationship among pavers according to average bitumen fume exposure but not to cumulative exposure. Additional analyses revealed that mortality from external causes was not elevated among long-term employees in asphalt application and mixing. Risk of mortality due to external causes was increased among short-term workers. However, none of the fatal accidents among short-term workers appeared to have occurred during employment in the studied asphalt companies [93]. A nested case–control study is being set up to distinguish between the possible carcinogenic roles of bitumen fume, other occupational exposures and life-style factors, chiefly tobacco smoking.

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

Although titanium dioxide (TiO_2) has produced lung tumours in rats, only limited information is available on carcinogenic risk in humans. A multicentre mortality follow-up study included 15 017 workers employed in 11 factories in Finland, France, Germany, Italy, Norway and the United Kingdom. Exposure to TiO_2 dust and other agents was reconstructed for each occupational title, based on occupational hygiene measurements and information from interviews with experts. A total of 2652 deaths were reported during the 371 067 person-years of follow-up of the cohort, yielding standardized mortality ratios (SMRs) of 0.87 (95% CI 0.83–0.90, based on 2619 deaths) among men and 0.58 (95% CI 0.40–0.82, 33 deaths) among women. Among men, the SMR of lung cancer was significantly increased (1.23, 95% CI 1.10–1.38). Mortality from lung cancer did not increase with duration of employment or estimated cumulative exposure to TiO_2 dust. The SMR of non-malignant respiratory diseases was 0.89 (95% CI 0.77–1.02) and mortality from other chronic diseases and from external causes was also not increased. Four deaths from pleural neoplasms were observed compared with 5.2 expected. Data on smoking status were available for over one third of cohort members. In Finland, Germany and Italy, the prevalence of smokers was higher among cohort members than in the national populations. Overall, the results do not suggest an increased risk of lung cancer from exposure to TiO_2.

Figure 13. Work in road paving with asphalt can entail multiple exposures

Other collaborative studies of occupational cancer

P. Boffetta, A. 't Mannetje, N. Travier, J. Hall, C. Cohet; in collaboration with H.-O. Adami, Stockholm, Sweden; F. Berrino, Milan, Italy; A. Blair, G. Gridley, Bethesda, MD, USA; D. Luce, Paris, France; F. Merletti, Turin, Italy; N. Pearce, Wellington, New Zealand; M. Peluso, Genoa, Italy; P. Srivatanakul, Bangkok, Thailand; L. Stayner, Cincinnati, OH, USA; K. Steenland, Atlanta, GA, USA; C. Wesseling, T. Partanen, San José, Costa Rica

In Sweden, a linkage has been established between information on occupation obtained from the census and information on cancer occurrence obtained from the cancer registry. This allows investigation of cancer risk among all workers employed in a given occupation at the time of the census. Data on **dry cleaners** and **veterinarians** have been analysed. Dry cleaners, launderers and pressers employed in the laundry, ironing or dyeing industry had significantly increased risks of Hodgkin disease for both sexes combined, of leukaemia among women only, and of cancers of the stomach and larynx among men only [512]. A similar analysis of veterinarians revealed increased risks of cancers of the oesophagus, colon, pancreas and brain, as well as of melanoma [511]. 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.

An analysis of incidence of **brain cancer** among Finnish women based on a similar linkage of census and cancer registry data revealed non-significantly increased risks for exposure to iron, oil mist, electromagnetic fields and chromium [555].

A pooled analysis of case–control studies on exposure to occupational agents other than wood dust and risk of **sinonasal cancer** included 195 adenocarcinoma cases, 432 squamous-cell carcinoma cases and 3136 controls. Occupational exposures to formaldehyde, silica dust, textile dust, coal dust, flour dust, asbestos and MMVF were assessed with a job–exposure matrix. A significantly increased risk of adenocarcinoma was associated with exposure to formaldehyde. The wood-dust-adjusted ORs for the highest level of exposure were 3.0 (95% CI CI 1.5–5.7) among men and 6.2 (95% CI CI 2.0–19.7) among women. Elevated risks of squamous-cell carcinoma were also observed among men (OR = 2.5, 95% CI CI 0.6–10.1) and women (OR = 3.5, 95% CI CI 1.2–10.5) with a high probability of exposure to formaldehyde. A high level of asbestos exposure was associated with significantly increased risk of squamous-cell carcinoma among men [278].

A pooled historical cohort study of workers exposed to **crystalline silica** included 10 cohorts from different countries. A common measure of exposure was developed across studies.

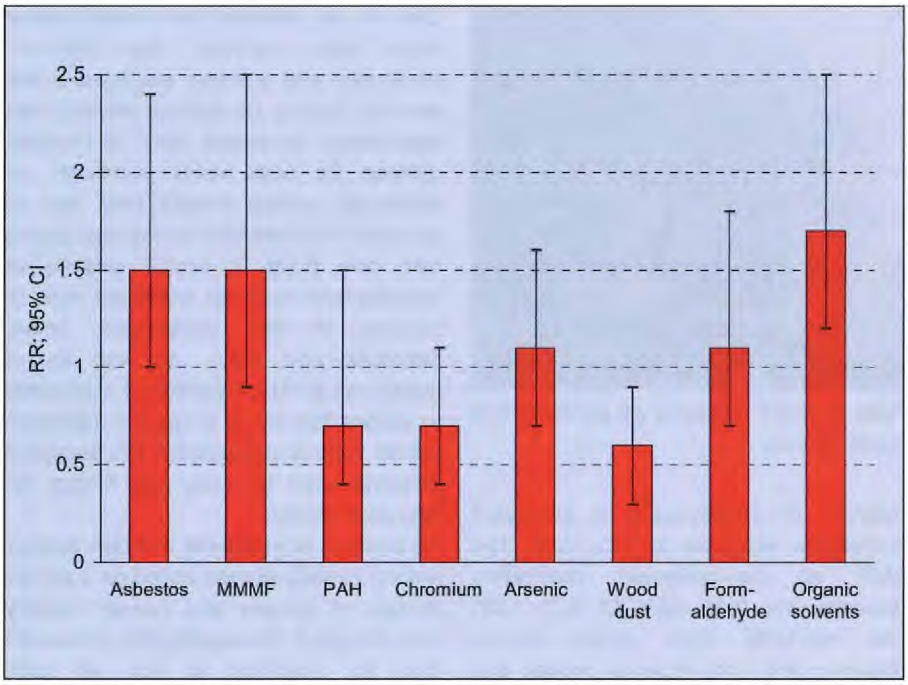


Figure 14. Relative risk of laryngeal cancer for occupational exposure to selected agents in the IARC multicentric study [59]. MMMF, man-made mineral fibres; PAH, polycyclic aromatic hydrocarbons

Analysis of silicosis mortality showed a monotonic increase in rate, from 4.7/100 000 for exposure 0–0.99 mg/m^3 to 233/100 000 for exposure above 28.1 mg/m^3. The estimated cumulative risk up to age 65 after 45 years of exposure at 0.1 mg/m^3 (the current maximum permitted in many countries) was 13/1000, and the corresponding risk for exposure at 0.05 mg/m^3 was 6/1000 [292].

A cohort study of 8456 **meat workers** in New Zealand employed during 1978–90 revealed lower mortality than in the national population (SMR = 0.80, 95% CI 0.70–0.89), but marginally increased mortality from lung cancer (SMR = 1.33, 95% CI 0.94–1.83) [301].

A multicentre case–control study of occupational exposures and **laryngeal** cancer was conducted in six centres in France, Italy, Spain and Switzerland. Occupational history was collected for 1010 male cases of laryngeal and hypopharyngeal cancer and for 2176 population controls. A job–exposure matrix was used to assess exposure to ten occupational agents. Excess risk was detected for construction workers, potters, butchers, barbers, shoe workers, loggers and labourers not otherwise specified, as well as for men who had been employed in rail transport, shipbuilding and hotels. No significant excess of risk was found for categories previously reported to be associated with laryngeal and hypopharyngeal cancer, such as drivers, mechanics, welders, machinists and painters [59]. Analyses of matrix-derived exposure assessments were restricted to 315 cases and 819 controls aged less than 55 years. Elevated risks were found for organic solvents (OR for ever-exposure = 1.7, 95% CI 1.2–2.5) and asbestos (OR = 1.5, 95% CI 1.0–2.4), while a decreased risk was associated with wood dust (Figure 14). The analysis also suggested positive associations of man-made mineral fibres with hypopharyngeal cancer and of formaldehyde with laryngeal cancer [32].

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 formation of bulky DNA adducts 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 polymorphisms are in progress.

Biology research laboratory workers

A.J. Sasco, H. Besson, A. Olsson, V. Luzon; in collaboration with A. Ahlbom, H. Wennborg, Stockholm, Sweden; A. Andersen, Oslo, Norway; S. Belli, Rome, Italy; S. Benhamou, A. Laplanche, Villejuif, France; C. Chilvers, T. Brown, Nottingham, UK; L. Daly, Dublin, Ireland; M. Gonzales, Bilbao, Spain; T. Kauppinen, I. Laamanen, Helsinki, Finland; J.J. Moulin, Vandoeuvre-lès-Nancy, France; L. Stayner, Chicago, IL, USA; M. Tirmarche, Paris, France; F. van Leeuwen, T. van Barneveld, Amsterdam, Netherlands, D. Vecchio, G. Viano, Genoa, Italy

Partly supported by the European Union, the Ligue Nationale contre le Cancer and the Fondation Weisbrem-Benenson (Fondation de France) of France

In a retrospective cohort study of all staff employed for at least one year and one day in public research institutions in the biomedical, agronomical and biological fields of seven European countries (France, Ireland, Italy, Netherlands, Norway, Sweden and United Kingdom) which included 45 163 workers who contributed 650 706 person-years, a marked deficit was seen in overall mortality, including all cancer mortality, in the cohort as compared to national populations, whereas intra-cohort analyses comparing laboratory work to non-laboratory work showed excesses of specific cancer mortality in certain scientific activities, such as female breast cancer and cellular biology, male lung cancer and molecular biology and male colon cancer and anatomopathology. In addition, excesses expected based on literature review [535], for pancreatic cancer and brain tumours, were found in technicians and male scientists respectively.

In a Finnish cohort of workers occupationally exposed to carcinogens, the most frequent exposures included chromium,

carbon tetrachloride, cadmium, benzene and chloroform. Slightly elevated risks were found for non-Hodgkin lymphoma and leukaemia [232].

As part of the Worksafe programme, supported by the European Union, to set up an internet-based information package and digital content-sharing services for health protection of workers and general workplace safety, a prototype is being developed.

2.3 Diet and nutrition

Even a relatively weak biological effect on cancer risk, either preventive or causative, related to widely consumed foods or to common metabolic characteristics such as being overweight and sedentary lifestyle, may have a large impact on the cancer burden at the population level. However, few nutrition-related factors have been unequivocally established as playing a role in human cancer occurrence. Agreement reached so far by various international expert committees is limited to such factors as overweight, obesity and alcohol consumption for cancer causation, and fruit and vegetable consumption for a probable protective effect (see Section 5.2).

It now appears that diet and lifestyle can affect the development of several cancers (particularly cancer of the breast, prostate, endometrium, ovary and colon) through modification of the endogenous hormonal milieu (see Section 2.4). Various other bioactive endogenous compounds such as prostaglandins, thromboxanes and leukotrienes, may be partially regulated by nutritional factors. Inter-individual variations in sensitivity to nutritional factors may be modulated by genetic characteristics and non-dietary lifestyle exposures.

European Prospective Investigation into Cancer and Nutrition (EPIC)

E. Riboli, W. Al-Delaimy, F. Canzian, C. Casagrande, G. Davey, M. Fahey, P. Ferrari, M.D. Friesen, B. Hémon, R. Kaaks, T. Norat, R. Saracci, N. Slimani; in collaboration with: *Denmark*: A. Tjønneland, Copenhagen; K. Overvad, Aarhus; *France*: F. Clavel, Villejuif; *Germany*: A.B. Miller, J. Wahrendorf, N. Becker, Heidelberg; H. Boeing, P. Lahmann, Potsdam; *Greece*: A. Trichopoulou, Athens; *Italy*: F. Berrino, V. Krogh, Milan; D. Palli, Florence; S. Panico, Naples; R. Tumino, Ragusa; P. Vineis, B. Terracini, Turin; *Netherlands*: H.B. Bueno de Mesquita, Biltthoven; P. Peeters, Utrecht; *Norway*: E. Lund, Tromsø; *Spain*: C. Gonzalez, A. Agudo, Barcelona; A. Barricarte, Navarra; M. Dorronsoro, San Sebastian; C. Navarro, Murcia; C. Martinez, Granada; J. Ramon Quiros, Oviedo; *Sweden*: G. Berglund, Malmö; G. Hallmans, Umeå; *UK*: N.E. Day, S. Bingham, K.-T. Khaw, A. Welch, Cambridge; T. Key, N. Allen, Oxford

EPIC is a multi-centre prospective cohort study initiated in 1992. It is designed to investigate the relation between food, nutritional status, various lifestyle and environmental factors and the incidence of and mortality from different forms of cancer with, in addition, the potential to investigate mortality from other causes such as myocardial infarction, stroke and other chronic diseases. It is unique among nutrition-related studies in its combination of five key features:

1. The size of the cohort (521 400 volunteers) makes it possible to investigate, with adequate follow-up time, even relatively rare cancers and anatomical, histological and molecular subtypes of common cancers. Already 20 175 incident cancer cases have been reported.
2. Subjects are recruited in 23 centres in 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom) in areas with very different rates of cancer occurrence and distribution of lifestyle and dietary habits. Heterogeneity of diet is a key condition for identifying variations in cancer risk associated with the consumption of specific foods and nutrients.
3. Food consumption and personal lifestyle data, as well as anthropometric measurements, were collected from all subjects at the time of enrolment in the cohort.
4. A new method was implemented to calibrate dietary measurements across countries, consisting of a second dietary measurement taken from a 7% random sample of the cohort (37 000 subjects) using a computerized, highly standardized 24-hour diet recall method (EPIC-SOFT; see below).
5. Blood samples, collected from about 400 000 subjects at enrolment and separated into 28 aliquots (plasma, serum, leukocytes, erythrocytes), have been stored in liquid nitrogen and constitute the largest biorepository in the world.

Follow-up for cancer incidence and overall mortality is based on population registries in seven of the participating countries. France, Germany and Greece, however, use a combination of methods including health insurance records, cancer and pathology registries and active follow-up of study subjects and their next-of-kin.

Study subjects are contacted every three to four years to obtain information on changes in various aspects of lifestyle known or suspected to be related to cancer risk and on the occurrence of other major diseases.

Diet influences many health and disease end-points other than cancer, which must be taken into account when formulating dietary recommendations. The prospective EPIC cohort offers an excellent infrastructure for the study of such end-points. Cardiovascular diseases present a natural starting point, given their major contribution to morbidity, mortality and, as a consequence, longevity.

EPIC is organized as a structured network, with a steering committee made

up of IARC scientists and principal investigators from each of the EPIC centres, and several working groups which specialize in methodological, cancer site and other disease-oriented topics. Preliminary results on diet and cancer risk were presented at the First European Conference on Nutrition and Cancer organized by IARC in Lyon in June 2001 [394]. The detailed methodology as well as baseline and further preliminary results have been published in a dedicated supplement of *Public Health Nutrition* [465].

Extensive analyses of the relationship between diet, dietary patterns and risk of specific cancers are in progress. Analyses carried out during 2003 have been based on the data-set established in October 2002 (Table 3).

Standardized 24-hour diet recall program (EPIC-SOFT)

N. Slimani, C. Casagrande, E. Riboli; in collaboration with the EPIC centres

The EPIC study used, in addition to the country-specific dietary questionnaires, a standard computerized face-to-face 24-hour diet recall interview program (*EPIC-SOFT*) used as a reference calibration method across countries [456]. The software was also used in telephone interviews, with overall results similar to those from the face-to-face interviews [88]. A single 24-hour diet recall was collected from a stratified random sample of about 37 000 subjects from the cohort between 1995 and 2000. In this calibration study, 70% of the 23 centres reported participation rates of between 75% and 93% [455].

Although the observed ratio of mean energy intake to basal metabolic rate, used to estimate the degree of under- or over-estimation of mean energy intake from the 24-hour diet recalls, was below the expected value, the difference between centres was quite small [154]. High correlations were also found between the mean nitrogen and total energy intakes estimated from the 24-hour diet recalls and mean 24-h urinary nitrogen excretion levels [454].

Although this software would need some adaptation and further development, it has been recommended as a reference method for future pan-European monitoring surveys (*EFCOSUM: European Food Consumption Survey Method*, Löwik & Brussaard, eds, *Eur. J. Clin. Nutr.*, **56** Suppl. 2, May 2002); it is already in use in regional and national monitoring surveys in Belgium, Germany, the Netherlands and Spain.

EPIC nutrient database (ENDB)

N. Slimani, J. Vignat, E. Riboli; in collaboration with J. Ireland, France; A. Moller, Denmark; A. Farran, Spain; I. Unwin, UK; E. Vasilopoulou, Greece; S. Salvini, Italy; S. Westenbrink, Netherlands; W. Becker, I. Mattison, Sweden; G. Skeie, Norway

In the absence of a reference European nutrient database, the EPIC Nutrient DataBase project (ENDB) was set up to develop comparable nutrient databases to allow calculation of nutrient intakes in the 10 participating countries. The main aims are (i) to develop methodological concepts to standardize the foods, nutrients and nutrient values and (ii) to document and compile 10 national databases for the 600 to 1500 foods (according to country) reported by the EPIC study subjects. Initially, about 30 nutrients (energy, macronutrients and a selection of vitamins and minerals) are being compiled by each of the 10 national compilers.

A data-management system (ENMan, Figure 15) is under development to help the compilers to import, document, compile, calculate and export their country-specific nutrient databases according to common formats, functions and instructions.

Development of statistical methodology

P. Ferrari, M. Fahey, R. Kaaks, N. Slimani, E. Riboli; in collaboration with EPIC centre scientists

New approaches in dietary assessment and statistical methods for multicentric studies on diet are being developed, with emphasis on methods to correct relative risk estimates for measurement error while taking into account the effects of energy and correlated errors [127].

Multicentric epidemiological studies give a unique opportunity to evaluate the relationship between exposure and

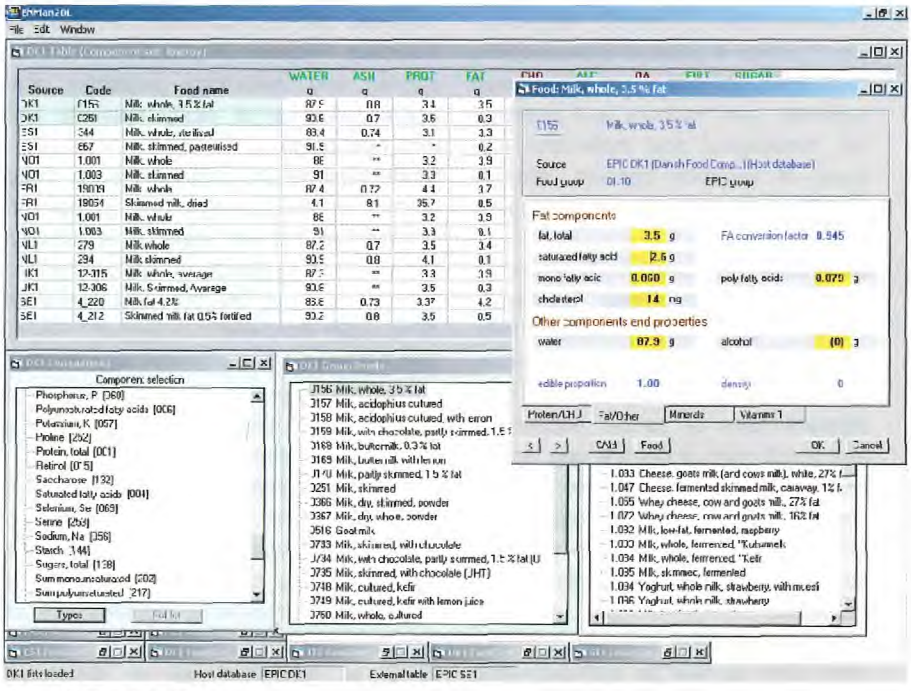


Figure 15. Sample ENMan screen

Table 3. Cohort structure and five incident cancers in the EPIC database, October 2002

	Cohort structure			Incident cancers				
	Men	Women	All	Stomach	Bronchus + lung	Colon + rectum	Breast	Prostate gland
Denmark	27 179	29 875	57 054	17	176	190	397	94
France	–	74 524	74 524	9	115	213	1923	–
Germany	22 833	30 258	53 091	40	95	131	248	154
Greece	11 944	16 611	28 555	15	32	28	46	10
Italy	15 171	32 578	47 749	52	70	114	403	41
Netherlands	10 280	29 792	40 072	20	77	147	449	16
Spain	15 632	25 808	41 440	31	65	116	253	79
United Kingdom	26 917	61 025	87 942	56	210	348	656	273
Norway	–	37 215	37 215	4	27	38	110	–
Sweden	23 494	30 332	53 826	62	217	328	690	609
Men	153 450			166	546	637	8	1276
Women		368 018		140	538	1016	5167	–
All	153 450	368 018	521 468	306	1084	1653	5175	1276

disease at the individual and the aggregate level. The two components can eventually be pooled together to corroborate each other. Dietary measurements are affected by measurement errors, particularly within-cohort. We have evaluated the variability of macronutrient intake distribution before and after calibration for measurement error in EPIC, using a two-level, random effects model to estimate within- and between-centre calibration effects. Evaluation of macronutrient densities revealed that energy has a considerable effect in the calibration model. These results suggest that the effect of calibration is much greater for within-cohort variability of macronutrient intakes, so that the relative importance of the between-cohort component is increased. Consequently, after calibration, the two components have similar weight. This observation has important implications for the analysis of multicentric studies.

Colorectal cancer

E. Riboli, T. Norat, P. Ferrari, N. Slimani, R. Kaaks, R. Saracci; in collaboration with EPIC centre scientists

The risk of colorectal cancer associated with several dietary exposure factors has been assessed. Dietary data were analysed by a Cox proportional hazard model, with age as a time-dependent variable, stratified by study centre and with energy, alcohol, tobacco, physical activity, height and weight as covariates.

Dietary fibre: Dietary fibre is thought to protect against development of colorectal cancer, though this has been challenged by recent studies. Mean fibre consumption varied greatly. The relative risk for consumption of 35 g/day compared to 15 g/day was 0.58 ($p < 0.001$) for large bowel cancer (Figure 16). The greatest protective effect was seen for the left side of the colon, and least for the rectum. Fibre from cereals was more strongly protective than fibre from vegetables, fruit and legumes, although the difference was not statistically significant [45].

Meat, processed meat, poultry, fish: Consumption levels varied substantially between and within study centres. Mean consumption in grams/day within quintiles ranged from 6.4 to 100.6 for red meat, 2.8 to 77.0 for processed meat and 4.2 to 95.1 for fish.

Statistical adjustment for fibre in the Cox model did not alter the protective effect of fish, but attenuated the risk increase associated with red and processed meats. These results support the hypotheses that moderate consumption of fish reduces colorectal cancer risk, independently of the protective effect of fibre. The increased risk found for meat, on the other hand, may be due, at least partly, to confounding by low fibre intake [333].

Fruit and vegetables: Preliminary findings show reduced risks for higher intake of fruit and vegetables combined and of fruit. There was a suggestion of a graded inverse association of risk with vegetable intake. Overall, there is support for the hypothesis of a causal association and the belief that regular consumption of certain subgroups of vegetables, specifically leafy vegetables, is protective against colorectal cancer [89].

Nuts and seeds: Average consumption of 15.7 g of nuts and seeds per day had a modest but significant protective effect against colon cancer in women (hazard ratio = 0.68) compared with non-consumers. There was no significant association for colon cancer in men or for rectal cancer in men or women. The high content of unsaturated fatty acids and phyto-nutrients/estrogens in nuts and seeds may contribute to the observed effect [217].

Stomach cancer

E. Riboli, M. Fahey, M.D. Friesen, F. Canzian; in collaboration with EPIC centre scientists

The EUR-GAST project, co-ordinated by EPIC collaborators in Spain, is examining the individual and joint effects of *Helicobacter pylori* infection, genetic

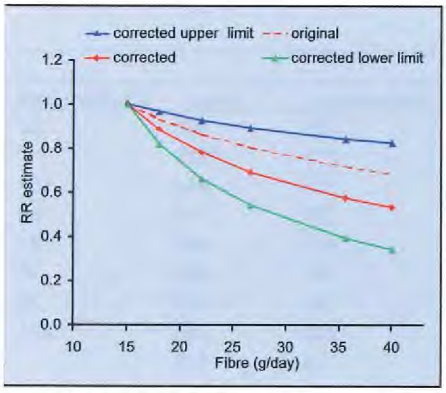


Figure 16. Relative risk for colorectal cancer according to dietary fibre intake

polymorphisms, dietary biomarkers, smoking, alcohol and environmental factors putatively involved in the etiology of gastric cancer in the European population.

Four controls per case have been matched to 294 incident stomach cancers diagnosed by November 2002, and laboratory measurements are well advanced. Preliminary results of statistical analyses on diet, lifestyle and stomach cancer risk suggest a modest protective effect of fruit and an increased risk associated with elevated consumption of processed meats and with tobacco smoking.

Prostate cancer

E. Riboli, R. Kaaks, P. Ferrari; in collaboration with EPIC centre scientists

In the first analyses, no significant association of prostate cancer risk with either fruit and vegetable consumption or intake of cruciferous vegetables was seen.

Breast cancer

E. Riboli, R. Kaaks, T. Norat, G. Davey, S. Rinaldi; in collaboration with EPIC centre scientists

No association has been found between breast cancer and total vegetable consumption. However, saturated fat intake is directly associated with increased risk. Smoking from a young age and for a long time before the birth of the first child is also associated with increased risk of breast cancer. Studies are in progress on excess weight, estrogen replacement therapy and hormone replacement therapy.

Lung cancer

E. Riboli, A. Lukanova, F. Canzian; in collaboration with EPIC centre scientists

Analysis based on 813 incident lung cancer cases revealed a significant inverse association of lung cancer risk with fruit consumption but no association with vegetable consumption [306].

GEN-AIR

P. Hainaut, E. Riboli, R. Saracci, E. Gormally; in collaboration with EPIC centre scientists

GEN-AIR is examining molecular changes and genetic susceptibility in relation to air pollution and environmental tobacco smoke, looking at non-smokers in the EPIC cohort. The predictive value of plasma DNA levels for development of neoplastic disease has been evaluated and a study of mutations in plasma DNA is in progress (see Section 6.1).

B vitamins, metabolism, related genes and cancer risk

E. Riboli, M.D. Friesen, R. Kaaks; in collaboration with S.E. Vollset, P.M. Ueland, Norway; D. Hunter, W. Willett, USA

Epidemiological and animal studies have found inverse associations between dietary folate intake and the risk of developing colorectal neoplasms. The folate metabolic pathway influences genomic methylation and the supply of nucleotides for DNA synthesis; these can also be influenced by the supply of vitamins B_{12}, B_6 and B_2. To elucidate the role of folate and other nutritional contributors to one-carbon metabolism in cancer of the gastrointestinal tract, we are analysing B vitamins and homocysteine levels in blood of cancer cases and matched controls within the EPIC cohort. Polymorphisms in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene and others will be measured.

Obesity, physical activity and other lifestyle factors

E. Riboli, N. Slimani, P. Ferrari, R. Kaaks, T. Norat, R. Saracci, in collaboration with EPIC centre scientists

Associations of overweight and obesity with increased risk of cancer of the endometrium, breast, colon, oesophagus and kidney have been established; physical activity has a cancer-preventive effect. EPIC is developing methods for better assessment of physical activity, body composition and dietary habits. Preliminary results confirm that excess body weight is associated with a moderate increase in risk of developing cancers of the colorectum and breast and a substantial increase in cancer of the endometrium.

Identification of dietary patterns in European populations and their relationship to cancer risk

N. Slimani, P. Ferrari, M. Fahey, E. Riboli; in collaboration with EPIC centre scientists

Extensive descriptive analyses of food consumption and dietary patterns, using the standardized 24-hour diet recalls collected from 37 000 EPIC subjects in 27 European regions, have been conducted, focusing on the mean consumption at the population group level [465]. Research on statistical methods to identify dietary patterns and investigate their association with cancer risk is continuing.

Identification of dietary patterns at the individual level and their relationship to cancer risk

M. Fahey, P. Ferrari, N. Slimani, E. Riboli; in collaboration with EPIC centre scientists

Identification of a small number of patterns in food consumption among individuals is of interest in order to assess the risks associated with particular dietary patterns. We are using finite mixture modelling and other latent variable statistical methods to identify such dietary patterns, focusing initially on the quantitative consumption of about 25 major food groups.

Biomarkers of diet

W. Al-Delaimy, M.D. Friesen, E. Riboli; in collaboration with EPIC centre scientists

Biomarkers are cellular, biochemical or molecular alterations that are measurable in biological media (such as human tissues, cells or fluids). The biomarker working group, established in February 2003, is coordinating work on analysis of blood samples for markers of diet and of DNA damage, and other developmental laboratory work in these areas. Studies at IARC are focusing on plasma carotenoids and their distribution in the participating European countries, and the relation between carotenoids in plasma and data from dietary questionnaires and recalls. New biomarkers of dietary intake are being investigated.

EPIC-Elderly

E. Riboli, R. Saracci, M. Fahey, P. Ferrari; in collaboration with EPIC centre scientists

EPIC-Elderly is investigating the relation of food items and food patterns to total mortality and for major disease classes in subjects aged 60 years and above within the EPIC cohort, who represent an increasingly large segment of most European populations.

EPIC-Heart

R. Saracci, T. Norat, R. Kaaks, E. Riboli; in collaboration with EPIC centre scientists

The medium-term objective of EPIC-Heart is to assess how specific nutritional components (foods and nutrients) may be related to specific forms of ischaemic heart disease and to specific groups of subjects who may be characterized by genetic or acquired susceptibility.

Analyses on a cohort basis (1126 myocardial infarction deaths) indicate that body mass index, smoking, hypertension and antecedents of hyperlipidaemia significantly increase the risk of fatal myocardial infarction, while decreased risk is associated with job physical activity, alcohol intake and being a woman. Preliminary results suggest that the risk of fatal myocardial infarction is significantly increased by high consumption of processed meat, but not significantly associated with red meat consumption (excluding processed meat). No significantly decreased risk of fatal myocardial infarction was detected with high levels of fish consumption. However, these are preliminary findings based on small numbers of cases in some centres and have not been adjusted for potential confounders such as high- or low-density lipoprotein cholesterol.

Except for leafy vegetables, no association has been observed between consumption of fruit and/or vegetables and cardiovascular mortality. Further analyses are in progress with a larger number of cases (deaths) and more detailed sub-groups of fruit and vegetables.

A case–control study within the cohort has been set up to investigate the relationship between fatal myocardial infarction and diet-related compounds assayable in stored plasma specimens: total cholesterol and fractions, triglycerides, homocysteine, seven carotenoids (lutein, zeaxanthin, cantha-xanthin, β-cryptoxanthin, lycopenes, α-carotene and β-carotene), α- and γ-tocopherols, retinol and 22 fatty acids, the latter being of special interest in view of the debate on the role (adverse or protective) of long-chain *n*–6 and *n*–3 fatty acids.

Case-control studies of breast cancer

M. Saadatian-Elahi, E. Riboli, P. Ferrari; in collaboration with P. Toniolo, A. Akhmedkhanov, A. Zeleniuch-Jacquotte, New York, USA; J. Goudable, Lyon, France; V. Pala, V. Krogh, P. Muti, V. Chajes, A. Micheli, S. Sieri, F. Berrino, Milan, Italy

The relationship between serum or erythrocyte membrane fatty acids and the risk of breast cancer was explored in two case–control studies, nested within large prospective cohort studies: the New York University Women's Health Study (NYUWHS) and the ORDET study, Italy. Higher serum levels of saturated fatty acids were associated with an approximately two-fold increased risk for breast cancer in the New York study but not in the Italian one. By contrast, in the latter study, high levels of monounsaturated fatty acids and particularly oleic acid in the erythrocyte membrane were directly related to an increase in breast cancer risk. The relatively small numbers of cases (197 for New York and 71 for Italy) and the nature of blood fraction used (serum versus erythrocyte membrane) may explain at least some of the discrepancy between the results of these studies.

Meta-analysis of breast cancer risk

M. Saadatian-Elahi, T. Norat, E. Riboli; in collaboration with J. Goudable, Lyon, France

A meta-analysis was performed of published results of epidemiological studies of the composition of fatty acids in biological samples and breast cancer risk, including 1790 cases and 2246 controls. Overall, there was no association between most of the fatty acids investigated and breast cancer risk. Case–control and cohort studies results did not yield the same results. In cohort studies, palmitic acid (C16:0), oleic acid (C18:1 n–9c) and total monounsaturated fatty acids were significantly associated with an increase in breast cancer risk, whereas n–3 polyunsaturated fatty acids showed a significant protective effect. For case–control studies, the only significant association was for linoleic acid, which had a protective effect on breast cancer risk.

2.4 *Endogenous hormone metabolism*

Alterations in the metabolism of endogenous hormones and growth factors represent a major class of mechanisms that may link cancer risk to nutrition and other lifestyle factors. Excess weight and physical inactivity lead to insulin resistance and chronic hyperinsulinaemia, which has been hypothesized to be a causal factor in the etiology of cancers of the colon [222], breast [223, 226, 425], pancreas and endometrium [227]. The tumour-enhancing effects of insulin may be mediated either directly by insulin receptors in (pre)neoplastic target cells or indirectly by changes in insulin-like growth factor-I (IGF-I) levels [284] or bioavailability. In addition, excess body weight is associated with increased levels of estrogens in postmenopausal women and in men, and can alter androgen synthesis and metabolism, especially in some genetically susceptible subgroups of women [40, 226]. Endogenous hormone metabolism is also affected by types and amounts of dietary fats, carbohydrates (insulin secretion and sensitivity) and protein (IGF-I synthesis) [4, 6, 228], or by use of exogenous hormones for contraception or postmenopausal replacement therapy.

Development and validation of hormone assays

S. Rinaldi, R. Kaaks, M.D. Friesen; in collaboration with H. Déchaud, Lyon, France; M. Kurzer, Minnesota, MN, USA

The IARC laboratory for measurement of steroid and peptide hormones and growth factors in blood and urine performs 20 000–25 000 hormone assays per year, for a variety of studies on hormones and growth factors in relation to cancer risk. For continuous quality control, the assays being used are examined regularly and extensively for reproducibility and validity [399,400]. In addition, new methods are developed and set up, e.g. for measurement of estrogen (hydroxy- and methoxy-) metabolites in blood by HPLC/mass spectrometry.

Breast cancer

R. Kaaks, S. Rinaldi, A. Lukanova, C. Biessy, L. Dossus, D. Achaintre, J. Bouzac, E. Riboli; in collaboration with P. Toniolo, A. Zeleniuch-Jacquotte, A. Akhmedkanov, R. Shore, New York, USA; M. Kurzer, Minnesota, MN, USA, P. Muti, Buffalo, NY, USA; G. Maskarinec, Hawaii, USA, I. Gram, Tromsø, Norway, and EPIC centre scientists

A number of prospective cohort studies are in progress or already complete to examine relationships of breast cancer risk with pre- and postmenopausal blood and urine levels of endogenous sex steroids (androgens, progesterone, estrogens), hydroxy- and methoxy-metabolites of estrogens, insulin, IGF-I and IGF-binding proteins (IGFBPs). Two large prospective studies within the NYUWHS cohort (297 cases, 563 controls) and in the EPIC cohort (640 cases, 1246 controls) show increasing risk of breast cancer with higher serum levels of androgens (dehydroepiandrosterone (DHEA) or its sulfate (DHEAS), androstenedione, testosterone) and total and bioavailable estrogens (estradiol, estrone) [566]. A third prospective study, within the Dutch 'DOM' cohort (300 cases and 300 matched controls), again among women who were menopausal at recruitment, also found increased risks of breast cancer in women who had elevated prediagnostic urine levels of estrone, estradiol, testosterone and 5α-androstane-3α,17β-diol [350]. Within the EPIC cohort and the NYUWHS, further analyses are being conducted to relate breast cancer risk to premenopausal serum concentrations of sex steroids (androgens, estrogens, progesterone). Within the DOM cohort, we have also started a further study on (postmenopausal) urinary hydroxy- and methoxy-metabolites of estrone and estradiol, to be measured by gas chromatography and mass spectrometry.

Besides sex steroids and their metabolites, there is increasing interest in the possible role of elevated levels of IGF-I as a risk factor especially for premenopausal breast cancer. Within the EPIC cohort, a large study is close to completion, to relate breast cancer risk in pre- and postmenopausal women to serum levels of IGF-I, IGFBP-3 and C-peptide (a marker for pancreatic insulin secretion).

We are also collaborating in two large studies of serum and urine levels of sex hormones and growth factors in relation to mammographic densities – a strong predictor of breast cancer risk – in women of different ethnic backgrounds in Hawaii and Japan [296] and Tromsø, Norway.

Endometrial cancer

R. Kaaks, A. Lukanova, S. Rinaldi, L. Dossus, E. Riboli; in collaboration with P. Toniolo, A. Zeleniuch-Jacquotte, A. Akhmedkanov, R. Shore, New York, USA; F. Berrino, A. Micheli, Milan, Italy; G. Hallmans, P. Stattin, E. Lundin, P. Lenner, Umeå, Sweden; P. Muti, Buffalo, NY, USA; and EPIC centre scientists

A large body of evidence suggests that endometrial cancer risk is increased in women who have low plasma levels of progesterone, if premenopausal, or who have increased levels of bioavailable estrogens. A relative androgen excess, as a consequence of chronic hyperinsulinaemia, may be an important metabolic link relating excess body weight to increased risk of endometrial cancer. Before the menopause, ovarian androgen excess frequently causes chronic anovulation and progesterone deficiency, while after menopause high androgen levels lead to elevated peripheral estrogen synthesis. In addition, chronic hyperinsulinaemia – a consequence of excess weight and physical inactivity – may also increase endometrial risk by downregulating endometrial levels of IGFBP-1 (Figure 17) [227].

In a prospective study combining blood samples and questionnnaire data from cohorts in the USA (New York), Sweden (Umeå) and Italy (Milan), increased risks of endometrial cancer were observed among both pre- and postmenopausal women with elevated plasma androgens (DHEAS, androstenedione, testosterone) and among postmenopausal women with elevated plasma levels of free estrogens

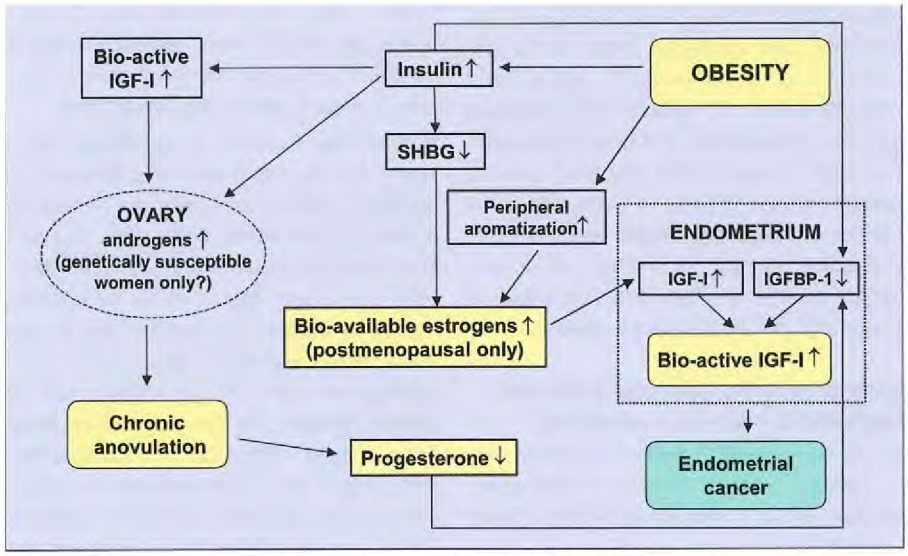


Figure 17. Endogenous hormones and endometrial cancer development (adapted from [227])

unbound to sex hormone-binding globulin (SHBG) [280]. There was a strong direct relationship of endometrial cancer risk with serum levels of C-peptide (OR = 4.40; 95% CI 2.1–10.7), which remained after adjustment for body mass index, but no association with levels of IGF-I or IGFBP-3 [282]. To confirm these findings, another larger study within the EPIC cohorts is being initiated.

Ovarian cancer

R. Kaaks, A. Lukanova, S. Rinaldi, L. Dossus, D. Achaintre, J. Bouzac, E. Riboli; in collaboration with P. Toniolo, A. Zeleniuch-Jacquotte, A. Akhmedkanov, R. Shore, New York, USA; P. Muti, Buffalo, NY, USA; F. Berrino, A. Micheli, Milan, Italy; G. Hallmans, E. Lundin, Umeå, Sweden; and EPIC centre scientists

Most ovarian cancers (> 85%) are of epithelial origin and probably develop from epithelial inclusion cysts. The transformation of epithelial cells into tumour cells is likely to be influenced by hormonal factors. Hormones that have been postulated to play a role are gonadotropins (luteinizing hormone (LH), follicle-stimulating hormone (FSH)), ovarian androgens, estrogens, progesterone and IGF-I.

Within three prospective cohorts in the USA (New York), Sweden (Umeå) and Italy (Milan), a nested case–control study of 132 ovarian cancer cases and 257 controls was conducted to examine ovarian cancer risk in relation to circulating endogenous hormone levels. Ovarian cancer risk was increased among premenopausal women who had elevated plasma levels of androstenedione [279], in line with findings from an earlier (very small) prospective study. In addition, risk was significantly increased among young women (diagnosis ≤ 55 years) who had elevated plasma IGF-I [283]. Ovarian cancer risk showed no association with body mass index [285], an inverse but non-significant association with prediagnostic blood levels of C-peptide and no association with IGFBP-1 or IGFBP-2 [281]. Among postmenopausal women, circulating levels of FSH were unrelated to ovarian cancer risk [3].

These data suggest that ovarian tumour development may be enhanced by increased ovarian androgen production and by elevated IGF-I levels. Further studies are planned within the EPIC cohorts to confirm these findings.

Prostate cancer

R. Kaaks, E. Riboli, S. Rinaldi, D. Achaintre, J. Bouzac, P. Ferrari, C. Biessy; in collaboration with P. Stattin, H. Grönberg, G Hallmans, Umeå, Sweden; H.O. Adami, Stockholm, Sweden; and EPIC centre scientists

Much indirect evidence suggests the implication of sex steroids, notably androgens, in prostate tumour development [228]. The dominant theory is that risk would be increased in men who have elevated intraprostatic concentrations of dihydrotestosterone (DHT), which is formed within the prostate from testosterone by the enzyme 5α-reductase type II (encoded by the *SRD5A* gene). It is not clear, however, what determines inter-individual variations in prostatic DHT concentrations and how such variations are related to lifestyle factors. Some prospective studies have shown a direct association of prostate cancer risk with measures of total or bioavailable testosterone in the circulation, but others did not. There is also increasing evidence that elevated levels of IGF-I can enhance prostate tumour development.

In earlier studies in collaboration with the Northern Sweden Health and Disease Study, prostate cancer risk was found to be significantly and directly associated with prediagostic plasma levels of both IGF-I and IGFBP-3 (Stattin *et al.*, 2000, *J. Natl Cancer Inst.*, **92**, 1910–1917), but not insulin [33] or leptin [3]. A large study of 900 cases of prostate cancer and 900 matched controls within the EPIC cohort has been initiated to relate cancer risk to serum levels of IGF-I and IGFBP-3, as well as to serum concentrations of androstenedione, testosterone, androstane-17,3-diol-glucuronide (Adiol-G; a breakdown product of DHT).

Genetic association studies are being set up to examine possible relationships of prostate cancer risk with polymorphic variants (single nucleotide polymorphisms and their haplotypes) in a series of candidate genes involved in hormone metabolism (see below).

Colorectal cancer

R. Kaaks, E. Riboli, S. Rinaldi, C. Biessy, N. Slimani, P. Ferrari; in collaboration with R. Palmqvist, P. Stattin, G. Hallmans, T. Olson, Umeå, Sweden; L. Le Marchand, Hawaii, USA; and EPIC centre scientists

In a study within the NYUWHS cohort (Kaaks *et al.*, 2000, *J. Natl Cancer Inst.*, **92**, 1592–1600), we found a strong direct association of colon cancer risk with (non-fasting) serum levels of C-peptide and an inverse association with serum IGFBP-1

and IGFBP-2 – two IGF-binding proteins that are generally downregulated by insulin. A further prospective study within the Northern Sweden Health and Disease Study provided only weak confirmation of our first observations for C-peptide (insulin) [352], but did show a significant association of colon cancer risk with plasma IGF-I concentrations [351].

A large study within the EPIC cohorts is being initiated to examine the relationships of colon and rectal cancer risks with serum levels of C-peptide, IGF-I and IGFBP-3. In this study, we also plan to examine relationships of risk with estimates of dietary glycemic load and average glycemic index (estimated from dietary questionnaire data and glycemic index values for different foods) – a determinant of postprandial insulin levels. In addition, we are collaborating in a large case–control study of C-peptide, IGF-I, and IGF-binding proteins in relation to risk of colorectal adenomatous polyps.

In studies in Sweden, strong direct associations were found between circulating levels of leptin, a hormone that is synthesized in adipose tissue, and risk of of colon cancer [469,473].

The "metabolic syndrome" in relation to overall cancer incidence and mortality

R. Kaaks, A. Lukanova, S. Rinaldi; in collaboration with P. Stattin, G. Hallmans, Umeå, Sweden

The term "metabolic syndrome" refers to a constellation of metabolic dysregulations that include insulin resistance and chronic hyperinsulinaemia, elevated fasting and non-fasting blood glucose and triglyceride levels, reduced total cholesterol and reduced blood levels of high-density lipoprotein (HDL) cholesterol. The syndrome has a very high prevalence in affluent societies and is a well established risk factor for diabetes and cardiovascular disease. There is increasing evidence suggesting that the same metabolic syndrome is associated with increased risk of a number of cancers.

In collaboration with the Northern Sweden Health and Disease Study, we are conducting case–cohort and nested case–control studies to examine global associations of total cancer incidence and mortality, and incidence rates of several common cancers individually, with plasma concentrations of fasting and postload glucose, triglycerides and total cholesterol. For major cancer sites, we plan also to perform measurements of C-peptide, as a marker of circulating insulin levels, and of C-reactive protein, a marker of inflammation which is often also increased in obese and insulin-resistant subjects).

Early pregnancy hormone levels and testicular cancer risk in offspring

A. Lukanova, S. Rinaldi, R. Kaaks; in collaboration with M. Lehtinen, Helsinki, Finland; H. Ögmundsdóttir, Reykjavik, Iceland; P. Stattin, Umeå, Sweden; J. Dillner, Lund, Sweden

Testicular cancer is the most common cancer in men 20–40 years old in the Nordic countries, even though it represents only about 0.5–1.5% of all male cancers. Animal studies and epidemiological observations have suggested that elevated maternal blood concentrations of estrogens and decreased androgens may increase testicular cancer risk. Other pregnancy-related hormones, such as human chorionic gonadotropin (hHG), Mullerian inhibiting substance (MIS), human placental lactogen (HPL) and alpha-fetoprotein (AFP) have also been implicated.

In maternity cohorts in Finland, northern Sweden, Malmö (southern Sweden) and Iceland, more than 1.3 million women provided a blood sample in weeks 10–12 of their pregnancies, which were stored. Within these four cohorts, about 60 cases of testicular cancer in the offspring have been identified. For the mothers of these 60 cases, blood levels of sex steroids and pregnancy-related hormones will be measured and compared with the levels of 180 matched controls.

Hormone-related genetic association studies

R. Kaaks, E. Riboli, F. Canzian, A. Lukanova, P. Ferrari, C. Biessy, C. Lallemand, C. Boillot, S. Landi, D. Cox, in collaboration with G. Thomas, Paris, France; H.O. Adami, Stockholm, Sweden; P. Stattin, H. Grönberg, Umeå, Sweden; B. Ponder, Cambridge, UK; EPIC centre scientists; and International Cohort Consortium on Gene–Environment Interactions: D. Hunter, Boston, MA, USA; M. Thun, Atlanta, GA, USA; B. Henderson, Los Angeles, CA, USA; L. Kolonel, Hawaii, USA; R. Hayes, D. Albanes, Bethesda, MD, USA

Part of the variation in circulating IGF-I levels can be explained by differences in nutritional status, especially the availability of energy and amino acids from diet and body reserves (Kaaks & Lukanova, 2001, *Proc. Nutr. Soc.*, **60**, 91–106). In addition, heritability studies have shown that in well nourished populations, about half of the variation in IGF-I is (co-)determined by genetic factors. So far no studies have been reported that include a comprehensive search for polymorphisms in genes covering the regulation of IGF-I synthesis. These genes include those encoding for IGF-I and IGFBP-3, but also those involved in pituitary release or biological action of growth hormone – the primary physiological stimulus for the synthesis of both IGF-I and IGFBP-3. Other genes that may also affect the risk of prostate cancer, probably without altering plasma and prostatic tissue levels of IGF-I and/or IGFBP-3, include those encoding the IGF-I receptor and IGFBP-1, -2, -4, -5 and -6.

Very similar questions can be asked with respect to sex steroid metabolism. Candidate genes include pituitary hormones (gonadotropins, adrenocorticotropin) and their releasing hormones and receptors, steroidogenic and steroid-metabolizing enzymes, SHBG and steroid hormone receptors.

Within the EPIC study, as well as in a large case–control study on prostate cancer ("CAPS") in Sweden, studies have been initiated to relate polymorphisms in more than 50 candidate genes involved in hormone and growth factor metabolism to risk of breast and prostate cancers. The EPIC studies are conducted in parallel with our studies on blood levels of sex steroids, IGF-I and IGFBP-3 (discussed above). The global strategy in these studies is to: (1) prepare an exhaustive catalogue of polymorphisms (coding and non-coding regions) in candidate genes that make up complete metabolic pathways; (2) determine haplotypes and haplotype-tagging single nucleotide polymorphisms (SNPs);

Table 4. Cohorts of the Consortium on Gene–Environment Interactions related to Hormone Metabolism

Cohort	*Institution*	*Total no. with DNA samples*	*No. of breast cancer cases*	*No. of prostate cancer cases*
EPIC	IARC	397 256	2050	900
American Cancer Society (CPS-II)	American Cancer Society	39 000	500	1450
ATBC	NCI	20 500	–	1000
Harvard				
Physicians' Health Study	Brigham and Women's Hospital	20 000	–	1500
Nurses' Health Study	Brigham and Women's Hospital	32 826	945	–
Health Professionals Study	Harvard School of Public Health	33 240	–	600
Womens' Health	Brigham and Women's Hospital	28 263	675	–
Multi-ethnic cohort (California and Hawaii)	University of Hawaii/University of Southern California	100 000	1990	2400
Prostate, lung, colorectum and ovary screening cohort	NCI	75 000	–	1000
Total		797 085	6160	8850

(3) assess the association of gene variants (haplotype-tagging SNPs) with plasma steroid hormones, IGF-I levels and cancer risk; (4) assess interactions between genetic polymorphisms and endogenous hormone levels in determining breast and prostate cancer risks; (5) assess interactions between polymorphisms and lifestyle and anthropometric factors, as determinants of endogenous hormone levels.

These studies involve a consortium of established prospective cohort studies in the United States and two institutions specializing in genomics and genetic epidemiology (the Whitehead Institute, Massachussetts Institute of Technology, Boston; the Centre d'Études des Polymorphismes Humains, Paris). The overall study will include a total of over 6000 cases of breast cancer and over 8000 cases of prostate cancer (Table 4), which will allow a powerful evaluation of genetic main effects and gene–gene or gene–environment interaction effects, as well as of the consistency of findings between cohorts or ethnic subgroups.

2.5 *Tobacco*

Tobacco is the most widely used carcinogen in the world. New evaluations of tobacco smoke and involuntary smoking, as well as of betel quid with tobacco, in the *IARC Monographs* programme, confirmed their carcinogenicity (see Section 2.1). Although some countries have made effective efforts to control its use and promotion, others clearly lag behind and for the developing world, predictions are extremely pessimistic. The annual world burden of tobacco-related deaths is already close to five 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.

Several studies of bladder, kidney, lung and head and neck cancers are addressing various aspects of the carcinogenic effect of tobacco smoke (Sections 3.6–8). For public health purposes, urgent action is needed with careful evaluation of its outcome.

Population studies of tobacco use

A.J. Sasco, V. Luzon, H. Besson, J. Berthiller; in collaboration with F. Ben Ayed, Tunis, Tunisia; P. Delormas, Grenoble; G. Freyer, M. Jambon, Lyon; J.P. Gérard, Nice; I. Grémy, Paris; J. Vulliet, Annemasse, France; R.E. Little, Chapel Hill, NC, USA, R.M. Merrill, Provo, UT, USA; P. Wangai, Nairobi, Kenya

Several studies have been carried out among children, adolescents and young adults to evaluate risk factors for smoking and other substance-abuse behaviour. Several descriptive studies have been completed. A cross-sectional survey of 913 children aged 9–11 years in 31 randomly selected schools in the Loire department of France demonstrated the early initiation of tobacco use, with 12.3% of the children having already tried tobacco; the risk of using tobacco was higher for boys, older age, those drinking alcohol and having team activities [426]. Among older adolescents in a study conducted over seven years in three schools, regular smoking was associated with the view that taking care of one's health is not important, not eating breakfast regularly, as well as belonging to groups and having best friends who smoke [427].

Health professionals constitute a group of specific interest because of its potential for role modelling. A study was conducted among all general practitioners of a town in the Rhône-Alpes region. About 25% are smokers and their smoking habits negatively influence their behaviour towards their patients. 85% of non-smokers systematically ask about their patients' smoking habits, while only 56% of smokers do so [174].

A detailed study of knowledge, attitudes and perceptions of the Paris population has been conducted to evaluate their relation to tobacco use. More than 2500 adults, aged 18–75 years, were included. Results clearly show that risks linked to tobacco use are underestimated in the general population and more so among smokers [188].

These studies indicate that smoking is still an important problem in France [412],

including passive smoking [420], despite the heavy associated disease burden [419]. In order to find new arguments against smoking that would be more convincing to young people, a large study of more than 16 000 subjects conducted in collaboration with the French Federation of Dermato-venereology is studying the association between acne and smoking [541].

Knowledge on precise frequency and determinants of tobacco use in parts of the world, such as Africa, is scanty. Some pilot collection of data using a standardized questionnaire developed at IARC has been carried out in several countries such as Algeria, Guinea, Kenya [545, 546], Senegal and Tunisia. At present, tobacco use remains limited mainly to men, but is beginning to increase among young women.

Anti-smoking strategies

A.J. Sasco; in collaboration with P. Mélihan-Cheinin, P. Mourouga, Paris, France; R. Roemer, Los Angeles, CA, USA

Several health promotion programmes, mostly based in schools, are being evaluated. Whereas descriptive studies often indicate some small impact, randomized design and strict analysis tend to yield less favourable results. For example, a study conducted over a three-year period among more than 6000 children aged 10–12 years, following a randomized design at the school level, failed to show any substantial effect on initiation of smoking. In contrast, positive results were seen for children belonging to non-smoking clubs such as those existing in France, but selection biases may be responsible in part for the favourable effect.

The EuroLego project, running since 1988, involves the continuing collection of all legislative texts pertaining to tobacco control in the 15 Member States of the European Union; these 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. More than 500 legislative texts have been assembled.

Figure 18. A *bidi* smoker in Mumbai, India

Analyses have been conducted on specific aspects, such as smoking in public places and at the work-place [429]. The collection of texts on additives and definition of tobacco products has also helped in the framework of specific reports, such as on reduction of harm from smoking [139].

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, M. Pedenekar, Mumbai, India; P. Jha, Washington DC, USA; A. Lopez, Geneva, Switzerland; K. Ramadas, B. Mathew, B. Jose Jacob, G. Thomas, K.T. Shenoy, Trivandrum, India

Little is known about the excess mortality due to different forms of tobacco use in India, such as *bidi* smoking (Figure 18) and various types of smokeless tobacco use. Two cohort studies in India, in Mumbai and Trivandrum, are addressing this issue.

The Mumbai cohort comprises 150 000 subjects. Analysis of the follow-up details of 99 598 individuals aged 35 years or above was recently completed. In an active follow-up undertaken after 5–6 years, 97.6% of these subjects were traced, among whom 7531 deaths were recorded. Cause of death information for 5470 deaths was abstracted from municipal records. The mortality rates for smokers were higher than those in non-users of tobacco across all age groups among men, the excess risk being higher for younger age groups (35–54 years). The relative risk adjusted for age and education was 1.36 (95% CI 1.22–1.52) for cigarette smokers and 1.68 (95% CI 1.52–1.85) for *bidi* smokers, with a significant dose–response relationship for frequency of smoking per day. Smoking among women is rare, but many women use smokeless tobacco, and the relative risk (compared with non-users) adjusted for age and education was 1.26 (95% CI, 1.16–1.37). In men, the risk of death from respiratory diseases, tuberculosis and neoplasms among smokers was double that for non-smokers.

The Trivandrum cohort consists of 154 000 subjects (aged 30 years or above) from rural areas and 116 000 adult males (25 years or above) from the city. Among the urban males, 48.3% were smokers and 16.5% were tobacco chewers, while in the rural males, the proportions were 49.8% and 23.5%, respectively; the proportion of chewers in the rural females was 20.3% and of smokers was 1.0%. Detailed analysis of this cohort has started.

Health effects of tobacco smoking and alcohol drinking in the Russian Federation

P. Brennan, P. Boffetta; in collaboration with I.N. Konobeevskaia, Tomsk, Russian Federation; A.P. Lazarev, V.I. Igitov, Barnaul, Russian Federation; R. Peto, Oxford, UK; L. Shkolnikova, Biysk, Russian Federation; V.G. Tcherenkov, Novgorod, Russian Federation; D.G. Zaridze, T. Men, Moscow, Russian Federation

Adult mortality rates in the Russian Federation increased rapidly in the period immediately after the break-up of the Soviet Union, but a sharp improvement was observed in the period 1995–98. Vascular diseases and external causes were responsible for the majority of these changes, which were probably influenced by increased alcohol consumption. After the economic crisis in 1998, an analysis of mortality rates

showed that life expectancy fell to 58.9 among men and 71.8 among women by 2001. Trends were similar in all parts of the country. Overall, 2 500 000–3 000 000 more Russian adults died in middle age in the period 1992–2001 than would have been expected based on 1991 mortality rates [305]. In order to investigate these trends in more detail and to assess the contributions of tobacco smoking and alcohol drinking, a retrospective cohort study on adults who died in the period 1991–2000 is being conducted in four Russian cities (Barnaul, Biysk, Novgorod and Tomsk). Family members are interviewed in order to obtain information on alcohol and tobacco consumption and other lifestyle habits of the deceased. All adult household members as well as neighbours also undergo a lifestyle interview, including measurement of blood pressure and body mass index, in order to form a prospective cohort for future follow-up. A blood spot sample is also collected. Recruitment will continue until 2005 for an expected sample size of 150 000 live household members and neighbours and 100 000 deceased subjects.

2.6 Radiation

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. The effects of non-ionizing radiation (such as radiofrequency (RF) radiation, particularly in relation to mobile telephones) are also being studied. This work has two goals: to strengthen the scientific basis of radiation protection and to improve our understanding of biological mechanisms of carcinogenesis.

Effects of protracted low doses of external ionizing radiation

International collaborative study of cancer risk among radiation workers

E. Cardis, M. Vrijheid, H. Tardy, E. Combalot, 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. Seltz, Cologne; *Hungary*, A. Kerekes, I. Turai, Budapest; *Japan*, T. Iwasaki, M. Murata, S. Ohshima, Tokyo; T. Yoshimura, Kitakyushu; *Lithuania*, J. Kurtinaitis, A. Mastaukas, Vilnius; *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; M. Pearce, Newcastle; *USA*, J. Fix, Richland, WA; E. Gilbert, Rockville, MD; B. Murray, D. Richardson, R. Rinsky, M. Schubaeur-Berigan, D.Utterback, Cincinnati, OH; G. Howe, New York

The International Collaborative Study of Cancer Risk among Radiation Workers, a retrospective cohort study of cancer mortality among nuclear industry workers (Table 5), has been completed. The objective of the study was 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 were received from 15 countries (and over 124 installations – 89 involved in the commercial production of nuclear energy and 35 mixed-activity facilities). Overall, data on 590 000 workers employed in the participating facilities between 1943 and 2000 were collected, using a common core protocol. The international data-set was finalized in late 2002.

The main analyses were carried out in 2003 and focused on slightly more than 400 000 workers who were employed for more than one year in any of the participating facilities, monitored for external radiation with the use of a personal dosimeter and whose dose came predominantly from external photon radiation. Subjects who received substantial doses from neutrons, very low-energy photons and internal contamination were excluded from these analyses because of difficulties in adequately quantifying doses from these radiation types. The analyses

Table 5. Countries, facilities and approximate number of workers included in the International Collaborative Study

Countries	Facilities	Workers
Australia	All	2327
Belgium	SCK, Belgo Process, BN: Belgo Nucléaire, Doel, Tihange	7206
Canada	All	54 492
Finland	All	11 966
France	CEA-COGEMA, civil	29 655
	Electricité de France	22 302
Hungary	All	3444
Japan	All	114 900
Korea	All	9063
Lithuania	Ignalina	4986
Slovakia	All	2776
Spain	All	3726
Sweden	All	29 718
Switzerland	All	1822
United Kingdom	All	121 686
United States	Oak Ridge National Laboratory	8314
	Hanford	44 106
	Idaho National Engineering Laboratory	69 388
	15 utilities	60 531

CEA, Commissariat à l'Energie Atomique; COGEMA, Compagnie Générale des Matières Nucléaires

include over 5 million person-years of follow-up and over 24 000 deaths, including 275 leukaemia deaths and over 6500 deaths from other cancers. Results were reviewed at a meeting of the study investigators in Lyon on October 2003.

Risk estimates have been derived for all cancers excluding leukaemia and for leukaemia excluding chronic lymphocytic leukaemia – the two main groupings of causes of death for which risk estimates have been derived from high-dose studies – and compared with estimates derived from the atomic bombing survivors' cohort. The results of this study are the most precise direct estimates of the effects of low-dose protracted exposures to date and as such are of direct relevance for the protection of workers and the general population. The detailed report of the study is being finalized.

The study of biases and random errors in the radiation dose estimates has been also been completed and a method to take these errors into account in the risk estimation has been developed and implemented, using Monte-Carlo simulations. Further analyses taking into account errors in doses are continuing.

The feasibility is being investigated of carrying out nested case–control studies of specific cancer types, particularly leukaemia and lung cancer, to evaluate separately the cancer risk related to (*a*) different types of radiation (-rays, neutrons, internal contamination with tritium, plutonium and other radionuclides) after adjustment for possible confounding factors and (*b*) low-dose radiation exposure in persons with deficiencies in DNA damage recognition or repair.

Case–control studies of leukaemia and non-Hodgkin lymphoma and of thyroid cancer among Chernobyl accident recovery workers

E. Cardis, A. Kesminiene, V. Drozdovich, E. Maceika, V. Tenet; in collaboration with V.K. Ivanov, S. Chekin, S. Khait, A.P. Konogorov, M. Maksyoutov, V. Matiash, V.A. Pitkevitch, N. Shchukina, Obninsk, Russian Federation; I. Golovanov, Yu. Gavrilin, V. Krjuchkov, M. Savkin, A. Tukov, Moscow, Russian Federation; I. Shantyr, St Petersburg, Russian Federation; A. Mirkhaidarov, Gomel, Belarus; V. Gapanovitch, E. Ivanov, I. Malakhova, S. Poliakov, N. Shabeka, Minsk, Belarus; J. Kurtinaitis, Vilnius, Lithuania; A. Stengrevics, Riga, Latvia; M. Tekkel, Tallinn, Estonia; E. Bakhanova, V. Chumak, Kiev, Ukraine; V. Andreev, V. Glebov, S. Illychov, A. Tsykalo, Chernobyl, Ukraine; A. Bouville, Bethesda, MD, USA; L. Anspaugh, Salt Lake City, UT, USA; P. Hubert, Paris, France

Two nested case–control studies have been 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 15 000 liquidators in Baltic countries, 66 000 Belarus and 65 000 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 Chernobyl registry of these countries. The study includes cases diagnosed between 1990 and 2000 (the study period slightly differs between the countries). Four controls were selected from the same study population for each case, matched on age, gender and region of residence at the time of the accident. 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 about exposure to potential confounding factors. In addition, a blood sample was obtained from prospective cases (before treatment) and relevant controls for future biological dosimetry. Overall, approximately 125 cases of leukaemia and lymphoma, 125 cases of thyroid cancer and their respective controls were interviewed. Diagnoses were reviewed by an international panel of pathologists and haematologists. Data collection has been completed and data validation and correction are in progress.

A method of analytical dose reconstruction (and estimation of associated uncertainties) using information collected by questionnaire together with dosimetric and environmental measurement data has been developed, validated extensively and applied to the estimation of doses and related uncertainties for all subjects. Dose reconstruction is nearing completion.

The European Childhood Leukaemia/ Lymphoma Incidence Study (ECLIS)

D.M. Parkin, A.H. Loos, E. Masuyer, E. Šteliarová-Foucher, P. Vizcaino; 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*, P. Kaatsch, 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; UK, *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

Supported by the Radiation Protection Research Action of the European Commission

The main aims of this project, initiated in 1988, are to evaluate the incidence of childhood leukaemia in Europe since 1980 and to determine whether any trends observed are quantitatively associated with estimated exposure to radiation due to the Chernobyl accident in April 1986.

Data have been collected for the period 1980–97 from collaborating centres in 24 countries. An analysis conducted in 2002 focused on the risk of leukaemia by age (six-month intervals) in relation to the estimated doses of radiation received *in utero* due to the Chernobyl accident. Estimates of the excess radiation doses that resulted from the accident were provided by UNSCEAR. The results suggest a small increase in risk in young (age < 6 months) and older infants (age 24–29 months). Possible sources of bias are

being checked, especially the possibility of differential availability of day/ month of birth and diagnoses. Further analyses of the association between exposure and incidence rates are being conducted with more flexible statistical models.

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; 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. The database is being updated with more recent data, and with thyroid cancers separated into the different histological types.

Feasibility study of effects of depleted uranium on civilians in Iraq

M. Vrijheid, E. Cardis; in collaboration with M. Repacholi, Geneva, Switzerland; A. Ahlbom, Stockholm, Sweden

Concern has been expressed by many organizations worldwide that use of depleted uranium in conflict is associated with increases in cancer incidence and birth defects in Iraq, and among military personnel using munitions containing depleted uranium. In the absence of detailed information on the relevant exposures and on the completeness and accuracy of the population and disease registries in Iraq, several feasibility and pilot studies have been initiated, in order to identify the main exposures of concern for the general population and to assess the most efficient mechanisms for conducting informative epidemiological studies (ecological or analytical epidemiological). These include: (*a*) an assessment of the feasibility of ecological studies of cancer incidence, considering regional differences and time trends as appropriate; (*b*) a feasibility study to evaluate the mechanisms and difficulties in identifying and following up populations exposed to depleted uranium; and (*c*) an evaluation of the feasibility of carrying out a case–control study of leukaemia among children in Iraq, focusing primarily on the effects of depleted uranium exposure during the 1991 and 2003 conflicts, as well as other case–control studies of specific relevant end-points.

Work on these projects has been suspended due to the military and security situation in Iraq.

Health effects of non-ionizing radiation

The INTERPHONE study

E. Cardis, I. Deltour, L. Richardson, M. Vrijheid, D. McLean, E. Combalot, N. Encrenaz, J. Hua, M. Rousch; in collaboration with: *Australia*, B. Armstrong, M. Carroll, M. Kilkenny, J. Browne, Sydney; *Canada*, P. Carty, M.C. Goulet, D. Krewski, Ottawa, M. McBride, Vancouver; L. Nadon, M.E. Parent, A. Pope, J. Siemiatycki, Quebec; *Denmark*, C. Johansen, H. Collatz-Christensen, Copenhagen; *Finland*, A. Auvinen, T. Salminen, Tampere; *France*, J. Wiart, Issy-Les-Moulineaux; M. Hours, L. Montestrucq, Lyon; *Germany*, M. Blettner, G. Berg, Bielefeld; J. Michaelis, J. Schuez, Mainz; K. Schlaefer, B. Schlehofer, Heidelberg; *Israel*, A. Chetrit, S. Sadezki, Tel-Hashomer; B. Modan, Tel Aviv; *Italy*: S. Lagorio, I. Iavorone, L. Ardoino, P. Vecchia, Rome; *Japan* M. Taki, T. Takebayashi, N. Yamaguchi, Tokyo; *New Zealand*, A. Cook, N. Pearce, A. Woodward, Wellington South; *Norway*, T. Tynes, L. Klaeboe, Oslo; *Sweden*, M. Feychting, S. Lönn, Stockholm; *UK*, L. Findlay, Edinburgh; P. McKinney, J. Doughty, R. Parslow, Leeds; A. Swerdlow, M. Schoemaker, Sutton; S. Mann, Oxford; M. Van Tongeren, Birmingham; *USA*, J. Bowman, Cincinnati, OH

A series of multicentric case–control studies is being conducted to determine whether mobile telephone use increases cancer risk and, specifically, whether the radiofrequency radiation emitted by mobile telephones is carcinogenic.

Separate studies are being carried out for acoustic neurinomas, gliomas and menin-

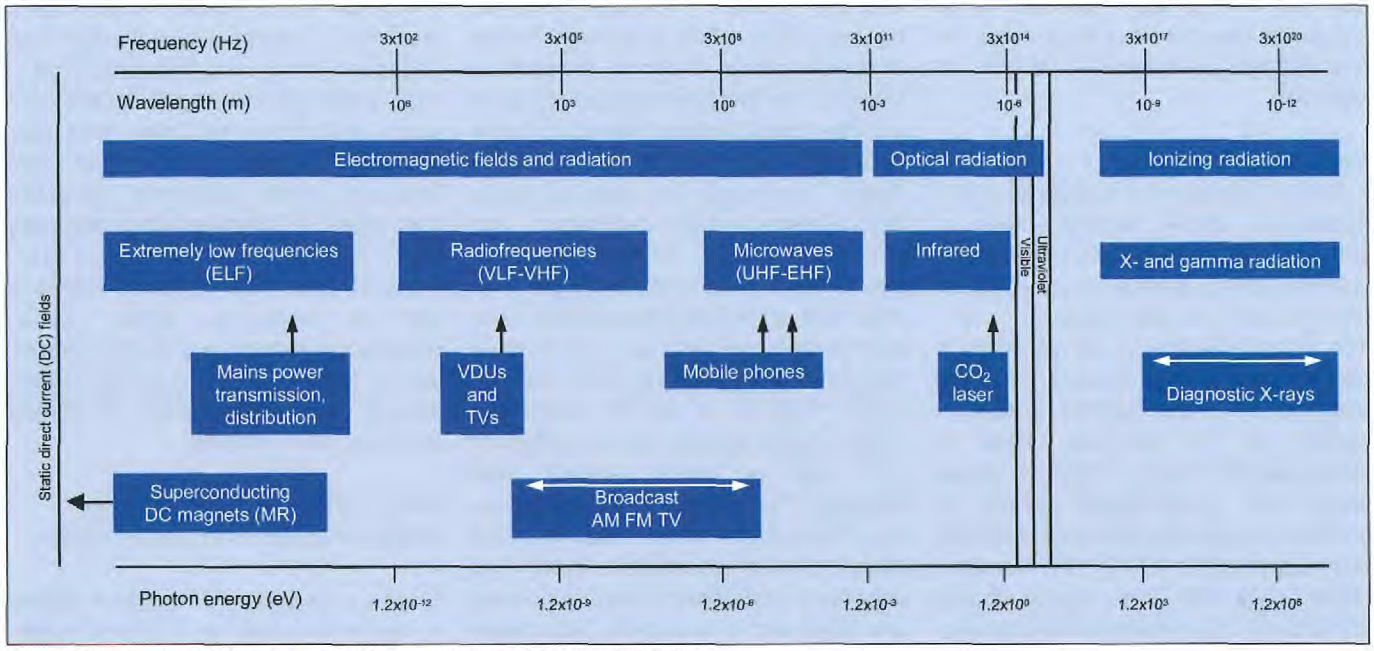


Figure 19. The spectrum of electromagnetic fields and radiations, and their uses in daily life

giomas and tumours of the parotid gland, the tumours that would be most likely to be related to mobile telephone use. The studies, using a common core protocol, are in progress in Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the United Kingdom.

Validation studies are being conducted to investigate the accuracy of self-reported use of mobile phones, including the use of software-modified telephones which allow collection of information on distribution of emitted power, in various countries or regions and by pattern of use.

An exposure gradient is being constructed, based on information from the questionnaire, the software-modified telephones, specific experiments and simulations of the spatial distribution of emitted power in the head and published data on radiation characteristics of commercial phones. A protocol to identify the anatomical origin of the tumour from magnetic resonance imaging and computerized tomography scans has been developed and tested and is now being used in all of the participating countries.

At 31 August 2003, the INTERPHONE study had completed about 8500 interviews (4502 cases and 3984 controls). Data collection was completed in 2003 in Denmark, Sweden and Finland and will be completed elsewhere in a few months. The first data-sets were received at IARC in late 2003.

International EMF project

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

The overall objective of this project is to pool resources of international and national agencies and key scientific institutions working on the biological effects of electromagnetic fields, in order to assess health and environmental effects of exposure to static and time-varying electric and magnetic fields (EMF) in the frequency range 0–300 GHz (this range is divided into static (0 Hz), extremely low-frequency (ELF, >0–300 Hz) and radiofrequency (RF, 300 Hz–300 GHz) fields).

IARC continues its involvement by assisting in the identification of gaps in scientific knowledge, making recommendations about research protocols and carrying out critical reviews of the literature on ELF and RF radiation.

Modifiers of radiation risk

Thyroid cancer in young people following the Chernobyl accident

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

A population based case–control study of thyroid cancer in young people has been carried out in the most contaminated regions of Belarus (Gomel and Mogilev) and the Russian Federation (Bryansk, Kaluga, Orel and Tula) to evaluate the risk of thyroid cancer related to exposure to iodine-131 in childhood and adolescence and the role of environmental and host factors that may modify this risk. Such factors include age at exposure, stable iodine intake, genetic background and reproductive history. The study population was all those living in these regions who, at the time of the Chernobyl accident, were aged 0–14 years(Belarus) or 0–18 years (Russia). Cases were recruited over the period 1992–98. In all, 301 cases and 1948 controls (489 matched on settlement and 1459 on *oblast* (region)) were recruited. The majority of subjects were from Belarus. Information was collected using a detailed questionnaire, clinical and ultrasound examinations were conducted and blood and urine samples were taken from subjects who consented. Data collection and verification were completed in 2002. A panel of pathologists met to review the diagnoses and, overall, the agreement with the original diagnosis was good when sufficient material was available for the review.

Validated methods for estimating individual thyroid doses of iodine-131 and short-lived isotopes (and associated uncertainties) have been used to finalize dose estimates. The median internal doses from iodine-131 were estimated to be approximately 400 and 30 mGy in Belarus and Russia, respectively.

Though the territories affected by the Chernobyl accident are known to have been and to remain iodine-deficient areas, no reliable and systematic index of iodine deficiency at the time of the accident was available for the entire territory of the study. The area-weighted iodine content in soils around the settlements where study subjects lived at the time of the accident and at least for one year afterwards was estimated in 2003 using different soil maps available in Russia and Belarus.

The main analyses have been carried out and the results were reviewed at a meeting of the study group in December 2003. Descriptive analyses showed that risk of thyroid cancer was significantly associated with a number of factors that are likely to reflect potential for exposure. Cases in Belarus more frequently lived in rural areas and in wooden houses, and drank milk from local cows than their respective controls. Controls had more frequently taken preventive measures than cases. A significant dose–response relationship for thyroid cancer was seen. Analyses of modifying factors (including age at exposure, iodine status, reproductive factors (in girls and women), dietary factors, history of benign thyroid disease and family history of thyroid diseases) are continuing.

CHILD-THYR: risk of thyroid cancer following exposure to iodine-131 early in life

E. Cardis, A. Kesminiene, V. Drozdovitch, E. Maceika, V. Tenet; in collaboration with S. Davis; K. Kopecky,

Seattle, WA, USA; F. Doyon, F. de Vathaire, Villejuif, France; P. Hall, Stockholm, Sweden; V.K. Ivanov, Obninsk, Russian Federation; I. Malakhova, Minsk, Belarus;E. Negri, Milan, Italy; S. Simon, Bethesda, MD, USA; K. Trott, M. Schoemaker, London, UK

A project has been initiated to bring together formally data from several recent epidemiological studies of thyroid cancer in relation to iodine-131 exposure in childhood and adolescence (including the IARC thyroid cancer case–control study outlined above). The studies considered for inclusion were carried out in Belarus, the Russian Federation, French Polynesia, the United States (Hanford site) and the Marshall Islands, in populations with different genetic backgrounds and distributions of host and environmental risk factors. This analysis will allow (*a*) more precise evaluation of the risk of thyroid cancer related to iodine-131 exposure in childhood and adolescence; (*b*) comparison of iodine-related thyroid cancer risk across studies in different settings and (*c*) assessment of the role of environmental and host factors that may modify radiation-induced thyroid cancer risk. As such, it will maximize the information that can be drawn for radiation-protection purposes from the various studies.

Gene–radiation interactions: their influence on pre-menopausal breast cancer risk after the Chernobyl accident

E. Cardis, A. Kesminiene, J. Hall, V. Drozdovitch, E. Maceika, V. Tenet, O. Sinilnikova; in collaboration with A. Bouville, Bethesda, MD, USA; R.A. Eeles, London, UK; L. Gulak, I. Likhtarev, L. Kovgan, Kiev, Ukraine; I. Malakhova, Minsk, Belarus; M. Savkin, S. Shinkarev, Moscow, Russian Federation

In recent years, an increase in breast cancer incidence, mainly in young women, has been reported in areas of Belarus and Ukraine contaminated by the Chernobyl accident. A project has been set up to explore whether this increase is related to radiation exposure due to the accident and to assess the feasibility of a population-based case–control study of a possible interaction between radiation exposure and genes (*BRCA1*, *BRCA2* and *ATM*) that are known to influence radiation sensitivity and the risk of breast cancer development. Four components of the project are in progress:

(1) Carrying out a full descriptive epidemiological analysis of breast cancer incidence in Belarus and Ukraine, focusing on age–cohort–period–region analyses to evaluate whether increases in pre-menopausal breast cancer incidence in Belarus and Ukraine seen since 1986 are related to radiation exposure from the Chernobyl accident.

(2) Evaluating the mechanisms necessary to carry out a population-based case–control study of breast cancer in the *oblasts* of Gomel and Mogilev in Belarus and of Kiev, Zhitomir and Chernigov in Ukraine.

(3) Testing the procedures for collecting and analysing relevant blood and tissue samples to be used within the case–control study to assess molecular alterations in breast cancer susceptibility genes.

(4) Developing and testing models to estimate individual doses for use in a population case–control study, if it is feasible. Both external and internal exposure pathways will be considered.

2.7 *Viral infections*

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 being tested. 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 liver cancer (Section 3.3), cervical cancer (Sections 3.4 and 5.1) and lymphomas (Section 3.9); the Gambia Hepatitis Intervention Study (Section 5.1) is examining the effect of vaccination against the hepatitis B virus in preventing liver cancer.

Studies of HIV/AIDS and cancer

Cancer trends in relation to HIV prevalence

D.M. Parkin; in collaboration with E. Chokunonga, M. Borok, Harare, Zimbabwe; C.Dzamalala, G.Liomba, Blantyre, Malawi; H. Sriplung, Hat Yai, Thailand; H. Wabinga, Kampala, Uganda

In Africa, the cancer registries of Kampala (Uganda), Harare (Zimbabwe) and Blantyre (Malawi) provide data for monitoring of trends in cancer incidence in relation to the HIV epidemic. Changes in age-specific rates of Kaposi sarcoma, non-Hodgkin lymphoma (including Burkitt lymphoma) and squamous-cell cancers of the conjunctiva are of particular interest.

An analysis of trends in Kaposi sarcoma and non-Hodgkin lymphoma from the cancer registries in Thailand (see Section 1.2) in relation to trends in prevalence of HIV infection in the population does not suggest that the incidence of either cancer has been influenced.

Case–control studies of Kaposi sarcoma, conjunctival carcinoma and non-Hodgkin lymphomas, in relation to HIV infection

D.M. Parkin; in collaboration with V. Beral, R. Newton, R. Weiss, Oxford, UK; K. deCock, London, UK; H. Jaffe, Atlanta, GA, USA; E. Katangole Mbidde, H. Wabinga, Kampala, Uganda; J. Ziegler, San Francisco, CA, USA

Further analyses from the large case–control study in Kampala, Uganda, carried out in 1994–98, have been completed. A comparison of 60 cases of conjunctival cancer with control subjects confirmed the strong risk posed by HIV infection (OR = 10.1), but there was no association with infection with certain common types of HPV, as measured serologically. A total of 669 cases of Kaposi sarcoma were recruited; HIV-positive cases had more

widespread or disseminated disease than those that were HIV-negative. Case–control studies of Kaposi sarcoma in HIV-positive and -negative subjects have been completed, with non-AIDS-associated cancer patients, and non-cancer patients, as controls. In both groups, human herpesvirus type 8 (HHV-8) (also known as Kaposi sarcoma-associated herpesvirus; KSHV) was a clear risk factor, although it was not related to the clinical presentation of the disease. HHV-8 is common in the Uganda population, with a prevalence of about 50% in adults. Prevalence increases with age, but there is no obvious geographical variation, and no association with other sexual and reproductive variables, or with HIV status.

Prospective study of the risk of cancer in individuals with HIV/AIDS in Uganda

D.M. Parkin; in collaboration with S. Mbulaiteye, E.A. Engels, Bethesda, MD, USA; E. Katabira, H. Wabinga, Kampala, Uganda

The Uganda AIDS–Cancer Match Study began in 2002 as a collaboration between the US National Cancer Institute, IARC and Ugandan scientists. The aim is to prospectively describe the spectrum of cancers occurring among patients with AIDS and quantify the risk, including the role of common viral infections (HHV-8, HPV type 16, hepatitis B virus (HBV), Epstein–Barr virus (EBV)) and other infections, as well as to study predictors of cancer occurrence among HIV-infected people (CD4 lymphocyte counts, cytokine profile, oncogenes, viral load etc.). The study depends upon linkage of records from an AIDS-support organization in Kampala and the cancer registry. As well as Kaposi sarcoma, the magnitude of risk for non-Hodgkin lymphoma (including Burkitt lymphoma) is of interest, as both appeared to be low in an earlier case–control study. A cohort of about 12 000 HIV-positive individuals will be followed up.

Excess cancer burden in persons infected with HIV

S. Franceschi, G. Clifford; in collaboration with C. Bouchardy, Geneva, Switzerland; L. Dal Maso, J. Polesel, Aviano Italy; G. Rezza, Rome, Italy; M. Rickenbach, P. Francioli, F. Levi, Lausanne, Switzerland

In addition to the malignancies indicative of AIDS in persons infected with HIV, namely Kaposi sarcoma, non-Hodgkin lymphoma [121] and invasive cervical cancer [442], increased relative risks (RRs) in HIV-infected persons have been reported for other infection-related malignancies [123]. These cancer excesses are likely to result from the combined effects of the HIV-associated immune suppression or dysregulation and viruses other than HIV (e.g., HPV, EBV). In a record-linkage study involving the Italian Registry of AIDS and 19 cancer registries between 1985 and 1998 (covering 23% of the Italian population), significantly increased RRs in HIV-infected persons were observed for Kaposi sarcoma (1749), non-Hodgkin lymphoma (352) and invasive cervical cancer (22), as well as for cancer of the anus (34), lung (2.4), brain (4.4), Hodgkin disease (16) and leukaemias (5.3) [123] (Dal Maso *et al.*, 2001, *J. Biomed. Inform.*, **34,** 387–395).

Another study has been performed to link records on a large cohort of HIV-infected persons with cancer registries across Switzerland. The advantage of using a registry of infected persons, rather than of AIDS patients, is that follow-up data are available for patients (i) who die from cancer or other causes before developing AIDS, (ii) in whom cancer occurs long before AIDS diagnosis; and (iii) who do not develop AIDS following cancer diagnosis. The analysis of these data now in progress should have the power to identify any changes in cancer risks associated with the introduction of the highly active antiretroviral therapies (HAART) in the mid 1990s, which has greatly modified the natural history of AIDS, reducing AIDS-associated morbidity and mortality. We have already observed reductions in the incidence of Kaposi sarcoma and non-Hodgkin lymphoma [121,161] (Dal Maso *et al.*, 2001, *Cancer Treat. Res.*, **104**, 1–18), but the effect of HAART on the incidence of other cancers in HIV-infected individuals remains unclear.

Genetic epidemiology of nasopharyngeal carcinoma

M. Corbex, D.E. Goldgar, C. Bonnardel, O. Yaqoubi, V. Gaborieau, F. Odefrey, H. Renard; in collaboration with F. Ben Ayed, W Ben Ayed, Tunis, Tunisia; K. Boualga, Blida, Algeria; L. Chouchane, Monastir, Tunisia; M. Hamdi-Cherif, Sétif, Algeria; M. Khyatti Casablanca, Morocco

Supported by the Association for International Cancer Research

Nasopharyngeal carcinoma (NPC) is a malignancy with unusually variable incidence rates across the world. In most parts of the world it is a rare disease (e.g., 0.5 cases/100 000 per year in the UK), but in some regions it occurs in an endemic form with an incidence 10- to 40-fold higher than elsewhere. Endemic regions include the southern parts of China, other parts of south-east Asia and the Maghreb (Morocco, Algeria and Tunisia). In the Maghreb, NPC is the most frequent ear, nose and throat cancer, accounting for 7–12% of all cancer. Moreover, it is the most frequent carcinoma affecting young people and may appear as early as ages 8–10 years. Thus, in contrast with the other high-risk populations, the Maghrebian population shows a bimodal age distribution of NPC, one peak occurring in the teens and the other at 45–50 years.

This project is investigating the role of genes and environmental factors, and their interactions, in the etiology of NPC. Its main component is a multi-centre case–control and family-based study in the Maghreb. In addition to testing previously suggested environmental risk factors in this population, the study aims to characterize the magnitude of familial risk of NPC in the Maghrebian population and examine the potential role of consanguinity in NPC incidence. It will also test suggested NPC susceptibility loci and map new genes using families with multiple cases, and examine the role of the HLA genes and

other candidate genes in the etiology of NPC.

A total of 443 cases and 180 controls have been recruited into the study, approximately half-way to the enrolment target. We have implemented a relational ORACLE database to manage the questionnaire and genotype data. Approximately 30 large families with multiple cases of NPC are also expected to be identified. Collaborating centres in Guangzhou, China, and in Kuching, Malaysia, are focusing on collection of high-risk NPC families for linkage studies. An international workshop on this disease was held in Paris in December 2003.

Association of human papillomaviruses and other viruses with conjunctival lesions

E. Weiderpass, S. Franceschi, M. Tommasino, M. Dai, A. Smet, W. Dong; in collaboration with C. Ateenyi-Agaba, B. Kahwa, C. Mbidde-Katongole, H. Wabinga, Kampala, Uganda

The association between squamous-cell carcinoma (SCC) of the conjunctiva and HIV-related immune impairment indicates a possible infectious etiology. A hospital-based case–control study of approximately 200 cases and 200 controls has been initiated in Uganda. The aim is to establish the presence of DNA of different HPV types and other viruses (such as HHV-8 and herpes simplex virus (HSV) types 1 and 2) in neoplastic and dysplastic lesions of the conjunctiva in order to identify any significant association with conjunctival cancer. Cases are patients with histologically proven SCC or pre-cancerous lesions of the conjunctiva. Controls are patients, selected from the same clinics as the cases, with histologically confirmed pterygium, pingueculae, solar keratosis, cataracts, eye trauma and other eye conditions requiring surgery.

A pilot study carried out in Uganda in 2002 and 2003 included 21 SCC cases and 22 controls with benign lesions of the conjunctiva. PCR-based assays were used to test for a broad spectrum of HPV types. Epidermodysplasia verruciformis (EV)-associated HPV types were found in 86% of SCC cases and 36% of controls (age-adjusted odds ratio = 12.0; 95% CI 1.7–312). No mucosal high-risk HPV types were detected in either cases or controls. The strong association that we found points to a possible role of EV HPVs in the etiology of SCC. Low educational level, outdoor occupation and heavy sun exposure were also risk factors for SCC.

2.8 *Second malignancies following cancer treatment*

Although cancer is still often a fatal disease, for which the use of aggressive therapies is justified, the combination of better and earlier diagnosis with more effective forms of treatment has led to the complete cure or at least much longer 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.

Analysis of second primary malignancies may also be useful in identifying shared etiology between different cancers.

Combined analysis of cancer registry data on second malignancies

P. Brennan, D. Colin, M. Shen, P. Boffetta; in collaboration with A. Andersen, Oslo, Norway; B. Armstrong, Sydney, Australia; R.J. Black, Edinburgh, UK; H. Botha, Sheffield, UK; K. Hemminki, Stockholm, Sweden. 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; E. Pukkala, Helsinki, Finland; J. Tomita, Saskatchewan, Canada

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 13 large cancer registers which have at least 20 years of follow-up, yielding a data-set of over four million primary cancers (Figure 20). 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; G. Gridley, Bethesda, MD, USA

The study of increased (or decreased) cancer risk following non-neoplastic diseases can provide useful information on the etiology and pathogenesis of cancer. For this purpose, data of the Swedish population-based registry of out-patients and in-patients have been linked to the national cancer registry. An analysis among 92 986 patients aged at least 20 years with a hospital discharge diagnosis of asthma during 1965–94 revealed 713 lung cancers (standardized incidence ratio [SIR] = 1.58, 95% CI 1.47–1.70). The SIR decreased with duration of follow-up and increased with calendar period and age at first hospitalization. The risk of lung cancer was higher for squamous-cell and small-cell carcinoma than for adenocarcinoma and was higher in patients with diseases other than asthma as the main diagnosis

[62]. A similar study in Swedish patients hospitalized for gout revealed increased risks for all cancers (SIR = 1.45, 95% CI 1.35–1.56) and for cancers of the oral cavity, colon, liver, lung, bladder, kidney and endometrium, as well as for Hodgkin disease and lymphocytic leukaemia. Although some of the excess risk can be attributed to overweight and alcohol consumption, metabolic alterations involved in gout may also play a role. Additional analyses of data on patients hospitalized in Sweden and in the Veterans Administration hospitals in the United States are being conducted.

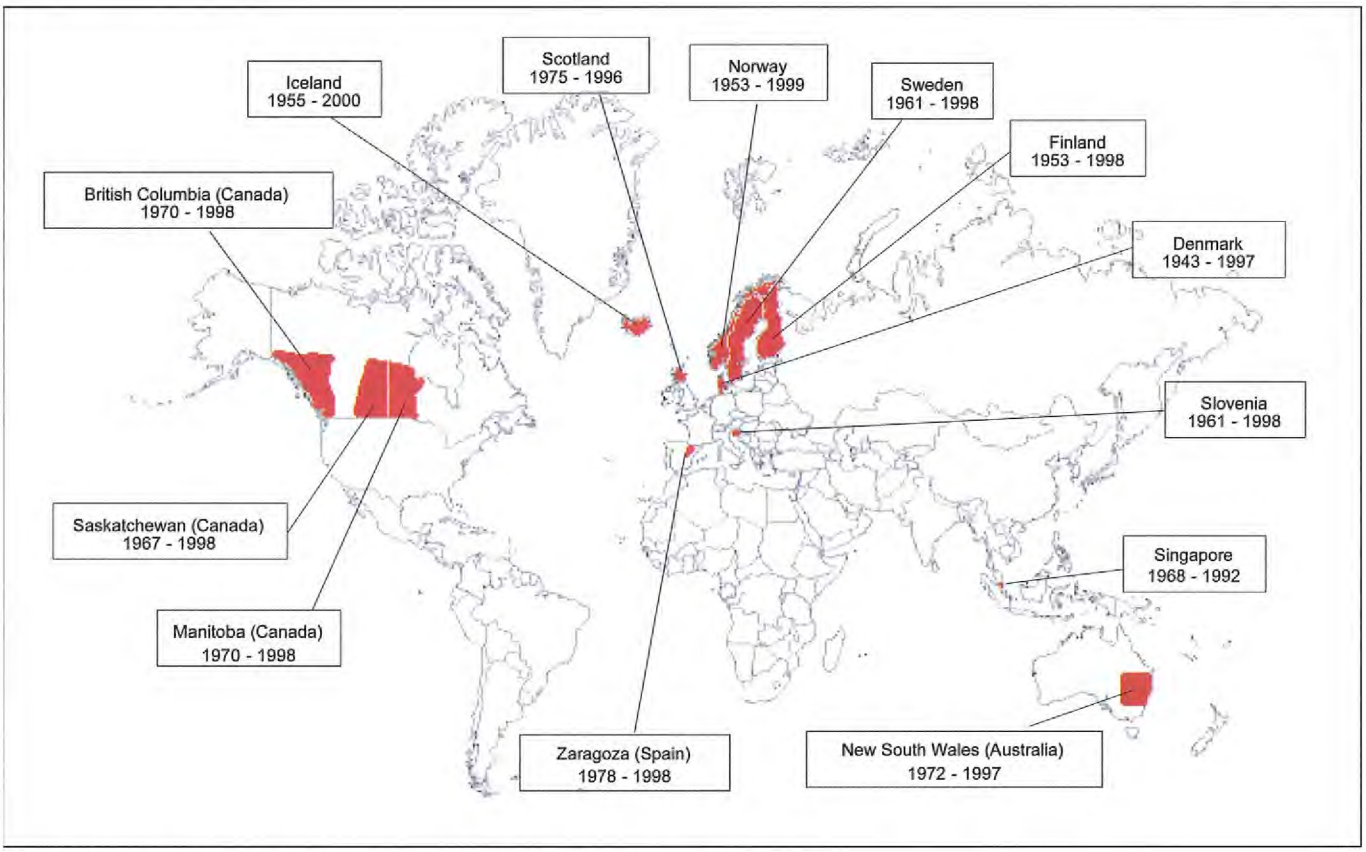
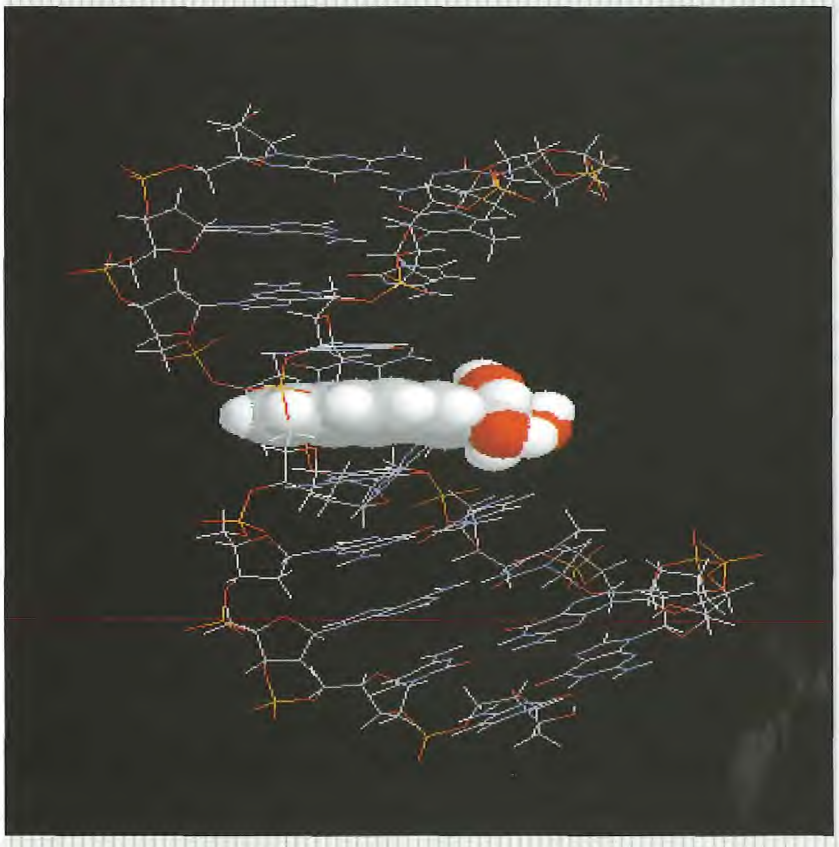


Figure 20. Cancer registries included in the combined analysis of second malignancies, with study periods

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.



Interaction of benzo[a]pyrene with DNA

3.1 Cancer of the oesophagus

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 risk factors 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 these patterns may reflect differences in the exogenous factors involved.

Case–control study of oesophageal cancer in Uruguay

P. Boffetta, P. Brennan, V. Sewram; in collaboration with E. De Stefani, Montevideo, Uruguay

A case–control study was conducted in Montevideo, Uruguay, including 344 cases with squamous-cell carcinoma of the oesophagus and 469 controls. Maté consumption was significantly associated with increased risk of developing oesophageal cancer, with a clear dose–response (RR = 2.84, 95% CI 1.41–5.73 for those drinking more than 1 L per day of maté versus non-drinkers). Subjects who reporting drinking maté at a very hot temperature had an almost two-fold increase in risk compared with those drinking warm to hot maté, after adjustment for cumulative maté consumption. The effects of amount and temperature were independent. The population-attributable fraction as a result of maté consumption was calculated to be 53%, of which the sole effects of amount and temperature were 15% and 12% respectively, while 15% was attributable to high maté consumption at high temperature [443].

Cohort study of oesophageal cancer in Iran

P. Boffetta, P. Brennan; in collaboration with S. Bahmanyar, Stockholm, Sweden; S. Dawsey, C. Abnet, F. Kamangar, M.J. Roth, P.R. Taylor, Bethesda, MD, USA; R. Malekzadeh, A. Pourhams, F. Islami, Teheran, Iran; M. Saadatian-Elahi, J.P. Steghens, Lyon, France; P.T. Strickland, Baltimore, MD, USA

Extremely high rates of oesophageal cancer (over 100/100 000) have been reported among both men and women in Golestan province in north-eastern Iran, which are not explained by alcohol and tobacco. Possible causes of these high rates are low consumption of fruit and vegetables, consumption of very hot tea and consumption of opium. Following an extensive feasibility study of 1000 individuals conducted in 2002, the establishment of a cohort of 50 000 adults in this region is planned. All subjects will be interviewed using validated lifestyle and food-frequency questionnaires. Blood, nail and hair samples will be obtained and tea drinking temperature will be measured. The cohort will be followed up for an initial five years, during which at least 500 squamous-cell carcinomas of the oesophagus are expected to occur.

Cellular and molecular alterations in oesophageal cancers

P. Hainaut, G. Martel-Planche, P. Tanière, E. Taranchon, D. Peixoto Guimaraes, E. Moraes, S. Fahimi, A. Hautefeuille, R. Lambert; in collaboration with E. Brambilla, Grenoble, France; A. Casson, Halifax, Canada; C. Gallo, Rio de Janeiro, Brazil; R. Malekzadeh, Teheran, Iran; J.Y. Scoazec, J.C. Saurin, C. Lombard-Bohas, Lyon, France; J.C. Soria, Villejuif, France

The long-term project to compare the distribution of mutations in the *TP53* gene in squamous-cell carcinomas from different areas of the world has continued. In western Europe, we have found different mutation patterns in cancers of patients from high- or low-incidence areas. In high-incidence areas such as Normandy and Brittany, the excess of mutations at A:T base pairs is compatible with a mutagenic mechanism involving acetaldehyde. This suggests that major metabolites of alcohol can act as direct mutagens in at least a subset of squamous-cell cancers. Further studies in other high-incidence areas of the world have confirmed that overproduction of nitric oxide as a result of chronic inflammatory stress

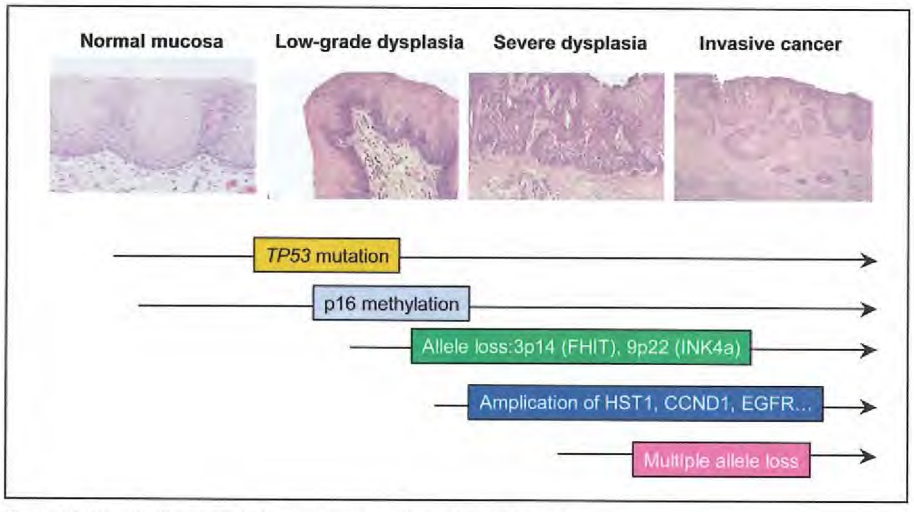


Figure 21. Genetic alterations during development of oesophageal cancer

plays an important role in *TP53* mutagenesis. We are now extending our studies on oesophageal cancer in northern Iran by analysing *TP53* mutation patterns and other molecular markers in tumour specimens collected in a cohort study in the Gombad area.

We are completing a seven-year follow-up of a cohort of patients with oesophageal cancers including over 250 subjects with squamous-cell or adenocarcinomas. Preliminary results clearly show that for both cancer types the presence of a *TP53* mutation correlates with poor overall survival. Further analyses are being conducted to determine whether *TP53* mutation has value as an independent pathological marker.

TP63 and *TP73* are two members of the *TP53* gene family that play an important role in epithelial differentiation and morphogenesis. We have shown that expression of *TP63* is restricted to the squamous epithelium and is increased in squamous carcinogenesis. Analysis of patterns of expression of all isoforms of p63 and p73 in a large series of well characterized pairs of oesophageal cancers and matched adjacent, uninvolved mucosa confirmed immunohistological findings that p63 expression is strongly decreased, if not lost, in adenocarcinoma. Furthermore, specific ΔN isoforms of p63 are expressed exclusively in squamous cancer tissues and not in matched, non-involved mucosa. The ΔN isoforms lack the N-terminal domain of the protein containing the main transactivation domain (see Section 4.6) and are thought to repress the capacity of the full-length isoforms to induce terminal differentiation. Thus, increased expression of ΔN forms may prevent squamous cells from undergoing normal differentiation and thus favour the maintenance of a large compartment of basal cells with higher proliferative potential. Taken together, these results support the notion that deregulation of p63 expression may be an oncogenic event in squamous-cell carcinomas. In contrast, loss of p63 expression may represent a crucial turning point for oesophageal stem cells between squamous and glandular differentiation pathways. Thus, selective loss of p63 expression may be an important step in the pathogenesis of Barrett's oesophagus.

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; S. Sriamporn, Khon Kaen, Thailand

In a case–control study conducted in the low-risk population of Khon Kaen, Thailand, 131 incident stomach cancer cases and twice as many hospital controls were interviewed and donated a blood sample. Information was collected on many sociodemographic and lifestyle factors. 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. Preference for spicy food (chilli) was not associated with risk. Non-significant excess risks were associated with tobacco smoking and with 14 or more years of alcohol drinking.

Anti-*H. pylori* immunoglobulins were determined by a commercial ELISA test. As in other case–control studies, more controls than cases were found positive, suggesting an apparent protective effect of the infection (relative risk for positives versus negatives = 0.6; 95% CI 0.4–1.0). 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, serum levels of pepsinogens I and II were measured as a modifier of the association between *H. pylori* and gastric cancer. In addition, anti-*H. pylori* antibodies were re-tested using antigens derived from bacterial strains endemic in eastern Asia in order to improve the accuracy of the test. The sensitivity and specificity of the commercial ELISA kit proved poor in this population. The apparent protective association of *H. pylori* and gastric cancer disappeared when infectious status was defined based on the specific assay. The ratio of pepsinogens A to C was strongly associated with the risk of gastric cancer. The relative risk of subjects below the first quartile of the observed distribution, indicating extensive areas of atrophic gastritis, was 6.2 (95% CI 2.7–14.3).

Surveys of *H. pylori* prevalence in areas of high and low risk for stomach cancer

E. Weiderpass, S. Franceschi; in collaboration with R. Herrero, San José, Costa Rica; E. Kasamatsu, Asunción, Paraguay; E. Lazcano-Ponce, Cuernavaca, Mexico; M.C. Matamoros, San José, Costa Rica; N. Muñoz, Lyon, France; H. Posso, M. Piñeros, Bogotá, Colombia; C. Saul, Porto Alegre, Brazil; X. Torres, Mexico City, Mexico

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 five Latin American countries (Brazil, Colombia, Costa Rica, Mexico and Paraguay) with high, intermediate or low incidence of stomach cancer. From each subject, a blood sample is collected and 12 gastric biopsies are obtained from six sites in the stomach under a strict protocol. Some of the biopsies are cultured for *H. pylori* at central laboratories, to genetically characterize the strains present in the different lesions. Markers of *H. pylori* under study include: (i) serological markers, including antibodies against the whole-cell antigen, vacuolating cytotoxin (VacA), cytotoxin-associated antigen (CagA), neutrophil-activating protein (NAP) and urease; (ii) bacterial genetic markers in tissue specimens: VacA, CagA, BabA and OipA, evaluated by means of polymerase chain reaction (PCR) assays; and (iii) markers of a functional Cag pathogenicity island, by means of an *in vitro* assay of cell morphology. Patient recruitment has been completed in Mexico and preliminary laboratory and data analyses are in progress. For the other countries, patient recruitment ended in December 2003.

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.

Case–control study of liver cancer in Italy

P. Boffetta; in collaboration with F. Donato, Brescia, Italy

In a case–control study of alcohol intake and hepatocellular carcinoma (HCC) risk, 464 cases and 824 hospital controls were enrolled during 1995–2000 in Brescia, northern Italy, an area of high HCC incidence. Spline regression models showed a steady increase in the odds ratio of HCC with increasing alcohol intake, with no difference between men and women. The effect of alcohol drinking was evident even in the absence of infection with hepatitis B or C virus (HBV or HCV); synergism was seen between alcohol intake and either infection [136].

Cohort study of liver and other cancers in Thailand

P. Pisani, D.M. Parkin; in collaboration with J. Fox, Cambridge, MA, USA; S. Sriamporn, P. Paiboon, Khon Kaen, Thailand; T. Wadström, Lund, Sweden; C.P. Wild, Leeds, UK

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 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 HCC is the predominant type everywhere else in the world.

Over 16 000 women and 8000 men enrolled by June 2001 provided interview data and samples of blood and faeces. Procedures to link the cohort with the database of the cancer registry have been developed. In this cohort, 245 cases of primary liver cancer have been identified during an average of 8.4 years of follow-up. Stored serum is available for 163 of them. Four times as many controls were drawn from the cohort, matched to cases by sex, age and recruitment period. The incidence of intra-hepatic bile-duct carcinoma in subjects infected with *Opisthorchis viverrini* at time of recruitment was twice that in subjects not concurrently infected, after at least one year of follow-up. Serum antibodies to *O. viverrini*, hepatitis B surface antigen (HBsAg) and HCV are being measured at the University of Khon Kaen. Collaborations are being established with laboratories in the USA and Sweden to investigate the

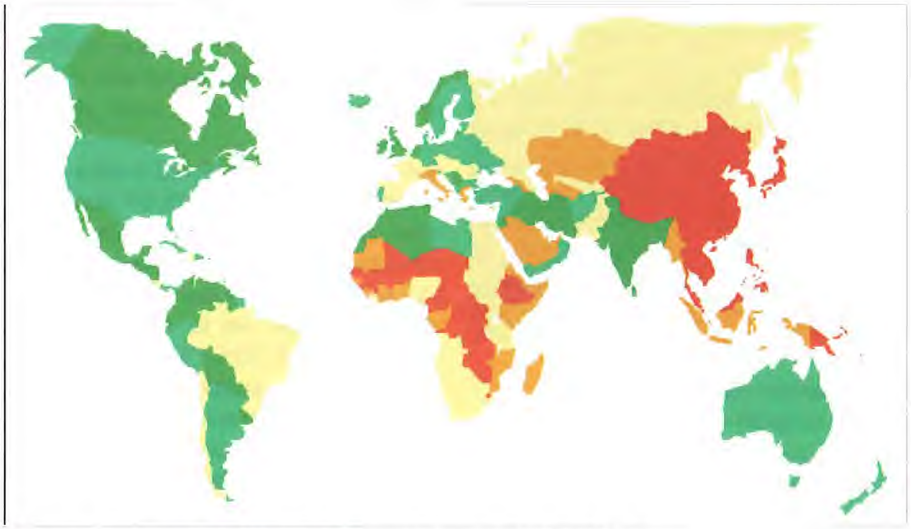


Figure 22. Age-standardized incidence of liver cancer in males (GLOBOCAN 2000)
< 3.3; < 5.6; < 9.0; < 15.0; < 98.9 per 100 000

presence and role of bile-tolerant *Helicobacter* species, the presence of which was recently demonstrated in the gall bladder of individuals from a high-incidence area of Chile.

Cohort study of liver cancer in Qidong, China

D.M. Parkin, P. Hainaut; in collaboration with Y. Cui, Los Angeles, CA, USA; C.P. Wild, Leeds, UK; Y.-R. Zhu, J.-G. Chen, Lu J.-H., Qidong, China

Supported by the World Cancer Research Fund

This cohort study is based on 6000 men (chronic HBV carriers) aged 30–59 years who were followed up as part of a screening programme for liver cancer in Qidong county, China, an area of high risk for liver cancer. In a nested case–control study, 130 subjects who developed liver cancer were compared with 130 normal subjects, to investigate the roles of infection with HCV and exposure to dietary aflatoxins, and the influence of polymorphisms in several metabolic enzymes on the effect of aflatoxin. A preliminary analysis suggests only a weak effect of HCV in these chronic HBV carriers (OR = 0.9, 95% CI 0.4–2.0); the levels of albumin–aflatoxin adduct in the pre-diagnostic sera were low, and there was no obvious association with liver cancer risk. None of the genetic polymorphisms studied (GSTT1, GSTM1, CYP2D6, XRCC1) appeared to influence the risk due to aflatoxin. Liver cancer tissue samples were analysed for the presence of a specific mutation (G:C→T:A transversion) at codon 249 of the *TP53* gene. This mutation was present in 13/17 subjects. In three out of seven cases (43%) for which peritumoral cirrhotic tissue was available, the same mutation was also detected. These results confirm earlier findings of an extremely high prevalence (around 75%) of this *TP53* mutation in liver cancer from high-incidence regions of China. However, no association was seen between presence or absence of the mutation and albumin–aflatoxin adducts in pre-diagnostic sera. DNA was extracted from serum samples 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.

Hepatitis C virus and hepatocellular carcinoma 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

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. HBV and HCV are major causes of chronic liver disease, such as chronic hepatitis and cirrhosis, as well as HCC.

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. 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 blood sample for virological and genetic (HLA and selected polymorphisms) investigations and a tumour biopsy is taken when possible. Up to September 2003, 286 cases of HCC and 525 control subjects had been recruited.

TP53 ser249 mutations in the management of hepatocellular carcinoma

P. Hainaut, C. Caron de Fromentel, H. Shi, G. Martel-Planche, K. Szymanska, R. Cui; in collaboration with O. Galy, I. Chemin, P. Merle, C. Trepo, Lyon, France; K. Wiman, G. Selivanova, Stockholm, Sweden

About 80% of cases of HCC occur in developing countries, with particularly high incidence in countries where the major risk factors for this cancer are chronic HBV infection and dietary contamination by aflatoxins. In these regions, mortality rates for HCC are extremely high and the possibilities for efficient treatment are very limited. Many of these cancers harbour a typical mutation of the *TP53* gene at codon 249, resulting in the substitution of arginine by serine (ser249). This mutation is infrequent in other cancers. We are attempting to exploit this unique molecular signature in early cancer detection (see Section 6.1) and design of new therapeutic strategies.

Although there is evidence that aflatoxin metabolites bind to and specifically mutate the third base of codon 249, site-specific mutagenesis alone does not explain the predominance of this mutation. Indeed, there is experimental evidence that aflatoxin can also induce mutations at other codons in *TP53*. One hypothesis is that the ser249 mutant p53 protein has special functional properties leading to its selection during hepatocellular carcinogenesis. To determine the molecular basis of such a tissue-specific "gain-of-function" effect of the ser249 mutant, we have derived stable clones of HCC cells constitutively expressing defined p53 mutants in a p53-null background. By comparing the properties of cells expressing either ser249 or gln248, a mutant common in many cancers but rarely detected in HCC, we are studying the cellular and molecular basis for selection of the ser249 mutant in liver cancers. Studies are being set up to identify sets of genes specifically up- or down-regulated in ser249-expressing cells. In parallel, the cell lines are also being used as model systems to screen for and identify drugs that exert specific cytotoxic effects towards ser249-expressing cells. Several such drugs have already been identified by us (amifostine) or others (PRIMA-1) as potential regulators of p53 protein conformation and function. We

are also developing structural approaches to purify the ser249 mutant to homogeneity and determine its crystal structure, in the context of a structural biology programme supported by the French Association de Recherche sur le Cancer (ARECA programme).

Role of the *TP53* homologues *TP63* and *TP73* in liver carcinogenesis

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Normal hepatocytes, as well as HCC cells, are relatively resistant to apoptosis induced by most common classes of chemotherapeutic agents. This resistance is one of the main obstacles to successful cancer therapy. The p53 protein seems to play a rather minor role in the control of liver cell responses to these agents. This led us to postulate that other members of the *TP53* gene family such as *TP63* and *TP73* may play complementary roles in the proliferation and survival of hepatocytes and in their resistance to cytotoxic treatments. The *TP63* gene encodes a transcription factor with similar structural features to p53. It is expressed as several isoforms, including in particular TA (transactivation-competent) and ΔN (transactivation-incompetent) isoforms, initiated at distinct promoters within the gene. ΔNp63 isoforms can act as dominant-negative inhibitors of TAp63 isoforms, as well as of the transcriptional activities of p73 or p53. Expression of the TA forms of p63 increased in normal or cancer hepatocytes in response to doxorubicin or etoposide, two DNA-damaging agents that inhibit topoisomerase II. This increase was accompanied by enhanced expression of several genes that are common targets of p63 and p53, such as WAF1/CIP1, 14-3-3σ or GADD45. Moreover, patterns of p63 isoforms in HCC cells differ depending upon their *TP53* status, suggesting that p53 may control the expression of specific p63 isoforms. We are now assessing the hypothesis that wild-type p53 specifically represses the promoter of ΔNp63. Overall, these results indicate that p63 and p53 may act in a coordinated manner in suppressing the growth of hepatocytes in response to some forms of DNA damage.

Alterations of RB1, p53 and Wnt pathways in hepatocellular carcinomas associated with hepatitis C, hepatitis B and alcoholic liver cirrhosis

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Major etiological factors associated with human HCC include HCV and HBV infection, excess alcohol intake and aflatoxin B_1 exposure. While the G→T mutation at codon 249 of *TP53* has been identified as a genetic hallmark of HCCs induced by aflatoxin B_1, genetic profiles associated with other etiological factors appear to be less distinctive. HCCs associated with HCV infection, HBV infection or excess alcohol intake were screened for alterations in genes involved in the RB1 pathway (p16INK4a, p15INK4b, RB1, CDK4, cyclin D1), the p53 pathway (p53, p14ARF, MDM2) and the Wnt pathway (β-catenin, APC). Alterations of the RB1 pathway, mainly *p16INK4a* methylation, loss of RB1 expression, and *cyclin D1* amplification, were most common (69–100% of cases). There was a significant correlation between loss of RB1 expression and *RB1* promoter methylation. All 24 HCCs with *RB1* methylation lacked RB1 expression, while none of the 67 cases with RB1 expression showed *RB1* methylation, suggesting that promoter methylation is a major mechanism of loss of RB1 expression in HCCs. Alterations of the p53 pathway consisted mostly of *TP53* mutations or *p14ARF* promoter methylation (20–48%). Mutations of the *TP53* gene were found at similar frequency (13–15%) in all etiological groups, without any consistent base change or hot spot. Mutations of β-catenin were found in 13–31% of cases, while no *APC* mutations were detected in any of the HCCs analysed. With the exception of only three cases (8%), *cyclin D1* amplification and β-catenin mutations were mutually exclusive, supporting the view that cyclin D1 is a target of the Wnt signalling pathway. Overall, the RB1, p53 and Wnt pathways were commonly affected in HCCs of different etiology, probably reflecting common pathogenetic mechanisms, i.e., chronic liver injury and cirrhosis, but tumours associated with alcoholism had more frequent alterations in the RB1 and p53 pathways than those caused by HCV infection [141].

β-Catenin mutations in mouse liver tumours induced by 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ)

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Heterocyclic amines are potent mutagens and carcinogens formed in cooked protein-rich foods. Liver tumours induced in CDF1 mice by 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ) were screened for β-catenin and *APC* mutations and other genetic alterations known to occur in human HCC. Mutations were detected in exon 2 of the β-catenin gene in two of 16 liver tumours and methylation of the E-cadherin gene promoter in one tumour. There were no mutations in the mutation cluster region of the *APC* gene, in exons 5–8 of the *TP53* gene or in codons 12, 13 and 61 of the H-*ras* gene, nor c-*myc* amplification in any of the MeIQ-induced liver tumours. These data indicate that except for the occasional disruption of the Wnt pathway through β-catenin mutations, the genetic pathways involved in the development of HCC differ significantly between human liver cancer and tumours induced in mice by MeIQ, but do not rule out the possibility that heterocyclic amines constitute a carcinogenic risk factor in humans [203].

3.4 Cancer of the cervix

Cancer of the cervix is the second most common cancer in women. Its association with human papillomavirus (HPV) infection 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. 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).

Studies of cervical cancer in Khon Kaen, Thailand

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In the Khon Kaen cohort study (Section 3.3), volunteer subjects not known to have cancer or other chronic diseases (men and women aged 35 years or above) resident in villages of Khon Kaen Province, were recruited. A total of 24 723 subjects, including 16 652 women, were interviewed using a structured questionnaire, including demographic, lifestyle, reproductive and health-related variables (including a section on diet), and height, weight and blood pressure were recorded. Pap smears were obtained from 10 954 women and cervical cells from 10 073 women have been stored. Women with an abnormal Pap test were informed and advised to seek treatment. Subjects also donated 10–20 mL of venous blood, from which specimens of plasma, buffy coat and clot were prepared and stored. Follow-up of this cohort is being carried out by linkage with the data of the provincial cancer registry.

Risk factors for cervical cancer are being examined in a nested case–control study of 58 cases of histologically confirmed cervical cancer (invasive or *in situ*) identified among the cohort subjects by the end of 2001. Four controls per case were selected from among women without cervix cancer at the time the case was diagnosed, matched on age and date of recruitment. Among the 33 cases for whom DNA could be extracted from stored cells, oncogenic HPV types were present in 31, equivalent to an odds ratio of 131. Number of pregnancies and age at having first child were associated with the risk of cervical cancer. In contrast to findings elsewhere, age at first sexual intercourse, number of sexual partners and infections with sexual transmitted agents were not associated with risk. The lack of effect may be simply due to the small size of the study, but these aspects of female sexual behaviour may not be very relevant to HPV transmission and risk of cervical cancer in this relatively conservative rural population.

All subjects (about 200) who had a positive Pap test at enrolment are being followed up. Women who agree to participate complete a short questionnaire (demographic, sexual, reproductive variables). Information on screening and treatment history since enrolment is obtained by interview and review of hospital and laboratory records. Subjects receive a Pap test and gynaecological examination, including colposcopy. Cervical cells, as well as the stored cells if available, are tested for HPV. The original Pap smear is independently reviewed. Comparison of the original Pap smear report and a review of cytology using the same smear showed agreement on 72% for any degree of abnormality and 86% for a diagnosis of low-grade squamous intraepithelial lesions or worse. This study is designed to provide information on (*a*) the efficacy of the Pap test in detecting cervical intraepithelial neoplasia (CIN) in this population, (*b*) the efficiency of the health care system in following up women with abnormal smears at the original examination, (*c*) determinants of acquisition, persistence and elimination of HPV, (*d*) risk associated with different types of HPV, and (*e*) the predictive value of HPV testing in this population (potential for use as a primary screening test).

The incidence of in CIN this population and determinants of CIN, in terms of HPV and other risk factors, are being assessed

Table 6. Risk factors for cervical cancer: HPV infection versus persistence and malignant transformation

Risk factor	HPV infection	HPV persistence and transformation
Multiple sex partners	+	n.e.
Partner's multiple partners	+	n.e.
Poor hygiene	+	n.e.
Absence of male circumcision	+	+
Immunodeficiency, HIV	+	+
High parity	n.e.	+
Oral contraceptives	n.e.	+
Smoking	n.e.	+
STDs other than HPV	n.e.	+
Poor nutritional status	n.e.	+

STDs, sexually transmitted diseases (especially *C. trachomatis*)
n.e., no evidence at present for being a risk factor

by re-examination of 1000 women from the cohort who were apparently well at enrolment, to identify those with CIN (at either enrolment or re-examination) and HPV infection.

Pooled analyses of studies of cervical cancer

S. Franceschi, M. Plummer, D. Colin; in collaboration with V. Beral, A. Berrington, J. Green, Oxford, UK; T. Farley, Geneva, Switzerland

The main purposes of the pooled analyses of the case–control studies coordinated by IARC in 11 different countries have been achieved with the publication of findings concerning the adverse effects of the use of oral contraceptives (OCs) [317], high parity [321], cigarette smoking [378], and the confirmation of a modest risk increase conferred by infection with herpes simplex virus 2 (HSV-2) [459] and *Chlamydia trachomatis*. The strong influence of HPV infection could, for the first time, be taken fully into account by means of stratification or adjustment for the presence of HPV DNA in the cervix among over 2000 cases of cervical carcinoma and the same number of control women. The pooling exercise has allowed reclassification of 34 HPV types according to the strength of their association with cervical cancer [320]. The study in Chennai, India, showed the highest prevalence of HPV ever found among control women (30%) [162] and suggested an association between paan chewing and cervical cancer similar to that seen for cigarette smoking [386].

This project is being expanded to include analysis of data from studies of cervical cancer etiology other than those within the IARC multi-centre case–control study, in collaboration with the Cancer Research UK Epidemiology Unit. Findings from 28 studies that included 12 531 women with cervical cancer and that reported on the relationship with the duration of OC use have been summarized in a systematic review [458]. The excess risk increases for OC use for less than five years, 5–9 years and 10 years or more were 10%, 60% and 120%, respectively. The results

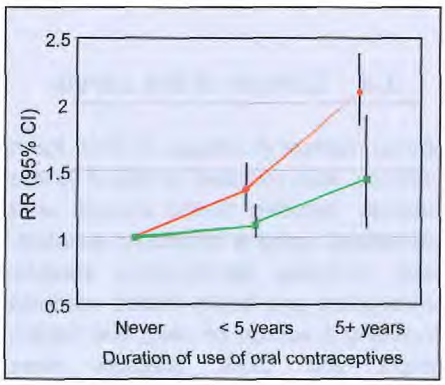

Figure 23. Relative risk of cervical cancer according to time since last use and duration of oral contraceptives

were broadly similar in developed and developing countries, and for invasive and in-situ cervical cancer, squamous-cell carcinoma (SCC) and adenocarcinoma. In addition, they did not differ when adjustment was made for HPV status, number of sexual partners, cervical screening, smoking and use of barrier contraceptives. The association with OC use was consistently stronger in cohort than case–control studies. Some evidence suggests that the relative risk of cervical cancer may decrease after cessation of OC use (Figure 23).

The persistence of any effect of OC is a critical point when considering the absolute risk of cervical cancer among past users and hence the public health implications of these findings. There is still a lack of published data on women cross-classified by duration of use and time since last use. Therefore, a collaborative re-analysis of individual data from all relevant studies on cervical cancer is being set up, with support of the WHO Human Reproduction Unit. All contributors have been contacted and asked to provide original data. Over 15 000 cervical cancer cases and 30 000 healthy women will be analysed. This re-analysis was discussed at a meeting in November 2003, in order to reach a consensus on ways to interpret and release the overall evidence on the role of OCs as well as other important risk factors (i.e., smoking, reproductive factors and indicators of sexual habits).

Distribution of different HPV types in invasive and pre-invasive cervical carcinomas

G. Clifford and S. Franceschi

Prophylactic vaccines against particular HPV types hold great promise for reducing the global burden of cervical cancer. The relative prevalence of at least 15 oncogenic HPV types known to be associated with cervical cancer may vary by region [320], so it is necessary to identify worldwide and regional priorities for HPV types to be included in potential vaccines. As the main endpoint in vaccine efficacy trials will be prevention of high-grade precancerous lesions [159, 377], we have also tried to determine if the distribution of HPV types in high-grade squamous intra-epithelial lesions (HSIL) is representative of those that go on to cause cancer or if certain types are more likely to progress to malignancy.

All published studies presenting type-specific HPV prevalence data in cervical cancer and/or HSIL have been classified by geographical region [111, 112]. HPV type-specific prevalence was estimated independently for SCC and for adeno- and adenosquamous carcinoma (ADC). The relative risk for each HPV type to progress from HSIL to malignancy was assessed by comparing HPV type distributions in HSIL and SCC.

The two meta-analyses included a total of 10 058 cervical cancer and 4151 histologically verified HSIL cases drawn from 85 and 52 published studies, respectively. The most common HPV types identified in cervical cancer were, in order of decreasing prevalence, HPV 16, 18, 45, 31, 33, 58, 52, 35, 59, 56, 6, 51, 68, 39, 82, 73, 66 and 70. Over two thirds of cases were associated with an infection with either HPV 16 (51.0%) or HPV 18 (16.2%). The next most prevalent types were HPV 45 (2–8%), HPV 31 (2–7%) and HPV 33 (3–5%) in all regions except Asia, where HPV types 58 (6%) and 52 (4%) were more prevalent than elsewhere (Figure 24). The HPV 16 family of viruses was more commonly found in SCC than in ADC, whereas the HPV 18 family was more

likely to be found in ADC. This study reinforces the view that HPV 16 and HPV 18 are the most important HPV types for vaccination in all regions. However, the relative priorities for these types vary somewhat by region.

HPV type-specific prevalence data were similarly summarized for HSIL, and the distribution of HPV types compared between SCC and HSIL [111]. HPV 16 was the most common type in both SCC (54.3%) and HSIL (45.6%), but was more prevalent in SCC (SCC:HSIL ratio 1.19). HPV 18 and HPV 45 were also more prevalent in SCC than in HSIL, whereas the opposite was true for all other high-risk types. Thus, HSILs with HPV 16, 18 or 45 infection appear to have greater potential for progression, so any beneficial effect in terms of the proportion of HSIL preventable by HPV16 or HPV16/18 vaccination in randomized trials may be an underestimate of the effect of the vaccine in prevention of invasive cervical cancer.

Risk factors for acquisition and persistence of HPV infection in women

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Even excluding countries where screening programmes have contributed to lowering rates of cervical cancer, incidence ranges from less than 10 per 100 000 women in parts of China, Viet Nam and Kuwait to more than 35 per 100 000 in sub-Saharan African and some areas in India and Latin America. To assess the extent to which such variation is attributable to differences in HPV prevalence at a population level, a series of population-based surveys of the prevalence of HPV DNA and serum IgG against HPV virus-like particles (anti-VLPs) is being conducted in various parts of Latin America, Asia and Africa and in Spain and Italy.

Prevalence surveys among random samples of women drawn from the general population have been completed in the Republic of Korea (Busan) [449], Thailand (Songkhla and Lampang) [479], Viet Nam (Hanoi and Ho Chi Minh City) [13], Argentina (Cordoba) [298], Colombia (Bogotá) [309–312], Nigeria [502] and Spain [128]. Surveys have also been started in Turin (Italy), Santiago (Chile), Ambillikai (India) and Kampala (Uganda). Questionnaire

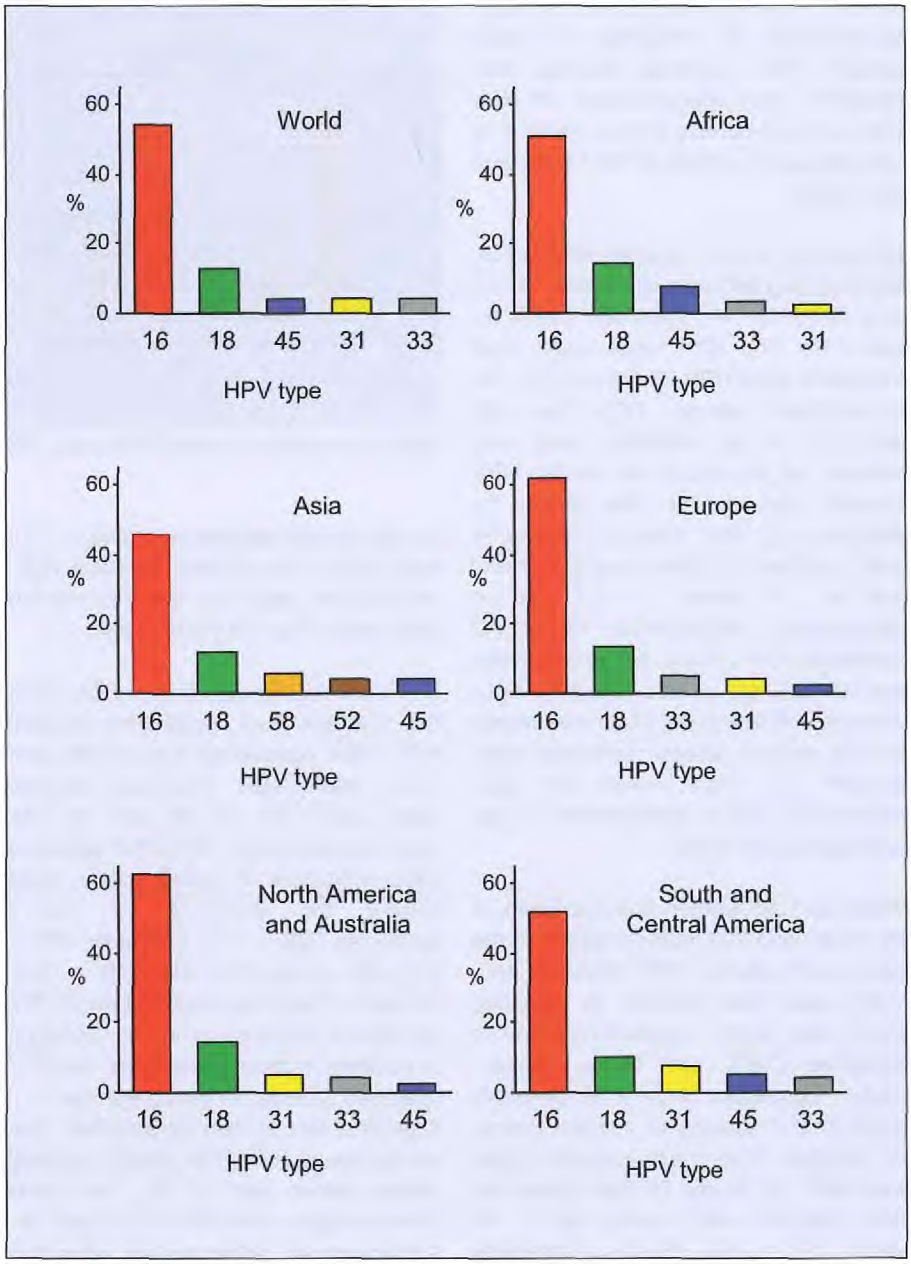

Figure 24. Most common HPV types in squamous cell carcinoma, by region

information and samples of exfoliated cervical cells and of blood were collected. Type-specific prevalence of HPV DNA from cervical cells was analysed using GP5+/6+ primers, whereas anti-VLPs for HPV 16, 18, 31, 33 and 58 and HSV-2 were assessed using ELISA.

The prevalence of cervical HPV-DNA in some of the countries studied is shown in Figure 25. It turned out to be very difficult, notably in Asia, to perform pelvic examinations of unmarried or virgin women. The following findings are, therefore, truly representative of HPV DNA prevalence only among married or sexually active women in the 15–65-year age-range.

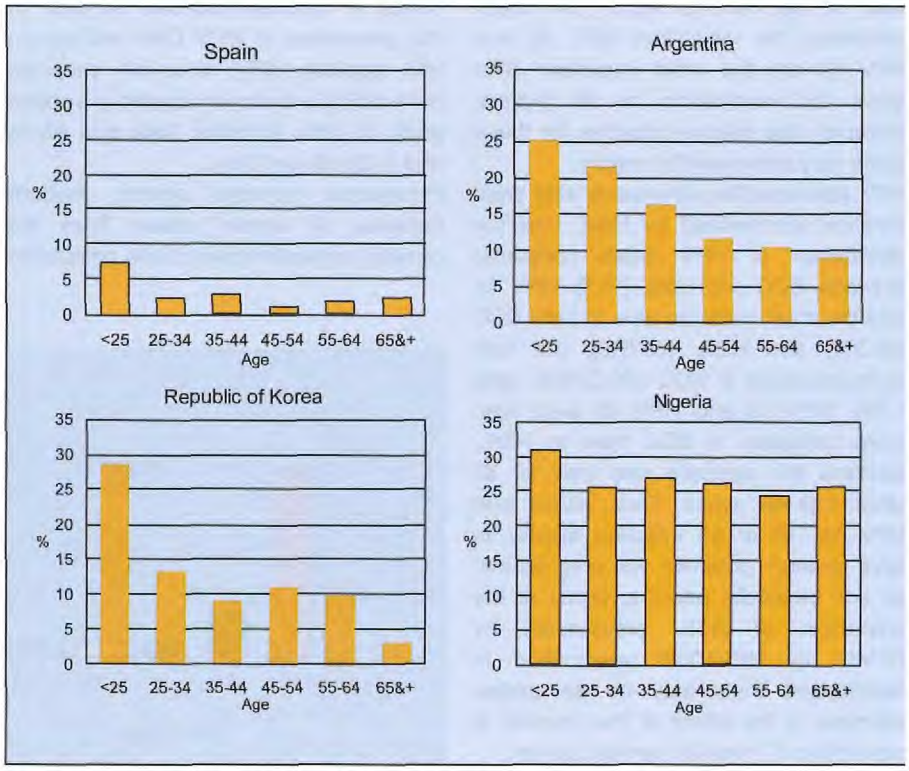

Figure 25. Prevalence of cervical HPV-DNA by age, 1995–2002

Republic of Korea: Overall HPV prevalence among 863 sexually active women was 10.4% for HPV DNA and 19.8% for anti-VLPs. The HPV types found most frequently were HPV 70, 16 and 33. The concordance between HPV DNA and anti-VLPs at an individual level was modest, but risk factors for the two HPV markers were similar. Risk factors for detection of HPV DNA or anti-VLPs were: number of lifetime sexual partners (OR for ≥ 4 versus 1 = 3.5 and 5.4 respectively), seropositivity for HSV-2 antibodies (OR 2.6 and 2.5, respectively) and being single or divorced. HPV DNA (but not anti-VLPs) detection was higher among women whose husbands were thought by their wives to have extramarital sexual relationships or had undergone vasectomy.

Thailand: 1035 women from Lampang, in the north, and 706 from Songkhla, in the south, were studied. HPV DNA and anti-VLPs were more common in Lampang (8.0% and 29.2%, respectively) than in Songkhla (3.8% and 10.9%, respectively), consistent with a north–south gradient in incidence of cervical cancer in Thailand. The most common types were HPV 16, 52 and 70. Risk factors for HPV infection were young age (< 25 years, OR = 2.5), HSV-2 seropositivity (OR = 2.1) and the husband's extramarital sexual relationships (OR = 2.1). Risk factors did not differ between high- and low-risk types nor between women below and above 45 years of age.

Viet Nam: 922 women from Ho Chi Minh City and 994 from Hanoi were studied. HPV DNA prevalence was 10.9% and 2.0%, respectively. The most common types were HPV 16, 58 and 18. The major risk factors for HPV DNA detection were: indicators of sexual habits, most notably the presence of HSV-2 antibodies (OR = 2.4), nulliparity (OR = 3.0) and current OC use (OR = 3.2). Women in Hanoi showed the lowest HPV prevalence found so far in HPV surveys. In contrast to other populations, no HPV peak was detected in young women.

Argentina: 987 women were studied. The prevalence of HPV DNA among sexually active women was 17.7%. The most common types were HPV 16, 35 and 18. Among women below age 45 years, the main risk factors for HPV detection were increasing lifetime number of sexual partners (OR = 3.0; 95% CI 1.9–4.8 for > 3 versus 1) and severe vaginal discharge. OC use was associated with a significant reduction in HPV detection. None of these risk factors was associated with infections in women aged above 45 years.

Colombia: 1859 cytologically normal women were studied in Bogotá. The overall prevalence of HPV DNA was 14.8% and the commonest types were HPV 16, 58 and 56. There were positive associations between HPV detection and age less than 20 years (OR versus 35–44 years = 9.6), three or more sexual partners (OR = 2.1) and OC use (OR = 1.4). In women below age 25 years, high education and intercourse with casual partners were associated with risk of infection.

A subset of 227 women with normal cytology, but positive for HPV DNA at study enrolment and at least one follow-

up visit, was studied [312] to search for determinants of HPV infection clearance. Infections with HPV 16 (RR = 0.6; 95% CI 0.4–0.8), but not with other high-risk HPV types, had a significantly lower clearance rate than infections with low-risk types. Infections with a single type and multiple infections had similar clearance rates. There was an indication that parous women cleared HPV infections less efficiently than nulliparous women, but OC users may have less persistence of infection.

Nigeria: We interviewed and obtained a sample of cervical cells from 932 sexually active women aged 15 years or older from Idikan, an inner-city area of Ibadan. Thirty-one different HPV types were identified, with an HPV prevalence of 26.3% overall. High-risk HPV types predominated, most notably HPV 16, 31, 35 and 58. One third of infections involved more than one HPV type. In contrast to most populations studied so far, HPV prevalence was high not only among young women, but also in middle and old age. Illiterate women (OR = 1.7; 95% CI = 1.1–2.5) showed increased HPV positivity. Associations were found also with anti-HSV-2 antibodies (OR = 1.6; 95% CI 1.1–2.1) and the husband's extramarital relationships (OR = 1.6; 95% CI 1.0–2.6). High prevalence of HPV in all age groups may be a distinctive feature of populations where HPV transmission continues in middle age and cervical cancer incidence is very high.

Role of natural variants of human papillomavirus type 16 and host genetic factors in cervical carcinogenesis

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Virtually all cervical cancers are caused by HPV infection, with HPV type 16 being the most prevalent type. However, the majority of HPV infections do not lead to the development of cervical lesions, but are cleared by the immune system in a relatively short time. Persistent infection is necessary for the formation of a high-grade lesion and invasive cancer. The factors that determine the persistence of an HPV infection are poorly understood. It appears that HPV16 polymorphisms together with host genetic factors (e.g., human leukocyte antigen class II) influence the host immune response and clinical outcome of an HPV infection. We have conducted a cross-sectional study in the Czech Republic, Italy and Sweden and shown that certain HPV16 E6 variants are differently distributed in low-grade cervical intraepithelial neoplasia (LCIN), high-grade cervical intraepithelial neoplasia (HCIN) and invasive cervical carcinoma. For instance, the HPV16 E6 variant L83V is more frequent in invasive cancer than in pre-malignant lesions (low- or high-grade CIN) in Swedish women. Our findings suggest that this phenomenon is associated with the ability of the E6 L83V variant to evade the cellular immune response. Indeed, we have observed that the prototype and the L83V variant are inversely associated with specific HLA types, indicating that a combination of a particular HLA type and E6 genotype may favour regression or progression of an HPV-induced lesion.

To corroborate our these findings, we have initiated a prospective study in a homogeneous French population. Women positive for HPV16 with no clinical manifestation or with an early stage of cervical lesion are followed for several months to establish the regression or progression of the viral infection. Simultaneously, we are determining natural variations of the HPV16 genome and HLA class I and II polymorphisms for each of these women.

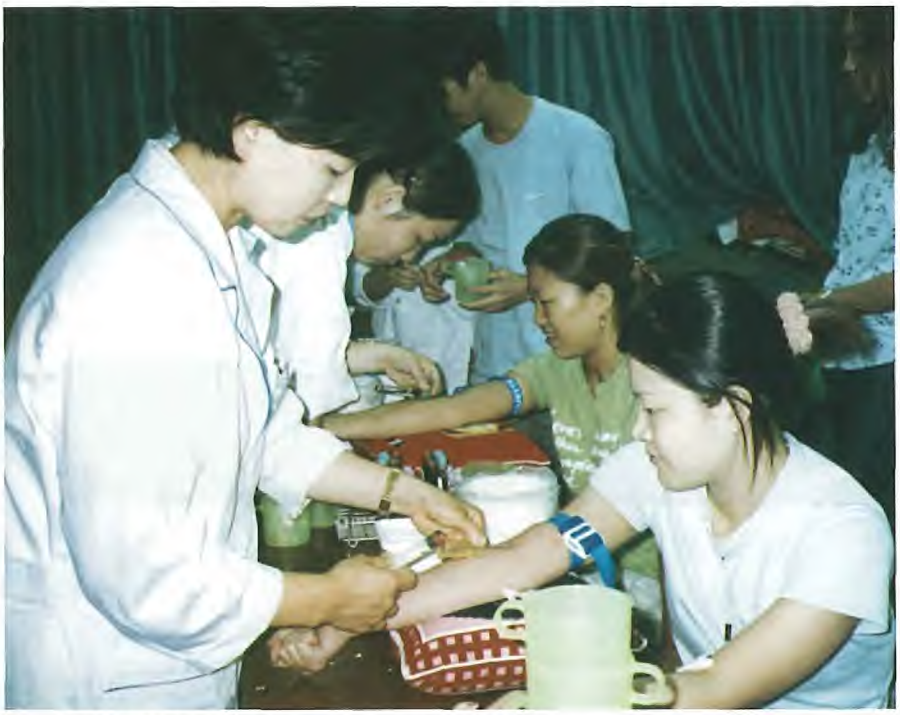

Figure 26. Taking blood samples from subjects in the Republic of Korea

The etiology of human brain tumours is less well understood than that of most other tumours. Gliomas are the most frequent human brain tumours, and of these, glioblastomas (WHO grade IV) are the most frequent and malignant histological type. The prognosis for glioblastoma patients is extremely poor, and most die within one year after diagnosis, despite advances in neurosurgery, radiotherapy and chemotherapy. Most glioblastomas develop very rapidly, without less malignant precursor lesions (*de novo* or primary glioblastomas), but some develop slowly by progression from low-grade astrocytomas (WHO grade II) or anaplastic astrocytomas (WHO grade III). The Unit of Molecular Pathology has demonstrated that these glioblastoma subtypes develop in different age groups of patients and carry different genetic and epigenetic alterations [339, 340, 342], indicating that different genetic pathways can lead to glioblastomas.

PTEN methylation and expression in glioblastomas

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The *PTEN* gene on chromosome 10q23.3, which regulates the Akt signalling pathway and modulates cell growth and apoptosis, is mutated in 20–40% of glioblastomas. Methylation-specific PCR revealed that CpG islands of the *PTEN* promoter were methylated in 27 of 77 (35%) glioblastomas and in four of 11 (36%) glioblastoma cell lines. Only two glioblastomas showed loss of PTEN immunoreactivity in the entire biopsy; both had a missense *PTEN* mutation and loss of heterozygosity (LOH) at the *PTEN* locus, but lacked *PTEN* methylation. In biopsies with focal loss of PTEN expression, DNA extracted from microdissected foci showed *PTEN* methylation only in areas with loss of PTEN expression. These results suggest that *PTEN* methylation occurs frequently in glioblastomas and may be associated with focal loss of PTEN expression. However, the correlation between *PTEN* methylation, *PTEN* mutations, LOH at the *PTEN* locus and loss of PTEN protein expression was inconsistent. The discrepancies between gene status and protein expression could be due to differences in the biological effects of specific *PTEN* mutations or to expression of the processed *PTEN* pseudogene on 9p21 in glioblastomas giving a product that co-reacts with the PTEN antibody [22].

Methylation of the *p73* gene in gliomas

T. Watanabe, H. Huang, M. Nakamura, P. Kleihues, H. Ohgaki, in collaboration with J. Wischhusen, M. Weller, Tübingen, Germany

The *p73* gene encodes a protein structurally and functionally homologous to p53, and maps to chromosomal band 1p36.33, where loss of heterozygosity has been observed in up to 90% of oligodendrogliomas and in 10–25% of diffuse astrocytomas. Promoter methylation of the *p73* gene was detected in five out of 28 (18%) glioblastomas and in four of 26 (15%) anaplastic oligodendrogliomas (WHO grade III), but not in grade II oligodendrogliomas, low-grade diffuse astrocytomas (grade II) or anaplastic astrocytomas (grade III). To assess whether *p73* methylation leads to loss of expression, 10 glioblastoma cell lines were analysed by reverse-transcriptase-PCR and methylation-specific PCR. *p73* methylation was found in two lines, one of which had no unmethylated *p73* (complete methylation) and showed loss of expression, while another had methylated and unmethylated *p73* (partial methylation) and retained *p73* expression. A third cell line showed loss of *p73* expression without *p73* methylation. These results suggest that complete *p73* methylation is associated with loss of expression, but that other mechanisms may also cause

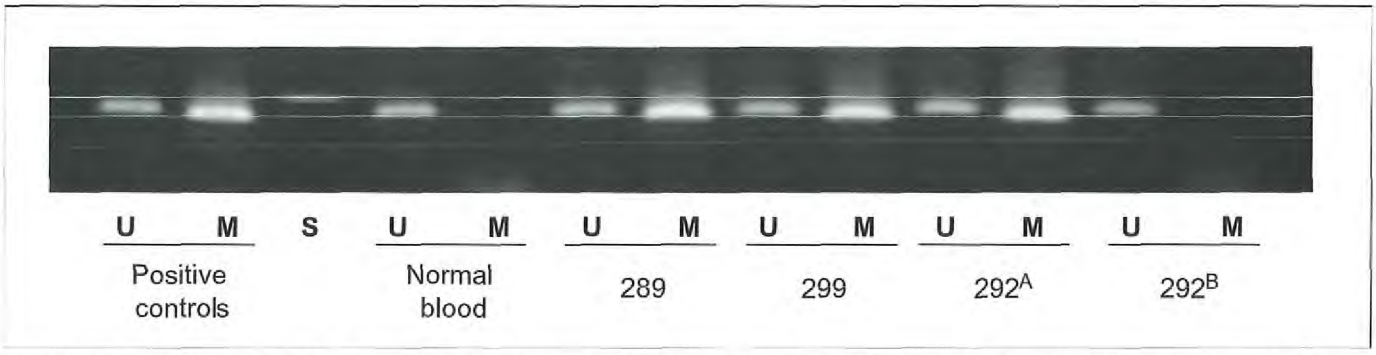

Figure 27. Methylation-specific PCR of CpG islands of the PTEN promoter in glioblastomas. Cases 289 and 299 showed both methylated (M) and unmethylated DNA (U). In glioblastoma 292, PTEN methylation (M) was restricted to a tumour area lacking PTEN immunoreactivity (292A), while another area with PTEN expression did not show PTEN methylation (292B). S, molecular size marker

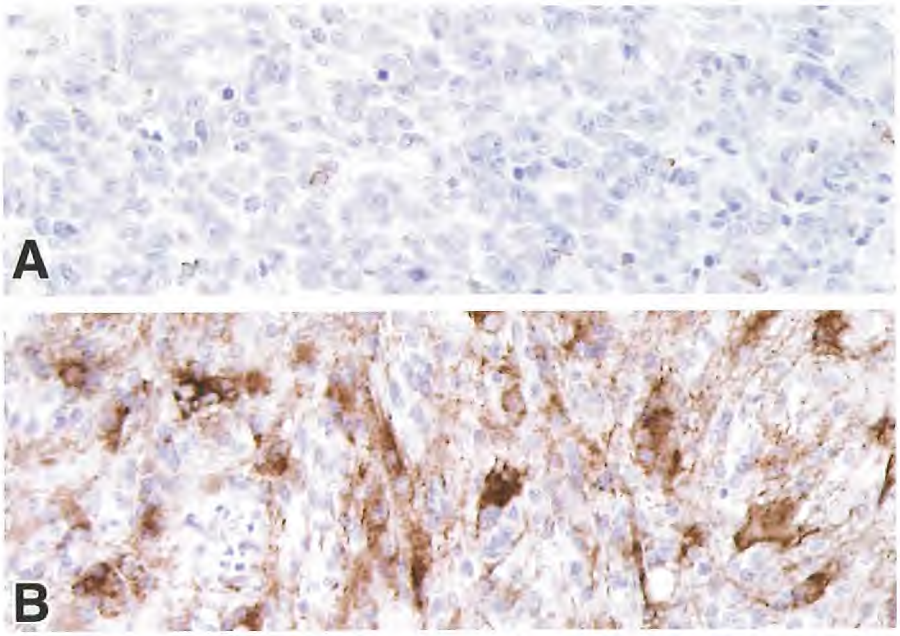

Figure 28. Heterogeneity of PTEN immunohistochemistry (glioblastoma 292), showing (A) an area with almost complete loss of PTEN expression, except in endothelial cells, while (B) the remaining biopsy reveals strong PTEN expression, though not by all tumour cells

loss of *p73* expression. Analysis of a polymorphic site in exon 2 showed that *p73* was mono-allelically expressed in six out of seven primary gliomas with heterozygous GC/TA polymorphism [547].

CD70-mediated apoptosis of immune effector cells as a novel immune escape pathway of human glioblastomas

H. Huang, H. Ohgaki; in collaboration with M. Weller, Tubingen, Germany

Interactions of CD70, a tumour necrosis factor (TNF)-related cell surface ligand and its receptor, CD27, are thought to play an important role in activation of T, B and natural-killer cells. However, ligation of CD27 can also induce apoptosis. CD70 was identified as a radioinducible gene in U87 MG glioma cells. Among 12 human glioma cell lines, 11 expressed CD70 mRNA and protein. CD70 mRNA expression was enhanced by irradiation in eight of the cell lines in a p53-independent manner, but no alteration in CD70 expression was observed after exposure to cytotoxic drugs such as lomustine. CD70 protein was also detected by immunocytochemistry in five of 12 glioblastomas and three of four anaplastic astrocytomas. CD27 expression was not detected in any glioma cell line, and there was no evidence for autocrine or backward signalling of the CD70 system in human glioma cells. Unexpectedly, CD70 expressed on glioma cells did not increase the immunogenicity of the cells. In contrast, CD70-positive glioma cells induced apoptosis in peripheral blood mononuclear cells (PBMCs) in a CD70-dependent manner. Neutralization of CD70 expressed on glioma cells prevented apoptosis and enhanced the release of TNF-α in co-cultures of glioma cells and PBMCs. The effects of CD70-expressing glioma cells on PBMCs were mimicked by agonistic CD27 antibodies. Conversely, the shedding of CD27 by PBMCs was identified as a possible escape mechanism from glioma cell-induced CD70-dependent apoptosis. Thus, induction of B-cell and T-cell expressed on glioma cells and CD27 expressed on B and T cells may be a mechanism for the immune escape of malignant gliomas [558].

Granular cell astrocytomas show a high frequency of allelic loss but are not a genetically defined subset

H. Ohgaki, H. Yokoo; in collaboration with P.C. Burger, Baltimore, MD, USA; A.A. Castellano-Sanchez, D.J. Brat, Atlanta, GA, USA; R.L. Hamilton, S.D. Finkelstein, Pittsburgh, PA, USA; B.W. Scheithauer, Rochester, MN, USA

Granular cell astrocytomas are an uncommon morphological variant of infiltrative gliomas that contain a prominent population of atypical granular cells. These tumours are more biologically aggressive than other gliomas. Eleven granular cell astrocytomas were analysed for genetic alterations of known significance to glial tumorigenesis, including LOH at 1p, 9p, 10q, 17p, and 19q, point mutations of *TP53*, deletions of *p16(CDKN2A)* and *p14ARF* and *EGFR* amplification. Overall, these tumours had higher frequencies of LOH than typical fibrillary astrocytomas of similar grades at 1p, 9p, 10q, 17p and 19q. In particular, losses on 9p and 10q occurred in nearly all granular cell astrocytomas, including grade II and III lesions. *TP53* mutations were identified in two grade IV granular cell astrocytomas, while combined *p14ARF* and *p16(CDKN2A)* homozygous deletions were noted in one grade IV granular cell astrocytoma. None of the tumours had *EGFR* amplification. These results suggest that granular cell change is associated with a high frequency of allelic loss [107].

Phenotype versus genotype correlation in oligodendrogliomas and low-grade diffuse astrocytomas

T. Watanabe, M. Nakamura, C. Burkhard, P. Kleihues, H. Ohgaki; in collaboration with J.M. Kros, Rotterdam, Netherlands; Y. Yonekawa, Zürich, Switzerland

Oligodendrogliomas typically show LOH on chromosomes 1p and 19q, and this

correlates with their response to chemotherapy, whereas low-grade astrocytomas are characterized by frequent *TP53* mutations and lack of sensitivity to alkylating therapeutic agents. Unequivocal histological distinction of low-grade diffuse astrocytomas from oligodendrogliomas and oligoastrocytomas is often difficult. To elucidate the relationships between morphological phenotype and genetic profile, oligodendrogliomas and low-grade astrocytomas (WHO grade II) were screened for *TP53* mutations and LOH on 1p and 19q. In oligodendrogliomas, LOH on chromosomes 1p and/or 19q was found in 15 (79%) and *TP53* mutation was detected in four (21%) cases. The presence of an extensive perinuclear halo and a chicken-wire vascular pattern was significantly associated with LOH on 1p or 19q, suggesting that oligodendrogliomas with classical histological features are likely to have a better prognosis. In low-grade diffuse astrocytomas, LOH on chromosomes 1p and/or 19q was found in three (13%) and *TP53* mutation was detected in 10 (43%) cases. Histologically, five astrocytomas (22%) contained small areas with oligodendroglial differentiation but this did not correlate with the presence of *TP53* mutations or LOH on 1p and 19q. In both oligodendrogliomas and astrocytomas, LOH on chromosomes 1p and/or 19q and *TP53* mutation were mutually exclusive [548].

Population-based study of incidence and survival rates of patients with pilocytic astrocytoma

C. Burkhard, P. Kleihues, H. Ohgaki; in collaboration with P.-L. Di Patre, Y. Yonekawa, U.M. Lütolf, D. Schüler, G. Schüler, Zürich, Switzerland; M.G Yasargil, Little Rock, AR, USA

The incidence of pilocytic astrocytomas and patient survival was analysed in a population-based study in the Canton of Zürich, Switzerland. Between 1980 and 1994, 987 astrocytic and oligodendroglial tumours were diagnosed, of which 55 (5.5%) were pilocytic astrocytomas.

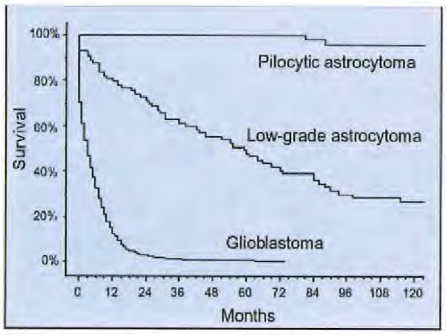

Figure 29. Kaplan–Meier plot of patients with pilocytic astrocytoma, compared with low-grade astrocytoma and glioblastoma from the same population-based study

The incidence rate, adjusted to the world standard population, was 4.8 per million population per year. The mean age at clinical diagnosis was 19.6 ⊥ 12.7 years, with a male/female ratio of 1.12. The most frequent tumour sites were the cerebellum (40%), followed by supratentorial locations (35%), the optic pathway and hypothalamus (11%) and the brainstem (9%). The mean follow-up period was 12.0 years. Observed survival rates were 100% at five years and 95.8% at 10 years after diagnosis (Figure 29). Seven patients (13%) received postoperative radiotherapy, but this did not significantly affect survival. All tumours were histologically classified as WHO grade I, except for two patients with anaplastic pilocytic astrocytoma (grade III), one of whom died after seven years, while the other was still alive after 10 years. This study shows that due to the benign biological behaviour of pilocytic astrocytomas and advances in microneurosurgery, the survival rates are excellent, irrespective of postoperative radiotherapy [90].

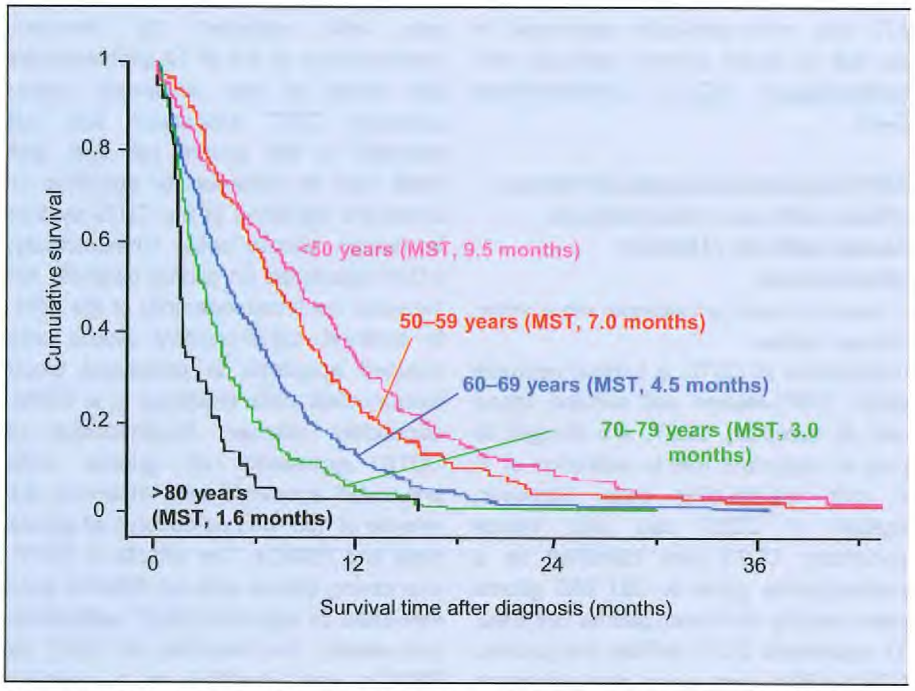

Figure 30. Younger age is predictive of longer survival in patients with glioblastoma (unpublished data from a population-based study of incidence of astrocytic and oligodendroglial tumours, genetic alterations and patient survival, in the Canton of Zurich, Switzerland)

AXIN1 mutations but not deletions in medulloblastomas

N. Baeza, J. Masuoka, P. Kleihues, H. Ohgaki

Medulloblastoma is a malignant, invasive embryonal tumour of the cerebellum which manifests preferentially in children. A subset of cases is associated with colon cancer and APC germline mutations (Turcot syndrome), and APC and β-catenin point mutations occur in up to 10% of sporadic cases, indicating the involvement of the Wnt pathway in the development of medulloblastoma. In 39 sporadic cerebellar medulloblastomas screened for alterations in the AXIN1 gene (another component of the Wnt pathway), AXIN1 mutations were detected in two tumours, CCC→TCC at codon 255 (Pro→Ser) and TCT→TGT at codon 263 (Ser→Cys). Furthermore, the A allele at the G/A polymorphism at nucleotide 16 in intron 4 was significantly overrepresented in medulloblastomas (G 0.76 versus A 0.24) compared with healthy individuals (G 0.91 versus A 0.09). Large deletions in the AXIN1 gene were found in five out of 12 (42%) medulloblastomas, consistent with a previous report (Dahman *et al.*, 2001, *Cancer Res.*, **61**, 7039–7043). However, such deletions were also seen at a similar frequency in normal brain tissue (6/12, 50%). Since there are multiple complementary, inverted sequences present in the AXIN1 gene, these large deletions may represent RT-PCR artifacts due to stem-loop secondary structures [21].

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. Studies are in progress to address 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, R. Hung, M. Shen, A. Hautefeuille; in collaboration with S. Porru, F. Donato, Brescia, Italy

In two hospitals in Brescia, Italy, 415 male cases of bladder cancer and frequency-matched controls were recruited, for a study of the effect of environmental and occupational exposures to bladder carcinogens on genetic polymorphisms of metabolic and DNA repair enzymes. Data collection was completed in 2000, laboratory analyses in 2001 and statistical analyses in 2002. Data on tobacco smoking and occupational exposures were pooled with those from another bladder cancer study, including 96 cases and 88 controls recruited in 1992 among men from the same region. Detailed information on smoking was collected, including time pattern, intensity, tobacco type and cigarette type. Lifetime occupational exposures were assessed by job title and industrial activity with detailed time pattern. Exposure to polycyclic aromatic hydrocarbons and aromatic amines in individual occupational activities was assessed by industrial hygiene experts in terms of reliability, intensity, frequency and mode. Polymorphisms of the *GSTM1*, *GSTT1*, *GSTP1*, *NAT2*, *NAT1*, *CYP1B1*, *SULT1A1*, *MPO*, *COMT*, *MnSOD*, *NQO1*, *XRCC1*, *XRCC3* and *XPD* genes were determined using the PCR–restriction fragment length polymorphism (RFLP) method. Interactions of these polymorphisms with tobacco smoking, occupational polycyclic aromatic hydrocarbons and aromatic amines were tested. Among other findings, a protective effect of *XRCC3* codon 241 variant genotype was seen (OR = 0.63, 95% CI 0.42–0.93), which was stronger among heavy smokers. A protective influence of the homozygous variant of *XRCC1* codon 399 was suggested among heavy smokers (OR = 0.38, 95% CI 0.14–1.02) [446]. These data have also been used to explore new methodological approaches for the analysis of genetic associations (see Section 6.2).

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, P. Stewart, Bethesda, MD, 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; 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 conducted 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 1127 cases have been enrolled. The control group partially overlaps with that of the lung cancer project. Analysis of the contribution of lifestyle risk factors including tobacco, obesity and hypertension is in progress. Blood samples are available on all subjects for an investigation of genetic susceptibility, and tumour samples from over 90% of cases are available for analysis of mutations in *VHL*, *TP53* and other genes.

3.7 Cancer of the lung

Lung cancer is the most frequent malignant neoplasm worldwide; tobacco smoking is the main risk factor [322, 414] and the main prevention strategy remains smoking avoidance and cessation [323] (see Section 2.4). Among the important 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 studies conducted in areas of high and low risk for lung cancer.

Lung cancer among non-smokers

P. Boffetta, P. Brennan, S. Lewis, J. Hall, G. Ferro, M. Shen, S. Borel, C. Cohet; in collaboration with W. Ahrens, Bremen, Germany; A. Andersen, Oslo, Norway; H. Batura-Gabryel, Poznan; S. Benhamou, Villejuif, France; I. Brüske-Hohlfeld, Munich, Germany; P. Buffler, Berkeley, CA, USA; V. Constantinescu, Bucharest, Romania; E. Fontham, New Orleans, LA, USA; F. Forastiere, Rome, Italy; A. Menezes, Pelotas, Brazil; F. Nyberg, Stockholm, Sweden; R. Peto, S. Clark, Oxford, UK; D.G. Zaridze, Moscow, Russian Federation

Results from two large case–control studies, one coordinated by IARC, found increased risks of lung cancer among non-smokers exposed to involuntary smoking (Boffetta *et al.*, 1998, *J. Natl Cancer Inst.*, **90**, 1440–1450; Fontham *et al.*, 1994, *JAMA*, **271**, 1752–1759). Although both studies 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 have therefore been combined in a pooled analysis based on 1263 never-smoking lung cancer patients and 2740 controls. An increased risk of lung cancer was associated with any exposure to involuntary smoking from spousal, workplace and social sources. The risk increased with duration of exposure from all three sources combined, with an odds ratio of 1.32 (95% CI 1.10–1.79) for long-term exposure from all sources [86].

In a separate study, blood samples and detailed questionnaire information were collected from about 250 non-smoking lung cancer cases and 250 non-smoking controls in Brazil, France, Germany, Italy, Poland, Romania, the Russian Federation and Sweden. Activity of the enzyme O^6-alkylguanine-DNA-alkyltransferase (AGT) was measured in leukocytes from a subset of 83 lung cancer cases and 105 controls. The risk of lung cancer increased with decreasing AGT activity. An interaction was suggested between exposure to environmental tobacco smoke and low AGT activity [58, 113]. Analyses of polymorphisms of genes involved in DNA repair are in progress.

The Janus biological bank in Norway includes serum samples from over 200 000 blood donors and other healthy individuals, who provided information on lifestyle factors at the time of enrolment and have been followed up for cancer incidence since the mid-1970s. Serum cotinine level was measured with a competitive immunoassay for 51 self-reported never-smokers who developed lung cancer during the follow-up and among 258 matched never-smoking controls. Cotinine levels above 10 ng/ml were excluded, being presumed to be due to undeclared smoking. Contrary to expectation, cases tended to have lower serum levels than controls (1.43 vs 2.16 ng/ml, $p = 0.03$) and the difference was more marked among men and older individuals. In an analysis based on categories of increasing cotinine level, no association was found with risk of lung cancer.

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

P. Brennan, P. Boffetta, F. Canzian, F. Gemignani, R. Hung, A. 't Mannetje, N. Travier, G. Ferro, S. Borel, A. Chabrier; 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.

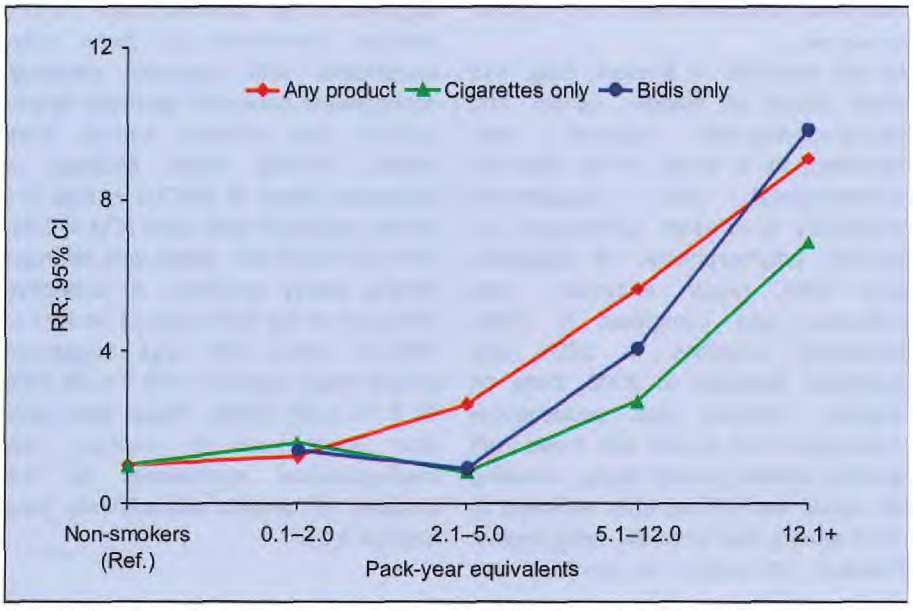

Figure 31. Relative risk of lung cancer due to smoking of selected tobacco products in India [168]

Szeszenia-Dabrowska, Lodz, Poland; J. Youngson, J. Field, 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. A study in nine areas of the Czech Republic, Hungary, Poland, Romania, the Russian Federation and Slovakia, as well as in Liverpool, UK, is assessing the relative contributions of tobacco smoking, occupational exposures and outdoor air pollution in lung carcinogenesis. More than 2800 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. Analyses have been completed on lung cancer risk following exposure to several highly reactive chemicals. A small, non-significant increase in risk of lung cancer with exposure to vinyl chloride was detected. Lung cancer risk was associated with exposure to acrylonitrile (OR = 2.20, 95% CI 1.11–4.36) and linear increasing trends in OR were observed for weighted duration of exposure and cumulative exposure (p = 0.05 and 0.06, respectively). No association was found between exposure to styrene and lung cancer risk. Analyses of risk of lung cancer following exposure to other agents are in progress. DNA extracted from blood samples of 4400 subjects is being analysed for a selection of genetic polymorphisms (see below). Preliminary statistical analyses conducted on several phase II metabolic, DNA repair and cell-cycle control genes revealed a protective effect of an Arg194Trp polymorphism in the *XRCC1* gene among young subjects and the heavily exposed group. Tumour samples from cases, when available, are being analysed for genetic alterations in relation to exposure to specific agents (see Section 6.1).

Multicentre case–control study of lung cancer in India

P. Boffetta, P. Brennan; in collaboration with U. Chattopadhyay, Kolkata, India; C.K. Gajalakshmi, Chennai, India; D.H. Jetly, Ahmedabad, India; A. Mathew, Trivandrum, India

Although the incidence of lung cancer is increasing in southern Asia, limited information on risk factors is available in these countries, in particular on the role of local tobacco products and other environmental and genetic factors. A hospital-based case–control study was conducted in Chennai and Trivandrum, India, including 778 lung cancer cases and 3430 controls. The results suggested a plateau in risk after 35 years of smoking or 10 cigarette-equivalent pack-years for both cigarettes and *bidis*. In analyses of smokers of only one product, *bidis* exerted a stronger carcinogenic effect than cigarettes (Figure 31). Quitting cigarette smoking led to a faster fall in lung cancer risk than that seen in former *bidi* smokers. No clear evidence was seen of an effect on lung cancer risk of chewing of tobacco-containing products, nor of alcohol drinking among never-smokers [168]. A further case–control study of lung and laryngeal cancer (see Section 3.8) was started in 2000 in Ahmedabad, Kolkata and Chennai, India, with the main objective of assessing interactions between genetic and environmental factors. Data collection has been completed, with a total of 1000 lung cancer cases and 1000 controls; statistical and genetic analyses are starting.

Case–control studies of lung cancer in northern Africa

A.J. Sasco, V. Luzon; in collaboration with M. Bartal, Casablanca, Morocco; F. Ben-Ayed, Tunis, Tunisia; M. Hamdi-Cherif, Sétif, Algeria

Conducting etiological studies of lung cancer in countries where the tobacco epidemic is rapidly growing is of great public health relevance and may also shed light on new etiological agents. An international case–control study of lung cancer was conducted in Morocco, Tunisia and Algeria, using a common protocol developed at IARC. Results from Morocco, based on 118 incident lung cancer cases and 235 age-, sex- and residence-matched controls showed, as expected, active smoking to be the strongest risk factor, with multivariate odds ratios ranging from 1.8 for former light smokers to 26.1 for current heavy smokers at the time of disease occurrence. Another strong risk factor was a history of chronic bronchitis. Slightly elevated risks were also found for exposure to involuntary smoking in adulthood but also in childhood, use of candles for lighting and poor ventilation of the kitchen. A new risk factor was suggested to be cannabis smoking [428]; this led us to expand the data collection on cannabis use (mode of preparation, frequency, duration) in the studies conducted in Tunisia and Algeria. Data collection has been completed in Tunisia and is continuing in Algeria.

Other studies of lung cancer

P. Brennan, P. Boffetta, J. Korte; in collaboration with E. De Stefani, Montevideo, Uruguay

In a meta-analysis of studies of risk of lung cancer from alcohol drinking, pooled smoking-unadjusted RRs were significantly increased in brewery workers and alcoholics. For cohort and case–control studies, a dose-specific meta-analysis for four levels of ethanol consumption relative to non-drinking resulted in increasing smoking-adjusted RRs for ascending dose groups (Figure 32). Further analyses indicated that smoking explained the elevated RRs in studies of alcoholics and that strong misclassification of smoking status could produce an elevated smoking-adjusted RR in cohort and case–control studies [242].

As part of a multi-site case–control study conducted in Montevideo, Uruguay, an analysis aimed at examining in detail the relationship between alcohol drinking and risk of adenocarcinoma of the lung included 160 cases and 520 hospital controls. Total alcohol intake and beer drinking were not significantly associated with risk, but wine drinking was associated with a marginally significant reduction and hard liquor intake with a 40% increase in risk of lung adenocarcinoma [132]. In a subsequent analysis of diet, red meat, total meat and fatty foods were associated with significantly increased risk of lung

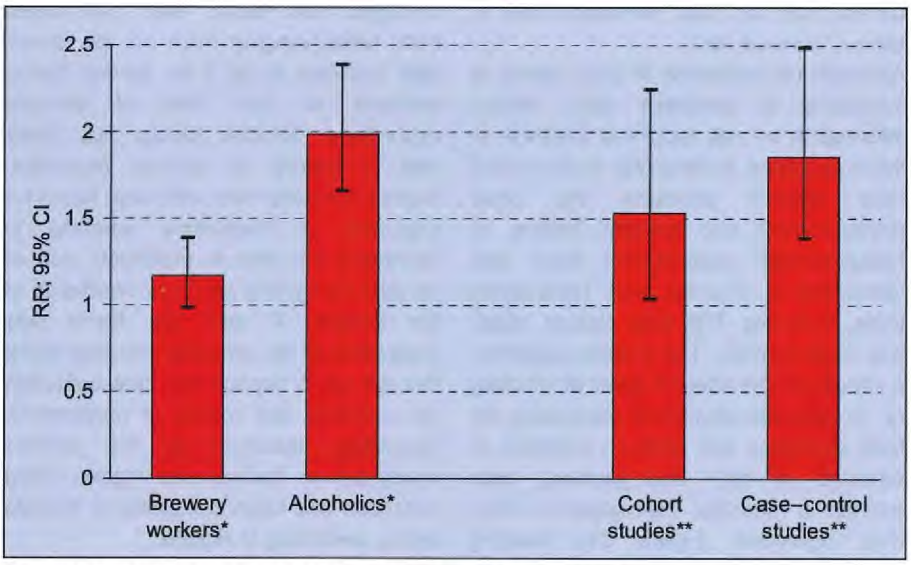

Figure 32. Results of meta-analysis of risk of lung cancer due to alcohol drinking [242]

* Relative risk not adjusted for tobacco smoking

** Relative risk in the highest category of alcohol drinking, adjusted for tobacco smoking

adenocarcinoma, while fruit, tubers and all plant foods displayed significant inverse associations. Among nutrients, total fat, other fats (saturated fat) and cholesterol were associated with increased risk. Carotenoids and vitamin E had significantly protective effects [130]. An enlarged study including 1032 cases with lung cancer (all histological types) and 1030 hospital controls revealed similar associations with total meat intake and with total vegetables and total fruits [131].

Susceptibility to lung cancer in relation to profiles of genetic polymorphisms and gene expression

D. Campa, F. Canzian, A. Chabrier, L. Gioia, S. Zienolddiny; in collaboration with A. Haugen, Oslo, Norway

Factors of susceptibility to lung cancer and mechanisms of lung carcinogenesis are being explored by correlating the polymorphic status of several enzymes involved in the metabolism of tobacco carcinogens with changes in gene expression in lung cancer samples compared with that of normal lung tissue.

Germline genetic variation in enzymes involved in metabolism of tobacco carcinogens and in DNA repair in relation to lung cancer is being addressed through a case–control study involving 300 lung cancer patients and 700 controls from the Norwegian population. Genotyping is being completed with the MetaboChip, a DNA microarray set up to genotype a battery of 166 single nucleotide polymorphisms in 54 relevant genes (see Section 4.2). Additional genotyping of polymorphic genes related to inflammation has been performed with TaqMan technology. So far, we have found associations between risk of lung cancer and polymorphisms located in the promoter of the *IL1B* gene [569] and in the 3' untranslated region of the *PTGS2* gene [102].

For the gene expression arm of this study, we defined a list of 500 candidate genes to study (the same genes analysed in the genotyping part, plus additional genes in the same pathways, and genes involved in other processes that may be related to lung cancer, such as inflammation and metabolism of reactive oxygen species). We plan to set up an expression microarray and to use it to profile cell lines derived from normal and malignant lung epithelium, as well as tumour samples obtained from a subset of the cases enrolled in the genotyping study.

3.8 *Head and neck cancer*

Tobacco, alcohol and a diet poor in certain micronutrients are the main identified etiological factors for cancer of the oral cavity and pharynx. However, only a small proportion of smokers and drinkers develop significant disease, suggesting the existence of genetic or environmental cofactors. Some studies have indicated a 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.

Molecular epidemiology of cancer of the oral cavity and oropharynx

S. Franceschi, A. Arslan, G. Clifford, S. Vaccarella, E. Weiderpass, M. Dai, P. Hainaut, 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; N. Muñoz, Lyon, France; A. Nieto, Seville, 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, USA; P. Snijders, C. Meijer, Amsterdam, Netherlands; H. Sridhar, Bangalore, India; R. Talamini, Aviano, Italy; A. Tavani, C. La Vecchia, Milan, Italy

HPV, the causal agent of cervical cancer and other anogenital malignancies, appears to be involved in the etiology of cancer of the oral cavity and oropharynx, but various aspects of the association remain unclear. In a multi-centre case–control study in nine countries (Australia, Canada, Cuba, India, Italy, Poland, Spain, Sudan and the United Kingdom (Northern Ireland)), 1670 cases and 1732 controls were interviewed. We obtained fresh biopsies from cases and oral exfoliated cells and blood from cases and controls.

HPV DNA was detected in biopsies of 4% of cancers of the oral cavity and 18% of cancer of the oropharynx (Figure 33). HPV 16 was found in the vast majority of HPV-positive cases. HPV DNA in exfoliated buccal cells was not associated with cancer risk, but detection in buccal cells was not correlated with HPV DNA in biopsies and could therefore not be considered a valid marker of HPV carcinogenesis. Antibodies against HPV 16 L1, that are considered markers of cumulative HPV 16 infection, were associated with ORs of 1.5 (95% CI 1.1–2.1) and 3.5 (95% CI = 2.1–5.9) for cancers of the oral cavity and oropharynx, respectively. Antibodies against HPV 16 E6 or E7, that reflect the presence of HPV 16-driven malignant transformation, were associated with ORs of 2.9 (95% CI = 1.7–4.8) and 9.2 (95% CI = 4.8–17.7), respectively.

The combined effect of smoking or paan chewing and HPV markers indicated that the two risk factors act according to an additive rather than multiplicative risk model. This suggests that these factors may operate on the same step of multistage carcinogenesis in the oral cavity and oropharynx, most probably p53 inactivation. Indeed, HPV 16 E6 protein inactivates p53 protein. Conversely, the chemical carcinogens contained in tobacco smoke generally block the *TP53* gene by means of specific mutations. We confirmed these alternative mechanisms of action in a substudy of 35 pairs of HPV-positive and HPV-negative cases of cancer of the oral cavity and pharynx, matched for age, sex, country and lifestyle factors (e.g., smoking, chewing, alcohol drinking). No HPV-positive cancer cases where the functional role of HPV was demonstrated by the presence of both HPV DNA and anti-HPV 16 E6 antibodies had a TP53 mutation.

In conclusion, HPV appears to play an etiological role in a substantial fraction of cancer of the oropharynx, and possibly in a small subgroup of cancers of the oral cavity. Non-smokers and non-chewers are more likely to have HPV-related tumours. The mechanism of transmission of HPV to the oral cavity warrants further study.

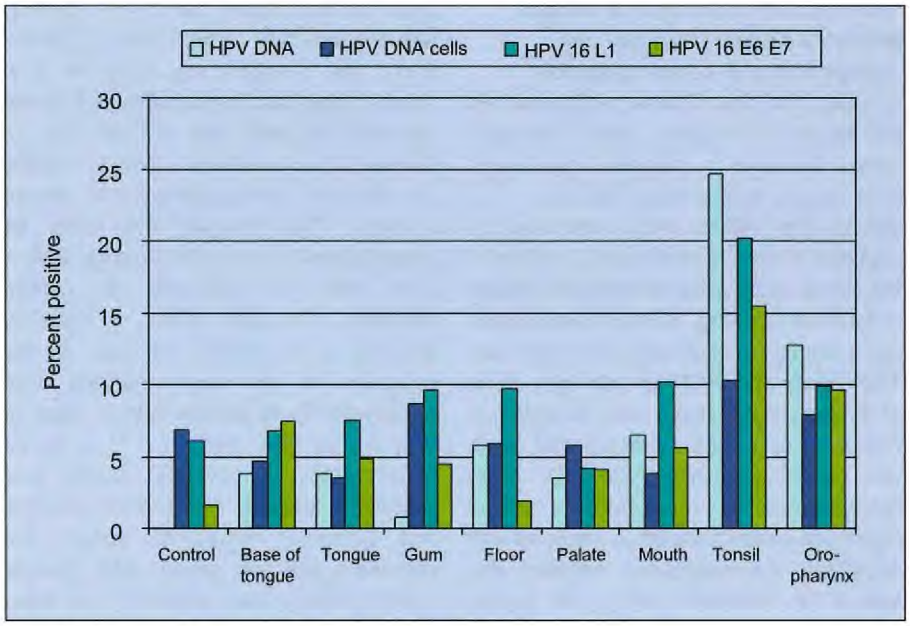

Figure 33. Prevalence of HPV markers by oral cancer sub-site

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

P. Boffetta, P. Brennan, A. 't Mannetje, N. Travier; in collaboration with M.P. Curado, Goiânia, Brazil; A. Daudt, Porto Alegre, Brazil; L. Fernandez, Havana, Cuba; 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

High incidence rates of laryngeal cancer in Argentina and southern Brazil do not seem to be explained only by exposure to known carcinogens such as tobacco smoking and alcohol drinking. A multicentre study of oral and laryngeal cancer has been conducted in five areas of Brazil (Rio de Janeiro, São Paulo, Pelotas, Porto Alegre and Goiânia), in Buenos Aires, Argentina, and in Havana, Cuba, in collaboration with an investigation of the role of HPV infection in oral cancer. 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 roles of other possible lifestyle risk factors, such as diet and maté drinking. Collection of interview data and biological samples has been completed and analyses have started.

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, Netherlands; 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 is being conducted 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, to assess the relative contributions of tobacco smoking, occupational exposures, diet and HPV infection. A total of over 400 cases of each neoplasm have been 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, K. Soldan; in collaboration with M.E. Ardanaz Aicua, Pamplona, Spain; C. Bouchardy, Geneva, Switzerland; P. Crosignani, Milan, Italy; T. Cuchi, Zaragoza, Spain; 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 consumption, occupational exposures and diet, with over 1100 cases and 3000 controls from areas of France, Italy, Spain and Switzerland. Follow-up for cancer incidence and death was conducted during 2000–2002. Data obtained from five centres for over 95% of cases and controls are being analysed with respect to the association between risk factors (as recorded during the original study) and survival from laryngeal or hypopharyngeal cancer, as well as occurrence of second primary tumours among cases, the occurrence of primary cancers among controls, and mortality (from all and selected causes) in both groups.

Multicentre case–control study of head and neck cancer in India

P. Boffetta, P. Brennan; in collaboration with U. Chattopadhyay, Kolkata; R. Dikshit, Bhopal; C.K. Gajalakshmi, Chennai; D.H. Jetly, Ahmedabad; A. Mathew, Trivandrum, India

India is the country with the largest estimated number of cases of laryngeal cancer worldwide, and the incidence is also relatively high in other countries of southern Asia. However, little information is available on risk factors in the region, in particular the role of chewing and smoking local tobacco products, as well as exposure to other environmental and genetic factors. A hospital-based case–control study included male oral (1563), pharyngeal (636) and oesophageal (566) cancer patients from Chennai and Trivandrum, as well as 1927 male healthy visitors from Chennai and 1711 other cancer controls from both centres. Dose–response relationships were observed with the amount and duration of tobacco smoking, chewing and alcohol drinking. Chewing emerged as the strongest risk factor for oral cancer, particularly chewing with tobacco (OR = 5.05, 95% CI 4.26–5.97). The strongest risk factor for both oropharyngeal and hypopharyngeal cancer was smoking, with ORs of 5.46 (95% CI 3.46–8.61) for oropharynx and 3.73 (95% CI 2.66–5.24) for hypopharynx in current smokers. The strongest risk factor for oesophageal cancer was smoking (OR = 2.83, 95% CI 2.18–3.66 for current smokers). The joint effect of smoking, chewing and alcohol drinking in the causation of the three cancers was additive [570]. In parallel with a study of lung cancer (see Section 3.7), a case–control study of laryngeal cancer was started in 2000 in Ahmedabad, Kolkata and Chennai, mainly to assess the interaction between genetic and environmental factors. Data collection has been completed, with a total of 1000 laryngeal cancer cases and 1000 controls; statistical and genetic analyses are starting.

Alcohol-related cancers and genetic susceptibility in Europe (ARCAGE)

P. Brennan, P. Boffetta, K. Soldan; in collaboration with W. Ahrens, Bremen, Germany; V. Bencko, Prague, Czech Republic; S. Benhamou, Paris, France; R.J. Black, Edinburgh, UK; X. Castellsagué, Barcelona, Spain; K. Kjaerheim, Oslo, Norway; R. Lowry, Newcastle upon Tyne, UK; G. Macfarlane, Manchester, UK; B. McCartan, Dublin, Ireland; F. Merletti, Turin, Italy; A. Metspalu, Tartu, Estonia; L. Simonato, Padua, Italy; R. Talamini, Aviano, Italy; D. Trichopoulos, P. Lagiou, Athens, Greece

Upper aerodigestive tract cancer is the fourth most common cancer in the European Union. Alcohol and tobacco are the major known risk factors, but cannot alone explain the enormous differences in incidence across Europe. A case–control study in twelve centres in eight European countries (ARCAGE) has been initiated to test hypotheses concerning genetic variation in alcohol metabolism, patterns of alcohol consumption and types of alcohol beverage, as well as dietary factors including low consumption of fruits and vegetables. Feasibility and pilot studies were completed during 2002. Cases and controls are now being recruited, with a target of over 2500 patients with upper aerodigestive tract cancer and a similar number of controls. All participants are interviewed using a standardized questionnaire. Blood samples for analysis of genetic factors, and histological slides and fresh tumour tissue if available, are being collected and stored.

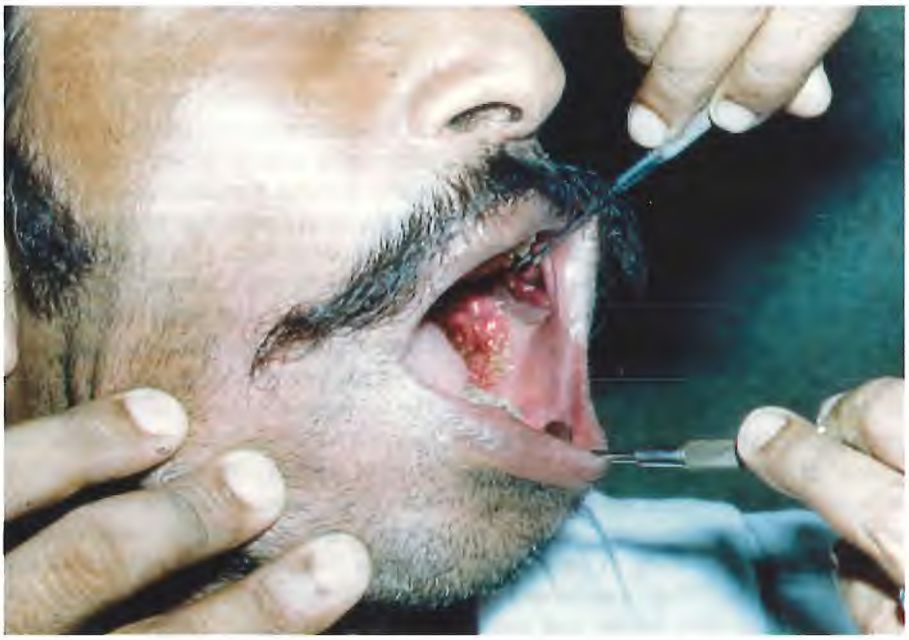

Figure 34. A moderately advanced invasive cancer in the buccal mucosa

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 geographical regions, so that international studies are of particular value. Attention is being given to viral factors (see Section 2.7 and below) as well as radiation (see Section 2.6) in lymphoma etiology.

Multicentre case–control study of lymphomas in Europe

P. Boffetta, P. Brennan, A. 't Mannetje; in collaboration with N. Becker, A. Nieters, Heidelberg, Germany; P.L. Cocco, Cagliari, Italy; L. Foretova, Brno, Czech Republic; J. Iscovich, Raanana, Israel; M. Maynadié, Dijon, France; C. Meijer, Amsterdam, Netherlands; S. de Sanjosé, Barcelona, Spain; A. Staines, Dublin, Ireland; M. Vornanen, Kotka, Finland

A case–control study is being conducted in seven European countries and Israel in order to test several hypotheses related to the increasing incidence of lymphomas. Over 2000 cases of lymphoid neoplasms and a group of comparable controls have been recruited. All participants completed 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 was also obtained from all cases and controls 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 has been established to test hypotheses regarding some infectious agents (e.g., human herpesvirus 8, Epstein–Barr virus, hepatitis C virus). Statistical and biological analyses are in progress.

The InterLymph consortium

P. Boffetta, P. Brennan; in collaboration with B. Armstrong, Sydney, Australia; P. Hartge, M. Linet, N. Rothman, Bethesda, MD, USA; and the InterLymph collaborators

Lymphoid neoplasms comprise a highly diverse group of diseases, and epidemiological analyses should ideally be conducted on specific histological subtypes. For this reason, a collaboration between the largest studies of lymphoma worldwide, including the European study described above, has been established under the coordination of IARC and the US National Cancer Institute. Subgroups have been established to either pool existing results or perform combined analyses on viral agents, occupational exposures, immunological markers, ultraviolet radiation, dietary factors and low-penetrance genes. A panel of pathologists has also been established to assess etiological factors of rare lymphoma subtypes. The genetic group has established an initial list of 14 SNPs, to be tested in the individual studies with the aim of pooling the results.

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

D.M. Parkin, E. Šteliarová-Foucher, E. Démaret, J.C. Hung, E. Masuyer; in collaboration with Nguyen Chan Hung, Cung Tuyet Anh, Ho Chi Minh City, Viet Nam; Hoang Dinh Cau, Vu Ngoc Phan, Viet Anh Tran, Hanoi, Viet Nam; S. Cordier, Villejuif, France; M. Kogevinas, Barcelona, Spain; M. Raphaël, Paris, France; J.M. Rivera-Pomar, Vizcaya, Spain; S. Stellman, New York, USA

Supported by the French Ministry of the Environment, the Ligue Contre le Cancer, the Association de Recherche sur le Cancer (ARC), the US National Institute of Environmental Health Sciences and the Italo-Vietnamese Committee in Lombardy

Excess risk of non-Hodgkin lymphomas and soft-tissue sarcomas is being evaluated in a case–control study among Vietnamese residents environmentally exposed to herbicides sprayed during the Second Indochina War. Agent Orange, known to be contaminated by the human carcinogen 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, represented about 60% of the volume of the sprayed herbicides.

Nine hundred subjects were recruited, comprising 150 soft-tissue sarcoma cases, 150 non-Hodgkin lymphoma cases, and two individually matched controls per case. One control was a cancer case, the other was another patient; all subjects were recruited through the referral hospital for cancer patients in Ho Chi Minh City. A large amount of information was obtained on each subject through a questionnaire and biological samples of tumours, serum and adipose tissue were collected. It has always been intended that the adipose tissue samples should be analysed for dioxin content, as an independent measure of exposure, but the cost of such analyses is prohibitive at present. The complete residence history of each subject was linked to detailed records on Agent Orange spraying, through the geographical location. Several measures of exposure were developed and compared. An exposure opportunity index was calculated for each place of residence and each subject in the study and the association between the estimated doses and the disease were evaluated using conditional logistic regression.

The data suggest a moderately elevated risk of cancer linked to exposure to Agent Orange, probably not restricted to the two groups of malignancies of interest, but rather for cancer in general. A trend of increasing risk with increasing level of exposure index was also observed.

Case–control study of non-Hodgkin lymphoma in Nigeria

D.M. Parkin; in collaboration with M.A. Durosinmi, Ile-Ife, Nigeria; M. Raphaël, Paris, France; J.O. Thomas, Y. Aken'ova, G. Falade, O. Ojemakinde, Ibadan, Nigeria; C. Trepo, Lyon, France

Supported by the Association de Recherche sur le Cancer (ARC)

A case–control study of non-Hodgkin lymphoma in adults and children is being conducted in Ibadan and Ile-Ife, Nigeria. The primary focus of interest is the etiological role of viral (including HIV, EBV and HCV) and other infections (especially malaria), but other exposures are being evaluated by questionnaires. By March 2003, 120 subjects had been recruited , including 24 children, among whom the majority of cases were Burkitt lymphomas.

Case–control study of non-Hodgkin lymphoma in France

A.J. Sasco, H. Besson, P. Renaudier; in collaboration with J. Fabry, C. Trepo, Lyon, France

A hospital-based case–control study of B-cell non-Hodgkin lymphoma (NHL) has been conducted in three public haematology services in Lyon, covering the whole Rhône-Alpes region. 180 cases were age- and sex-matched to 360 hospital controls with a variety of diagnoses. The role of smoking was evaluated. For the study population as a whole, as well as for men, no association was found. In contrast, current smoking elevates the risk of NHL among women, with an odds ratio of 2.4 (95% CI 1.2–4.8). Among ever-smokers, the risk reaches 5.0 for women having smoked for more than 30 years compared with never-smokers. The association is stronger in the total population of women and men for follicular lymphoma than for other histological subtypes [36].

Further analyses are in progress to evaluate the etiological role of occupations. Preliminary results indicate increased risk among laboratory workers as well as printers or doctors, with specific histological types associated with different occupations. Analyses of the role of several hepatitis virus types are also being conducted.

Role of hepatitis B and C viruses in non-Hodgkin lymphomas

S. Franceschi; in collaboration with M. Crovatto, Pordenone, Italy; A. Mele, Rome, Italy; M. Montella, Naples, Italy; E. Negri, C. La Vecchia, Milan, Italy; R. Talamini, L. Dal Maso, Aviano, Italy

HCV infection is frequently accompanied by autoimmune manifestations, most notably mixed cryoglobulinaemia. There is increasing evidence that HCV infection may be involved in a subset of non-Hodgkin lymphomas (NHL). NHL is one of the few cancers that have shown unexplained upward trends in incidence and mortality in recent decades in most areas of the world. We have been conducting two hospital-based case–control studies in Italy [304] and a systematic review of HCV and lymphohaematopoietic tumours, mainly NHL.

The first case–control study was conducted between 1998 and 2001 in 10 Italian hospitals that belong to the Italian Cooperative Group for the Study of Haematological Diseases in Adults (GIMEMA). HCV prevalence was 17.5% among 400 NHL cases and 5.6% among 396 controls. The OR for B-cell NHL, adjusted for age, sex, educational level and place of birth, was 3.1 (95% CI 1.8–5.2). ORs were similar for indolent and aggressive B-cell NHL. The HCV-attributable fraction was estimated to be 4.6%. The second case–control study was carried out between 1999 and 2002 in the Cancer Institutes of Aviano and Naples. The prevalence of HCV was 20.2% among 228 NHL cases and 8.7% among 504 hospital controls (adjusted OR = 2.9; 95% CI 1.8–4.6). As in the first study [304], the association with HCV was found for a broad range of B-cell NHL histological subtypes and was similar for low-grade and high-grade NHL. A significant association emerged also for a few HBsAg-positive individuals. In both case–control studies, HIV-positive patients were excluded and major findings were confirmed after adjustment for history of blood transfusion, thus helping to rule out the possibility of inverse causation (i.e., HCV infection as a result of treatment).

A systematic review of 66 studies on the role of HCV in lymphomagenesis included over 6000 NHL cases from Europe, the United States and Asia. High HCV prevalence in B-cell NHL patients was found especially in southern and eastern Europe, Japan and the southern United States, but not in central or northern Europe, Canada or the northern United States. Relatively few studies had included an adequate control group. Among these, the OR for B-cell-NHL among HCV-positive versus HCV-negative individuals ranged between 2 and 4. The most important source of heterogeneity in the findings from major studies was the vast variation of HCV prevalence between study areas (between 1% and over 10%). In countries where the prevalence of HCV is very low, or only increased very recently, a moderate association between HCV and NHL may be undetectable in relatively small studies.

The likeliest biological mechanisms for the role of HCV in lymphomagenesis include chronic antigenic stimulation by HCV that leads to a proliferation of specific B-cell clones. This mechanism would explain the lack of substantial difference in the association between major NHL histological subtypes. HCV may, in fact, be associated at least with all types of lymphoma whose B-cell of origin has gone through germinal centre-like structures (i.e., nearly all the most common lymphomas).

3.10 Breast cancer

Breast cancer is the most common cancer in women worldwide. As well as in 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, Japan and Thailand. In developed countries, advances in chemotherapy, radiotherapy and surgery have led to much improved prognosis. Screening by mammography has been implemented in many high-risk countries, either as organized programmes or as sporadic activities available to the whole population, and has been reviewed in the IARC cancer prevention programme (Section 5.2). However, in the many parts of the world where there are no organized screening programmes, disease is more commonly diagnosed at advanced stages and overall survival is therefore poorer.

Despite extensive research, many questions remain regarding the etiology of breast cancer, including the role of the environment, the interaction between genetics and other factors (Section 4.2) and the role of diet and hormones (Sections 2.3 and 2.4).

Natural history of breast cancer

A.J. Sasco, J. Berthiller; in collaboration with M. Abrahamowicz, Montreal, Canada; J. André, J.Y. Bobin, F. Descotes, Lyon, France; C. Bouchardy, Geneva, Switzerland; T. Fisch, Saint Gallen, Switzerland; C. Quantin, Dijon, France

Supported in part by the Ligue Nationale contre le Cancer of France and the Federal Office of Public Health, Switzerland

Hormonal metabolism is known to be central both to the occurrence [422, 423, 425] and to the clinical course [417] of breast cancer. With the development of screening for breast cancer [415], an increasing proportion of cases are diagnosed at an early stage. The classical prognostic factors of tumour size, nodal status and hormonal receptors are not adequate to precisely evaluate the prognosis of the early tumours. Based on a series of more than 1000 hospitalized cases in the Rhône-Alpes region of France, studies are being conducted in particular on biochemical tissue markers such as UPA, PAI 1, PAI 2, TK, ST 3 and VEGF with the aim of clarifying the role of extracellular disease in cancer development [438].

Another event of interest is the occurrence of second cancers. 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, 86 cases of ovarian cancer and 508 and 334 controls, respectively, matched on age and period of diagnosis, as well as duration of period at risk. The role of tamoxifen has been confirmed in relation to endometrial cancer, but in a preliminary analysis is less clear for ovarian cancer, a cancer less directly linked to hormones.

Case–control study of breast cancer in southern Asia

P. Brennan, P. Boffetta; in collaboration with U. Chattopadhyay, Kolkata, India; R. Dikshit, Bhopal, India; C. Gajalakshmi, Chennai, India; A. Mathew, Trivandrum, India; S. Sangrajrang, Bangkok, Thailand

Rural populations in southern Asia experience very low breast cancer incidence (age-standardized rates of the order of 10 per 100 000, compared with 80 in Europe and North America). However, the incidence among urban women in southern Asia is increasing and is more than twice as high as among rural women. A feasibility study conducted in 2001 provided the basis for a case–control study of low- and intermediate-risk populations in areas of India and Thailand, to investigate risk factors that may be responsible for the rapid increase. The main risk factors under study are changes in body mass and in reproductive habits, as well as diet, exposure to exogenous chemicals and genetic factors. Collection of questionnaire data and biological samples is progressing in four centres in India and two in Thailand.

Case–control study within the Breast Cancer Screening Trial cohort

P. Pisani; in collaboration with D. Esteban, Manila, Philippines

Supported by the US Army Medical Research and Material Command under Contract DAMD17-94-J-4327

Follow-up of 154 000 women interviewed in the context of the randomized controlled trial of clinical breast examination (see Section 5.3) was undertaken by the two population-based cancer registries serving the Manila area of the Philippines. Overall, 137 new cases of invasive breast cancer occurred in the study population after an average of three years of follow-up. A nested case–control study has been undertaken to investigate factors associated with the

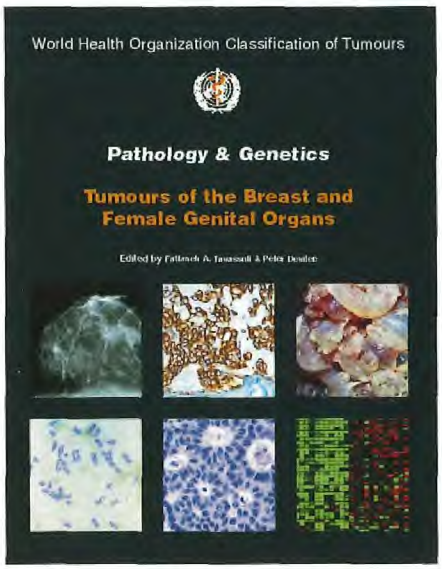

Figure 35. Volume 4 of the WHO Classification of Tumours includes full coverage of female breast tumours

risk of breast cancer in this population. For each case identified, eight controls were randomly selected from among all women in the cohort having the same municipality of residence, the same age and clinical breast examination during the same period. Vital status of cases and controls is being assessed. Those traced and alive will be re-interviewed or proxies will be approached to update the information on reproductive factors that may have changed since recruitment. The follow-up will also cover all women who reported a family history of breast or ovarian cancer (about 3000). A pilot study is being designed to test compliance with blood donation among participants of the original cohort. The aim is to conduct cross-sectional studies of characteristics of this population that may help to explain their high risk.

PROGNOCHIP

E. Lazaridis; in collaboration with S. Bassilaros, Athens, Greece; D. Kafetzopoulos, G.Thireos, E. Stathopoulos, Heraklion, Greece

Supported by the Greek Ministry of Development

The PROGNOCHIP project is developing DNA microarray technology for identification and validation of classification and prognosis markers for breast cancer, and involves researchers in computer science, molecular biology and bioinformatics. Its specific objectives are to identify and validate new and known classification markers for breast cancer, and to evaluate their predictive potential for the overall outcome of the disease. Work has started on the development of software for analysing microarray data as well as the collection, archiving and testing of appropriate biological samples.

Breast cancer genomics network

E. Lazaridis; in collaboration with M.J. Piccart, C. Sotiriou, P.Therasse, M. Buysse, Brussels, Belgium; T. Tursz, Villejuif, France; L. van t'Veer, Amsterdam, Netherlands

Supported by the European Commission

The main goal of the Trans-BIG Network of Excellence project (Translating Molecular Knowledge into Breast Cancer Management: Building on the BIG (Breast International Group) Network for Improved Treatment Tailoring) is to develop one or more readily available 'gene prognosis signatures', carefully validated in different breast cancer patient populations and translated into a widely available and user-friendly tool. The network spans over 40 institutions in nearly 20 countries. A pilot study of about 300 node-negative breast cancer patients is being conducted to prospectively validate a molecular signature related to poor prognosis using multiple microarray technologies.

3.11 Skin cancer

Skin cancer incidence is the highest among all cancers and solar radiation, especially ultraviolet radiation, is considered to be the major risk factor for both melanocytic and non-melanocytic cancers. Viral factors seem also to be involved in non-melanoma skin cancer, and the molecular mechanisms of this association are being studied.

Role of human papillomaviruses in the development of non-melanoma skin cancers

S. Caldeira, R. Accardi, I. Malanchi, W. Dong, A. Smet, S. Franceschi, M. Tommasino; in collaboration with P. Boukamp, E.-M. de Villiers, Heidelberg, Germany; R. Filotico, Bari, Italy; A. Giuliano, Tucson, AZ, USA; I. Zehbe, Mainz, Germany

Non-melanoma skin cancer (NMSC) is the most frequently occurring malignancy in the Caucasian population. Several lines of evidence suggest the involvement of infective agents in its etiology and in particular the epitheliotropic human papillomaviruses (HPV). Studies on the mucosal HPVs have shown that their ability to induce tumours in humans is tightly dependent on the *in vitro* transforming properties of the major viral oncoproteins, E6 and E7, which alter the regulation of apoptosis and the cell cycle. To further evaluate the possible role of HPV in skin carcinogenesis, we have characterized *in vitro* properties of the E6 and E7 proteins from three cutaneous HPV types, 10, 20 and 38, which are frequently detected in skin lesions. We found that HPV38 E6 and E7 corrupt the cell cycle and senescence programmes in primary cells, inducing active and long-lasting proliferation of primary human keratinocytes, the natural host cells, while E7 from HPV10 and HPV20 did not display any such activity.

To extend these *in vitro* findings, we have performed a cross-sectional study, in which healthy skin, actinic keratosis and the two epidermal tumour types, squamous-cell carcinoma (SCC) and basal-cell carcinoma (BCC) from 180 human subjects were tested for the presence of HPV38 DNA. HPV38 DNA was more frequently detected in BCC (55%, $p < 0.0001$), SCC (46%, $p = 0.0011$) and actinic keratosis, (32% $p = 0.02$) than in healthy skin (10%). To obtain further data on the suggested role for HPV38 infection in skin carcinogenesis, we have initiated an epidemiological study in Arizona, where there is a high prevalence of NMSC.

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 it can 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 the 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.

Spectral karyotyping of hepatocellular carcinomas

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. This delay may provide a mechanism allowing time for detection and repair of DNA damage. Defects in molecules involved in the response to DNA damage caused by endogenous or environmental carcinogens play an important role in human cancer development. Studies are in progress of 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 after exposure to genotoxic agents, including double- and single-strand breaks as well as accumulation of DNA adducts formed by lipid peroxidation.

ATM mutations in ataxia-telangiectasia families: genotype–phenotype correlations

M. Fernet, S. Angèle, N. Moullan, B. Chapot, S. Gutiérrez-Enríquez, J. Hall; in collaboration with J.-O. Bay, Clermont-Ferrand, France; N. Janin, Liège, Belgium; D. Stoppa-Lyonnet, A. Lauge, E. Cavaciuti, N. Andrieu, Paris, France; and the European AT group

Supported in part by INSERM, Ministère de la Recherche, Fondation de France and Electricité de France (EDF)

Recent studies of ataxia-telangiectasia (AT) families living in France have confirmed previous reports that heterozygotes for the *ATM* gene have an increased risk of developing breast cancer. To follow up this observation and to assess the contributions of different risk factors, a French cohort of some 1000 AT patients is being established, with *ATM* heterozygotes and non-*ATM* heterozygotes. The health status and exposure to risk factors of each individual will be reviewed every two years. Lymphoblastoid cell lines and a DNA and tumour bank are being established and the latter will be used to compare the etiology of breast tumours in the *ATM* heterozygotes and non-*ATM* heterozygotes at the molecular level.

Genotype–phenotype correlation in terms of the cellular response to ionizing radiation in lymphoblastoid cell lines from the AT homozygotes [10, 151] and heterozygotes is in progress. The fourteen AT heterozygote (AT het) cell lines examined to date display a wide range of radiation-induced responses: despite lower average levels of *ATM* mRNA and protein expression compared with normal cells, the majority of cell lines examined were capable of phosphorylating certain ATM substrates, leading to normal cell-cycle progression after irradiation. However, they showed lower cell survival after irradiation than the normal cell lines [152]. Using the micronucleus test to assess induction of chromosomal damage in response to irradiation *in vitro* [190], the presence of heterozygous *ATM* mutations was found to be associated with increased radiosensitivity. However, for many of the endpoints assessed, some overlap was noted between the response seen in cell lines carrying a wild-type *ATM* gene and that of the individual AT het lines, underlining the difficulty in establishing a reliable test for determining *ATM* heterozygosity.

Role of the *ATM* gene in breast cancer

S. Angèle, M. Fernet, S. Gutiérrez-Enríquez, N. Moullan, B. Chapot, D. Cox, M.D. Friesen, J. Cotterall, N. Lyandrat, C. Carreira, S. Roche, O. Sinilnikova, J. Hall; in collaboration with A. Brémond, I. Treilleux, P. Romestaing, Lyon, France; T. Dörk, Hannover, Germany; J.-P. Gérard, Nice, France; C. Jones, S. Lakhani, London, UK; P. Tanière, Birmingham, UK

Supported in part by a grant from Electricité de France (EDF)

To further 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. Differential expression of ATM is seen in normal breast tissue, with nuclear expression in luminal breast epithelial cells but low levels in myoepithelial cells (Angèle *et al.*, 2000, *Clin.Cancer Res.*, **6**, 3536–3544). A reduction in the nuclear ATM expression has been found in up to 75% of the 99 epithelial tumours studied [12]. The molecular basis of these altered expression profiles in terms of methylation status of the *ATM* gene promoter or loss of heterozygosity (LOH) is being examined.

Fifteen benign breast lesions with a prominent myoepithelial compartment have also been evaluated. ATM was over-expressed in the myoepithelial compartment of three of these breast lesions and reduced ATM expression in the luminal compartment was noted in eight. In the malignant myoepithelial neoplasms examined, over-expression of ATM was noted in only one case, suggesting that ATM over-expression is a rare event in this tumour type.

The second approach has involved genotyping 16 *ATM* sequence variants in 254 breast cancer patients, 70 of whom were adverse responders to radiotherapy, and 312 control subjects. The tightly linked intronic *ATM* polymorphisms IVS22-77 T→C and IVS48+238 C→G in the homozygote state were associated with increased breast cancer risk and in the heterozygote state with clinical radioprotection. Homozygote carriers of the 5557A variant were over-represented in the adverse radiotherapy responders compared with the normal breast cancer cases. These three single nucleotide polymorphisms (SNPs) were associated with the three major *ATM* haplotypes present in over 80% of the study population [11].

The biological significance of these missense alterations in relation to ATM function and the cellular response to ionizing radiation is being investigated using lymphoblastoid cell lines carrying these sequence variants. An increased level of induced micronuclei after irradiation was found in cell lines carrying certain *ATM* variant alleles. The presence of certain *ATM* variants thus appears to be associated with either an increased risk of breast cancer or enhanced clinical radiosensitivity, as well as with certain *in vitro* cellular radiation response phenotypes [11].

Role of DNA repair variants in radiation sensitivity and breast cancer risk

N. Moullan, B. Chapot, D. Cox, S. Angèle, S. Borel, M.D. Friesen, J. Hall; in collaboration with T. Dörk, Hannover, Germany; J.-P. Gérard, Nice, France; P. Romestaing, Lyon, France

The possible association between polymorphisms in genes other than the *ATM* gene (described above) that encode for proteins involved in the cellular response to DNA damage produced by ionizing radiation (e.g., *XRCC1, APE1, XRRC2, XRCC4*) and the risk of developing an adverse response to radiation for breast cancer is being assessed. An association has been found between the exon 9 codon 280His allele of the *XRCC1* gene and increased breast cancer risk. This variant in combination with the exon 10 codon 399Gln allele was found more frequently in cases than controls. The exon 6 194Trp allele was associated with the risk of developing an adverse response to radiotherapy. This allele in combination with the 399Gln allele was found more frequently in radiosensitive than non-radiosensitive breast cancer cases [319]. Thus it appears that distinct combinations of *XRCC1* polymorphisms may be associated with increased risk of either breast cancer or developing an adverse reaction to radiotherapy, as seen in some patients.

Expression of DNA double-strand break detection and repair proteins in breast tumours

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Expression of the members of the NBS1, MRE11 and Rad50 (NMR) complex, implicated in the repair of DNA double-strand breaks, and of p53 has been analysed in 99 *in situ* and invasive ductal breast carcinomas of different grades using an immunohistochemical approach. The protein levels of the members of the NMR complex were reduced in 46%, 31% and 28% of the tumours, respectively, while p53 was over-expressed in 30%. In most of the tumours (92%), a good correlation in the expression of the three proteins of the NMR complex was observed. A low level of NBS1, MRE11 or Rad50 expression was rarely found alone, suggesting that this arises after the deregulation in expression of other DNA repair proteins. The pattern of changes observed supports our hypothesis that alterations in DNA double-strand break repair capacity are involved in mammary carcinogenesis [12]. The expression of these four proteins has also been examined in fifteen benign breast lesions with a prominent myoepithelial compartment. p53 was consistently absent in these lesions and expression of the NMR complex was significantly more reduced in myoepithelial cells (up to 73%) than in luminal cells (up to 40%) ($p = 0.0005$).

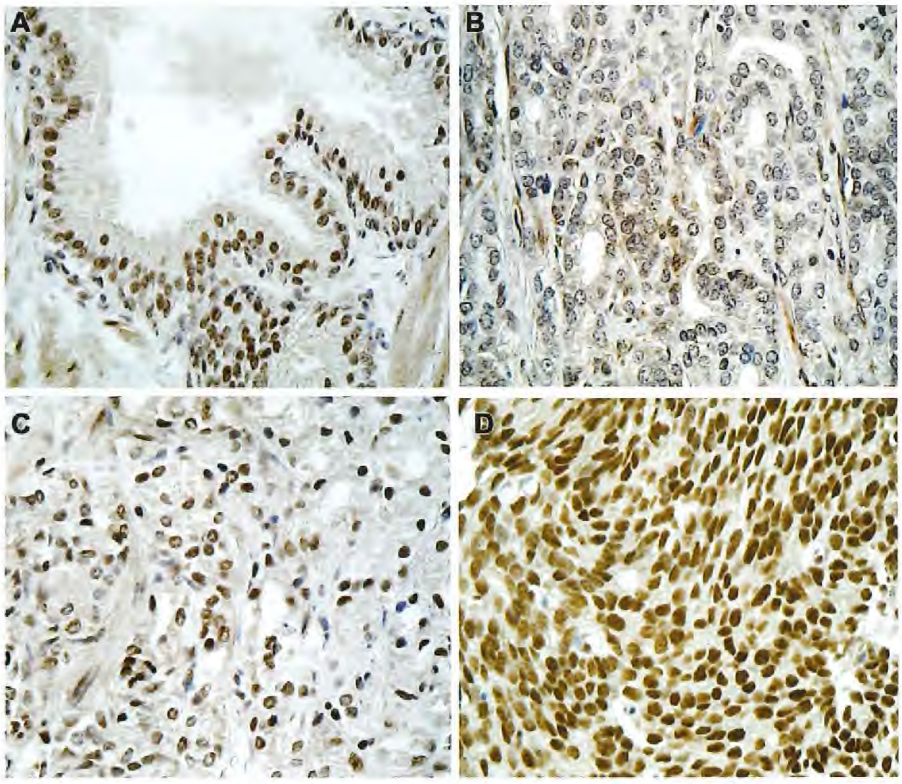

Figure 36. Normal prostate tissue and prostate carcinoma samples immunostained for ataxia-telangiectasia mutated (ATM) protein (x400)

A, ATM expression in hyperplastic glands of the transitional zone; **B**, prostate adenocarcinoma with high ATM staining – few of the nuclei are prominently stained; **C**, prostate carcinoma with normal ATM expression with respect to the number of nuclei stained and the intensity of nuclear staining; **D**, prostate carcinoma with high ATM staining – virtually all nuclei are stained intensely

Role of the *ATM* gene in prostate cancer

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Supported in part by a grant from the Association for International Cancer Research

The presence of mutations in proteins involved in the *ATM*-dependent DNA damage signalling pathway in prostate cancer patients suggests that alterations in this pathway may be an important risk factor for the disease. DNA samples from 618 prostate cancer patients and 445 controls from the United Kingdom are being analysed for the presence of five *ATM* polymorphisms.

It has been postulated that telomere dysfunction and telomerase activation play important roles in prostate tumorigenesis. Since the ATM protein is involved in maintaining telomere length and integrity, we examined its profile in 49 prostate tumour samples (Figure 36). The majority (32 samples) had ATM protein levels higher than those observed in normal tissue, with only five samples having reduced levels or an absence of ATM. Three of these were from a group of six young-onset/sibling-pair tumours. These findings support our hypothesis that the presence of the ATM protein at levels the same as or higher than those in normal prostate cells plays an important role in the maintenance of the shortened telomeres commonly found in prostate cancer cells [9].

Role of RDM1 in DNA-crosslink repair, spermatogenesis and tumorigenesis

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Cisplatin is one of the most widely used anti-cancer drugs. A DNA-damaging agent, it forms a variety of DNA adducts, the most prevalent being intrastrand crosslinks. DNA-crosslink repair in vertebrates involves in part nucleotide excision repair (NER) and homologous recombination (HR), and these repair pathways play an important role in the mechanisms by which cells develop resistance to cisplatin. For reasons still unknown, cisplatin has proved most effective in the treatment of testicular cancer. An understanding of the mechanisms of action of cisplatin in relation to testicular tumorigenesis might hold clues for improving the response of a broader range of tumours to cisplatin.

To address this question we have begun the molecular and biochemical characterization of the product of *RDM1*, a gene originally identified in chicken DT40 cells where its ablation leads to cisplatin sensitivity. The RDM1 protein carries an RNA recognition motif found in a variety of

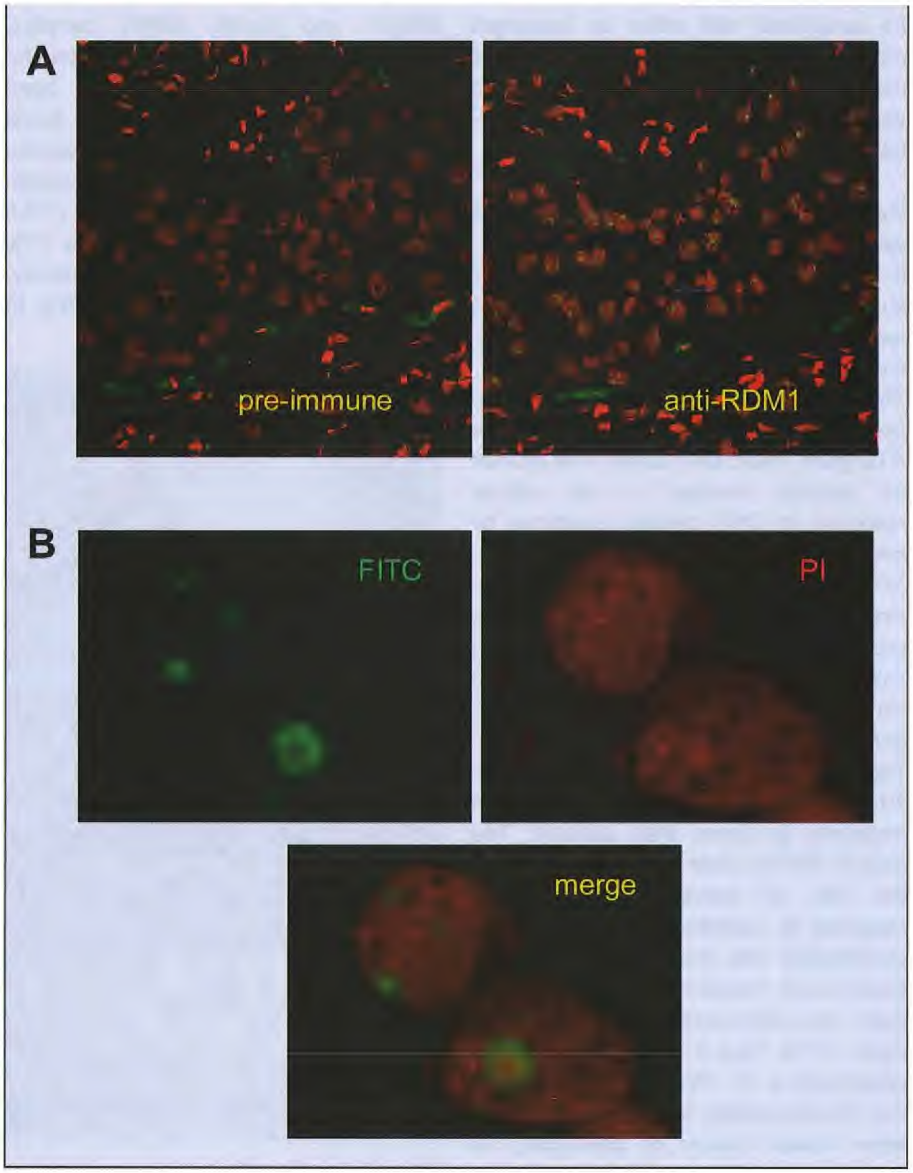

Figure 37. Nuclear structures assembled by RDM1 in the seminiferous tubule of a human seminoma specimen. (A) Indirect immunofluorescence analysis of sections of a seminiferous tubule probed with pre-immune (left panel) or anti-RDM1 (right panel) serum. The RDM1 protein was subsequently visualized with the tyramide signal amplification system, using fluorescein. Nuclei were counterstained with propidium iodide. (B) Magnified, two-dimensional view of a portion of a tubule showing RDM1 foci and circular structures.

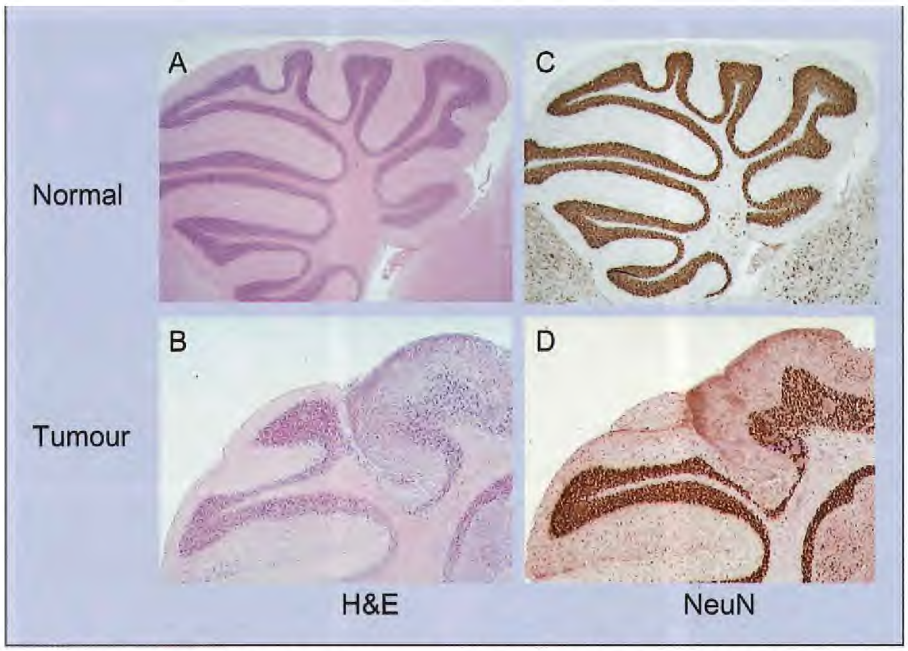

Figure 38. Histological examination of medulloblastomas in PARP-1/p53 double-null mice. H&E staining of normal (A) and neoplastic lesion (B) arising from outer surface of the cerebellum through the molecular layer. Tumour cells are immunoreactive for neuron-specific factor NeuN (D).

proteins that bind RNA and/or single-stranded DNA (ssDNA). In addition, expression of the human *RDM1* homologue, *hRDM1*, is almost exclusively confined to the testes, where its mRNAs were very highly expressed. Taken together, these observations suggest that *RDM1* may function in the resistance of testis cells to cisplatin.

Consistent with a role in DNA metabolism, we have now shown that RDM1 protein binds ssDNA and RNA, and recognizes DNA distortions induced in duplex DNA by cisplatin adducts *in vitro*. In a human seminoma, we have found that the RDM1 protein is expressed in the nucleus of specific cells within seminiferous tubules, where it organizes into foci and spherical structures (Figure 37). We are now examining the nature of the nuclear structures assembled by RDM1 and the stages of spermatogenesis at which RDM1 associates with chromatin in this seminoma. We are also comparing the pattern of RDM1 expression in healthy testicular tissue and well characterized testis tumours (carcinoma *in situ*, seminoma, non-seminoma, combined tumours).

We have identified two proteins interacting with RDM1 which point to a role for *RDM1* in spermatogenesis, chromatin metabolism and tumorigenesis. The first is a protein involved in heterochromatin formation and transcription repression both in somatic cells and during spermatogenesis. The second is a component of the aryl hydrocarbon receptor (AhR), a transcription activator that is induced by a variety of environmental pollutants and whose role in gametogenesis and tumorigenesis is well documented. Work is in progress to confirm these interactions *in vitro* and to explore their roles in the mechanisms of gametogenesis and tumorigenesis. We are also using a reporter gene system to examine the involvement of *RDM1* in heterochromatin formation and gene silencing *in vivo*.

Genes whose normal expression is restricted to the testes, but are also overexpressed in a variety of human cancers are called cancer-testis (CT) genes. CT genes represent promising targets for immunotherapy and gene therapy. We have therefore started to investigate the expression of RDM1 in hepatocellular carcinoma biopsies, and have detected overexpression of RDM1 and RDM1 splice-site variants in certain specimens.

Finally, experiments are in progress to study the phenotypes associated with inactivation of *RDM1* by RNA interference (RNAi) and to determine the importance of this gene in protecting human cells against crosslink damage.

Functional analysis of DNA end-processing proteins

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Function of poly(ADP-ribose) polymerase (PARP-1) in genomic stability and tumorigenesis

Genomic integrity and efficient DNA repair are essential for suppressing tumorigenesis. Poly(ADP-ribosyl)ation is an immediate cellular response to DNA damage generated due to either exogenous or endogenous causes. This post-translational modification is catalysed by poly(ADP-ribose) polymerase (PARP-1). Biochemical and genetic studies suggest that PARP-1 plays a multifunctional role in many cellular processes, including DNA repair, recombination, cell proliferation and death, as well as genomic stability [200].

To investigate the role of PARP-1 in the regulation of chromosomal stability, we examined centrosome function, which is crucial to the accurate transmission of chromosomes to the daughter cells in mitosis. We found that PARP-1 localizes to centrosomes and catalyses poly(ADP-ribosyl)ation of centrosomal proteins. Moreover, centrosome hyperamplification is frequently observed with PARP inhibitors as well as in PARP-1-null cells. Thus, it is possible that the chromosomal instability seen in PARP-1-null cells is attributable to centrosomal dysfunction. The p53 tumour-suppressor protein has also been shown to be localized at

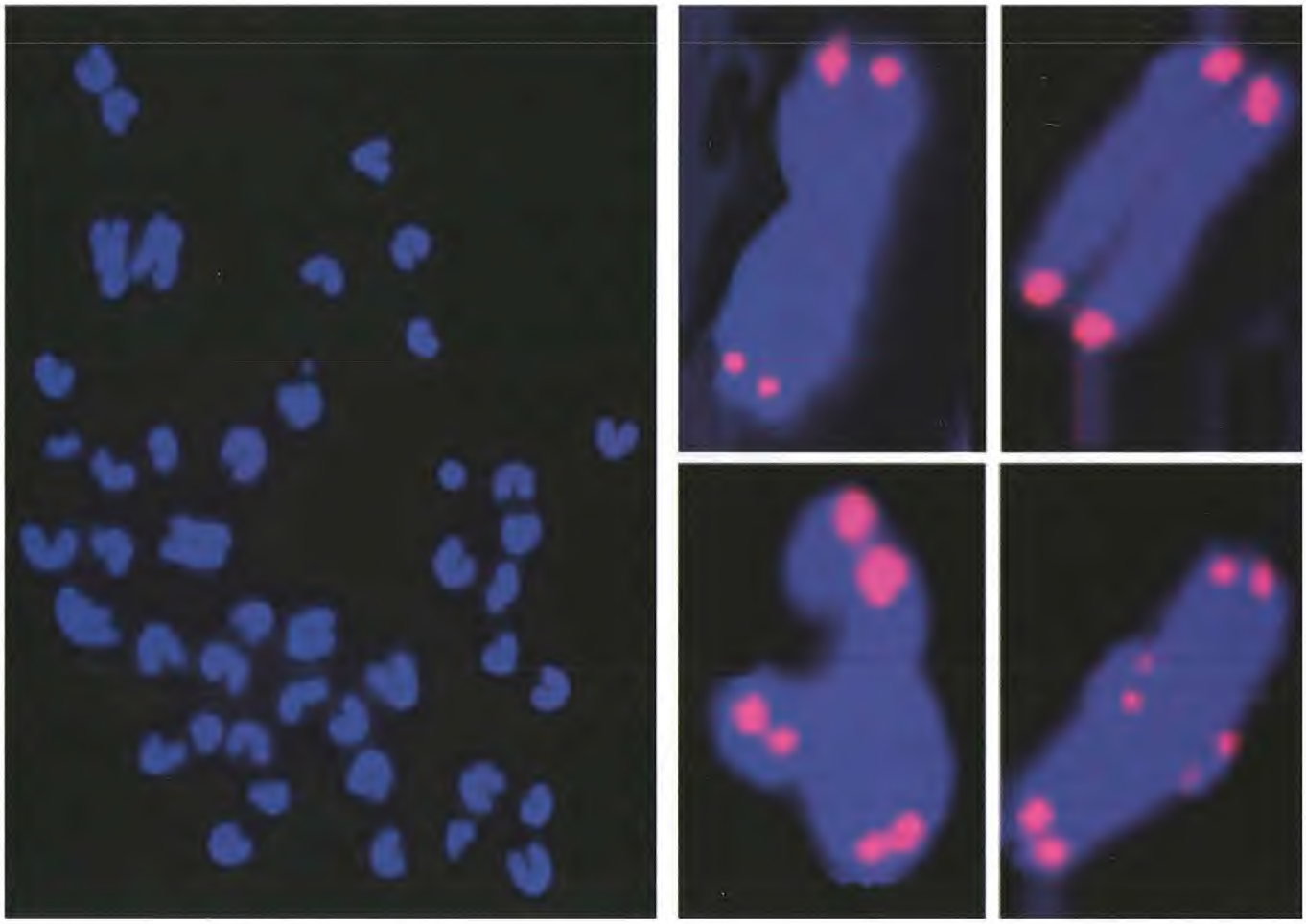

Figure 39. Cytogenetic analysis of medulloblastoma cells derived from PARP-1/p53 double null mice. Metaphase chromosomes were prepared from primary medulloblastomas and stained with the telomeric FISH probe and then counter-stained with 4,6-diamidino-2-phenylindole (DAPI). A representative metaphase spread from medulloblastoma cells is shown in (A) and chromosomal abnormalities include Robertsonian-like fusions (B), chromosomal break (C), triradial (D) and quadriradial (E) chromosomes.

centrosomes and to be involved in the regulation of centrosome duplication and the monitoring of chromosomal stability. We found that centrosomal p53 is poly-(ADP-ribosyl)ated *in vivo* and centrosomal PARP-1 directly catalyses poly(ADP-ribosyl)ation of p53 *in vitro*. These results indicate that PARP-1 and PARP-1-mediated poly(ADP-ribosyl)ation of centrosomal proteins are involved in the regulation of centrosome function [230].

In addition, we investigated the role of PARP-1 in DNA double-strand break repair and replication-mediated homologous recombination. We found that PARP-1$^{-/-}$ embryonic stem cells and fibroblast cells carry out normal homology-directed repair of genomic double-strand breaks, either by homologous recombination or by non-homologous end-joining pathways *in vivo*. However, in the absence of PARP-1, there was enhanced formation of Rad51-containing repair complexes at stalled replication forks induced by hydroxyurea, suggesting that PARP-1 is dispensable in cell cycle-independent homologous recombination induced by double-strand breaks, but that it participates in the repair of damaged replication forks. The role of PARP-1 in replication may explain the hyper-recombination and the genomic instability phenotype found in PARP-1-null cells.

The role of PARP-1 in suppressing tumorigenesis

We have previously shown that PARP-1 deficiency leads to a higher frequency of mammary gland carcinomas and brain tumours in p53-mutant mice. These tumour spectra mimic the human Li–Fraumeni syndrome (Tong *et al.*, 2001, *Mol. Cell. Biol.*, **21**, 4056).

We have generated a large cohort of PARP-1/p53 double-null mice, which have a high incidence (49%) of aggressive brain tumours, with typical features of human cerebellar medulloblastomas (Figure 38). Progression of these tumours was associated with reactivation of the neuronal specific transcription factor

Math1, dysregulation of the Shh/Ptc1 signalling pathway and chromosomal aberrations, including triradial and quadriradial chromosomes (Figure 39). These findings indicate that loss of function of molecules involved in DNA double-strand break sensing and repair is an etiological factor in the evolution of cerebellar medulloblastomas. These PARP-1/p53 double-null mice represent a useful new model for studying the pathogenesis of human medulloblastomas [508].

In PARP-1-deficient mice, mammary carcinoma formation occurred with long latency and the primary mammary epithelial cells showed centrosome amplification, chromosomal aberrations and compromised p53 function. Introduction of p53 heterozygosity into PARP-1 mutant female mice accelerated mammary carcinoma formation. In addition, PARP-1 deficiency caused mammary epithelial hyperplasia and dysplasia, and carcinomas in p53-null mice at a young age. Our results demonstrate that the centrosome amplification and chromosomal instability induced by PARP-1 deficiency trigger genetic alterations and, consequently, compromised p53 function in primary mammary epithelial cells, leading to mammary malignancy.

To study possible interactions of PARP-1 with other DNA repair molecules in relation to carcinogenesis, PARP-1 knock-out mice were crossed with mice lacking Ku80, a molecule responsible for double-strand break repair. Mice doubly null for PARP-1 and Ku80 died in the early embryonic stages, indicating that interaction of these proteins is essential in early embryonic development, and PARP-1+/–Ku80–/– mice showed severe growth retardation, developing a high frequency of T-cell lymphomas. Haploinsufficiency of Ku80 in PARP-1–/– mice promoted the development of hepatocellular adenomas and hepatocellular carcinomas (HCC), which showed multistage tumour progression associated with loss of E-cadherin expression and mutation of β-catenin. Ku80 heterozygosity was associated with chromosomal instability in PARP-1–/– cells and the liver tumours in these mice harboured a high level of chromosomal aberrations reminiscent those seen in human HCC [507].

Taken together, these data suggest that PARP-1 acts synergistically with other DNA repair or chromosomal guardian molecules to minimize chromosomal aberrations and cancer development, and that it functions as a co-factor in suppression of tumorigenesis.

Although PARP-1 deficiency increased the susceptibility to chemical tumorigenesis of mice with deficiency in other DNA repair molecules, PARP-1 mutation has not been found in human tumours. To determine whether PARP-1 mutation or deficiency is a potential factor in human cancers, we examined the expression of the PARP-1 protein in breast cancer tissue by immunohistochemistry and western-blot analysis using a specific antibody against PARP-1. Many breast cancer samples expressed very low levels of the PARP-1 protein, and loss of PARP-1 expression was frequently associated with lymph node metastasis of human breast cancer. These data suggest that the alteration of PARP-1 may be an additional factor involved in human breast carcinoma development.

The implication of PARP-1 in human endometrial carcinogenesis was also studied using biopsies of pre-neoplastic and neoplastic endometrial lesions. Surprisingly, although PARP-1 is believed to be an abundant nuclear protein, the expression profile of the PARP-1 protein varied in normal endometrium between the proliferation and secretory phases; pre-neoplastic lesions from simple to atypical hyperplasia, and carcinomas from low to high grade. Notably, the levels of PARP-1 protein correlated well with the expression of progesterone receptors (PRs) in each stage of endometrial carcinomas (Figure 40) [177], suggesting that PARP-1 may play an important role in endometrial carcinogenesis. Since PARP-1 associates with the DNA-binding domain of PRs and is believed to regulate the transcriptional activity of steroid hormones, this *in vivo* study suggests that dysregulation of PRs in endometrial carcinogenesis may be partly due to the alterations of PARP-1 function.

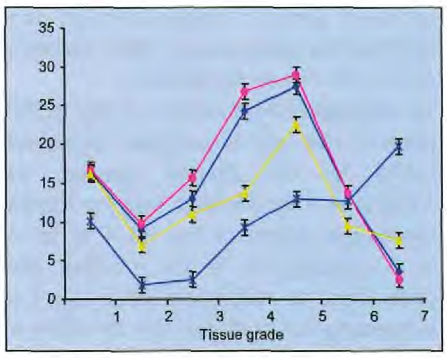

Figure 40. Expression of PARP-1 (♦), progesterone receptor (●), estrogen receptor (▲) and the marker of proliferation, Ki67 (x) in normal human endometrial and malignant tissues. Normal endometrium at proliferative phase (**1**) and secretory phase (**2**), simple (**3**) and atypical (**4**) hyperplasia, grade I (**5**), grade II (**6**), and grade III stage (**7**) endometrial carcinomas.

Functional study of the DNA damage response gene *NBS* in mouse models

P.-O. Frappart, W.-M. Tong, Z. Herceg, C. Barrucand, Z.-Q. Wang; in collaboration with A. Aguzzi, Zürich, Switzerland; M. Digweed, Berlin, Germany

The autosomal recessive disorder Nijmegen breakage syndrome (NBS) is associated with microcephaly, growth retardation, immunodeficiency, chromosomal instability and extreme susceptibility to cancer. NBS patients are sensitive to radiation. NBS heterozygous carriers also appear to be prone to malignancy development and they show an increased frequency of chromosomal translocations compared with unaffected controls. Because the average carrier frequency of the *NBS1* founder mutation is 1 in 177 among newborns in Slavonic populations in central and eastern Europe, even a moderately elevated cancer risk in heterozygous carriers could result in several hundreds of new cancer cases in these populations. The product of *NBS1*, nibrin, forms a complex with the proteins Rad50 and Mre11, which performs a multifunctional role in DNA repair and damage signalling, mainte-

nance of genomic stability through non-homologous end-joining, DNA recombination and cell-cycle regulation.

To elucidate the function of the *NBS1* gene *in vivo* and to establish an animal model for this human disease, we introduced a modification into the murine homologue (*Nbn*) of the gene in mice. Mice homozygous for the modified *Nbn* gene died at embryonic days 3.5–7.5, suggesting an essential role for nibrin in the fundamental function of cells. Heterozygous knock-out mice developed a wide array of spontaneous and radiation-induced tumours affecting the liver, mammary gland, prostate and lung, in addition to lymphomas. Moreover, γ-irradiation enhanced tumour development in $Nbn^{+/-}$ mice, giving rise to a high frequency of epithelial tumours, mostly in the thyroid and lung, as well as lymphomas. These mice also developed numerous tumours in the ovary and testis. Southern and western blot analyses showed a remaining wild-type allele and nibrin expression in $Nbn^{+/-}$ tumours. Sequencing analysis confirmed no mutation in the *Nbn* cDNA derived from these tumours. Primary $Nbn^{+/-}$ embryonic fibroblasts and tumour cells contained elevated levels of chromosomal aberrations. These data suggest that haploinsufficiency, not loss of heterozygosity, of *Nbn* could be the mechanism underlying tumour development. Overall, these observations confirm that our knock-out mice are a useful model to study the consequences of *NBS1* heterozygosity on tumour development [140].

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

Z. Herceg, H. Li, V. Shukla, C. Cuenin, Z.-Q. Wang; in collaboration with S. Jackson, Cambridge, UK; P. Steinlein, Vienna, Austria

Mutations in the genes involved in cell cycle and checkpoint control have been associated with a variety of human cancers. A loss of checkpoint function leads to genomic instability and genesis of cancer. Trrap (TRansactivation/tRansformation–domain Associated Protein) is a member of the ataxia telangiectasia (AT) mutated (ATM) superfamily of proteins, and is a component of several multi-protein histone acetyltransferase (HAT) complexes implicated in both transcriptional regulation and Myc- and E2F-mediated oncogenic transformation. Recently, we identified Trrap as an essential protein involved in proliferation and mitotic checkpoint control. In order to explore the function of Trrap *in vivo*, we have generated an *in vivo* model in which Trrap can be inactivated in a 'conditional' manner. This unique model is now being used to study the function of Trrap and its partners in basic cellular processes such as transcription regulation, cell-cycle checkpoint control, as well as oncogenic transformation and tumour development.

Since Trrap is essential for proliferation and is a cofactor for several transcription factors, we analysed the expression profiles of Trrap-responsive genes, using a cDNA microarray in specific cell-cycle stages. From a panel of 17 664 transcript elements, we found that loss of Trrap led to altered expression of a large fraction of genes at the quiescence stage, S-phase and mitosis. Functional classification of these genes indicates that Trrap influences a variety of genes related to cell-cycle progression, the cytoskeleton and cell adhesion, protein turnover, metabolism and signal transduction. Although the majority (71%) of differentially expressed genes were down-regulated in Trrap-deficient cells, a significant fraction (29%) were up-regulated, suggesting that Trrap may also play a role in transcriptional silencing [199].

We further analysed protein expression of major mitotic checkpoint regulators including Mad2 and Bub3 as well as APC

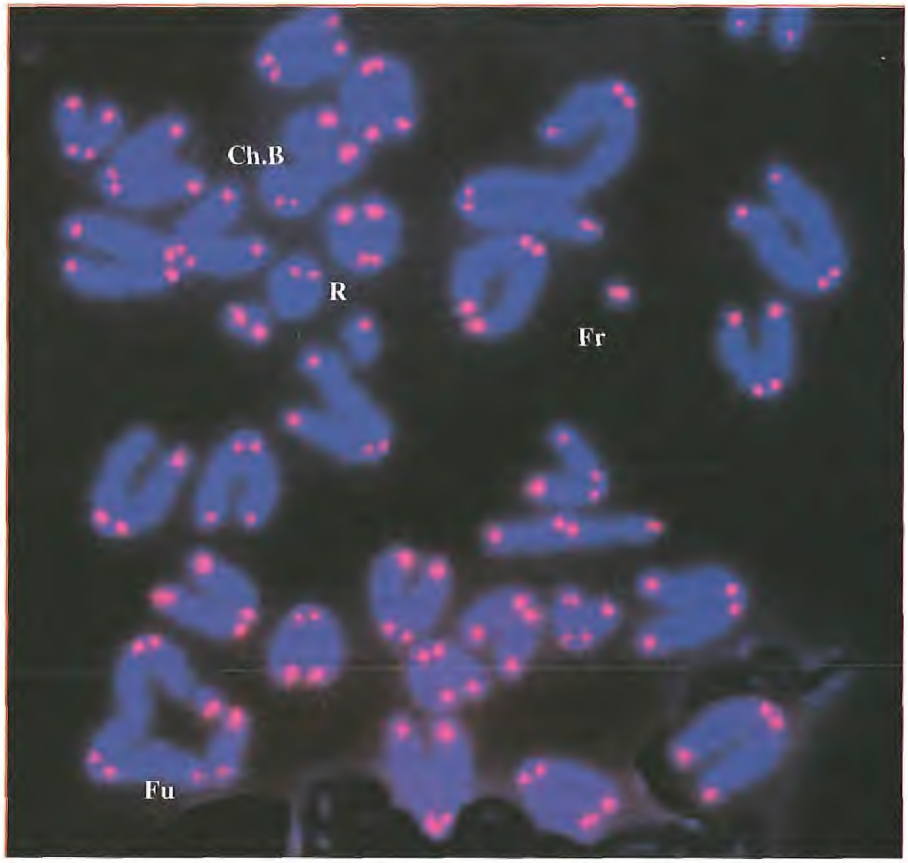

Figure 41. NBS1 heterozygosity renders mice susceptible to spontaneous and radiation-induced tumorigenesis. These tumours contain a high level of chromosome aberrations, including chromosome breaks (Ch.B), fragments (Fr), fusion (Fu), and ring chromosomes (R).

components, such as cdc27 and Cdh1. Expression of all these regulators was severely compromised in Trrap-deficient cells. Chromatin immunoprecipitation (ChIP) assays on promoters of these genes, with antibodies specific to either acetylated histone H3 or H4, revealed that Trrap modulates acetylation of different histones depending on the promoter context and cell-cycle stage, most likely through selective recruitment of specific HAT complexes.

In order to investigate the role of Trrap in cell proliferation *in vivo* and tumour development, we generated mutant mice carrying the Trrap 'conditional' knock-out allele and the Cre recombinase transgene under the control of the constitutive or inducible promoter. We have already generated Trrap/Mx-Cre mice that allow us to inducibly delete Trrap in liver and other tissues. These mice are now being used to investigate the impact of Trrap deficiency on cell proliferation and organ regeneration *in vivo* (following chemical damage or partial hepatectomy) as well as tumorigenic potential after carcinogen treatment.

Repair of etheno DNA adducts and carcinogenesis

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Etheno adducts such as 1,N^6-etheno-adenine (εA) and 3,N^4-ethenocytosine (εC) are promutagenic DNA lesions (Barbin, 2000, *Mutat. Res.*, **462**, 55–69) formed by some environmental carcinogens and by the lipid peroxidation product *trans*-4-hydroxy-2-nonenal (Yang *et al.*, 2000, *Carcinogenesis*, **21**, 777–781). We are studying some host factors that may modulate the formation, persistence and biological consequences of these lesions. To measure εA and εC in DNA, we use a sensitive method based on immunoaffinity purification and ^{32}P-postlabelling of 3'-εdAMP and 3'-εdCMP (Nair *et al.*, 1995, *Carcinogenesis*, **16**, 613–617).

Etheno DNA adducts and aldehydic DNA lesions (ADLs) in human tissues

Background levels of DNA damage in humans have been, in general, measured in one selected tissue but rarely compared between different tissues of the same individual. To obtain insight into variations of background DNA damage between different tissues in humans, two types of endogenous DNA lesions, ethenobases (εA and εC) and aldehydic DNA lesions (ADLs), were measured in several tissues (liver, lung, kidney, colon, colon mucosa, cerebellum and grey and white matter of the cerebrum) obtained during autopsy examination of 12 individuals. ADLs were analysed with the aldehyde-reactive probe-slot-blot assay (Nakamura & Swenberg, in: Hensley & Floyd (eds), *Methods in Biological Oxidative Stress*, pp. 109–115, Humana Press, 2003).

Issues relating to changes in levels of DNA damage with disease and after death were addressed. The extent of DNA damage in autopsy samples was not associated with the length of the post-mortem interval and was similar to levels observed in surgical samples, suggesting that endogenous, steady-state levels of etheno adducts and of ADLs are relatively stable during the hours immediately after death. In this limited series of samples and with a few possible exceptions, the disease status before death was not associated with increased endogenous DNA damage in the affected tissue. Levels of DNA ethenobases were lowest in the cerebellum and highest in the grey matter and white matter of the cerebrum. There was a good correlation between the levels of εA and εC (r = 0.80, p < 0.0001). Levels of ADLs were similar in the liver, lung, kidney and white matter of the cerebrum, higher in the colon and grey matter of the cerebrum and lower in the cerebellum. There was no correlation between levels of ethenobases and amounts of ADLs (εA versus ADLs, r = 0.12, p = 0.33; εC versus ADLs, r = 0.024, p = 0.85). Although there is inter-individual variation in the extent of endogenous DNA damage (four-fold for εA and εC, two-fold for ADLs), which may be in part determined by DNA repair capacity and may be related to the pathology or treatment of the patients, these results suggest that the cerebrum contains more endogenous DNA damage than the other tissues. These data are in line with previous results showing that brain tissues are more susceptible to oxidative stress and lipid peroxidation (LPO) than other tissues [24].

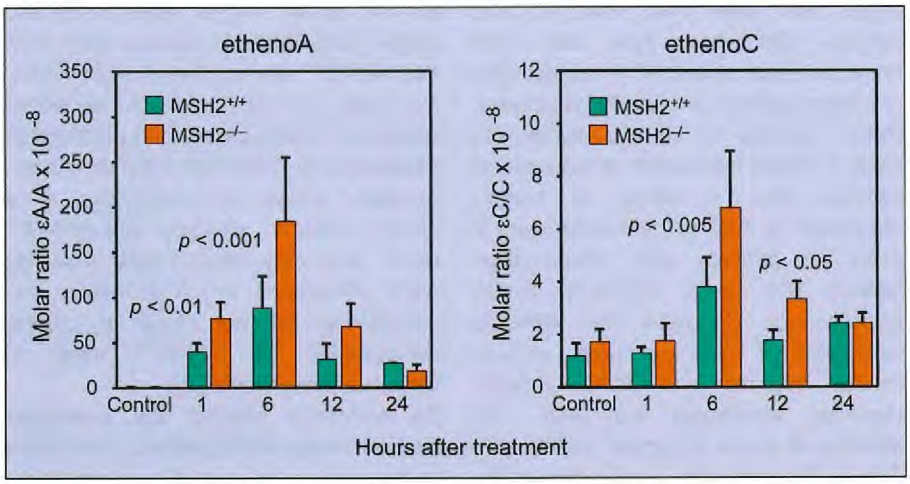

Figure 42. Levels of ethenobases formed in liver DNA from 10-day-old MSH2$^{+/+}$ and MSH2$^{-/-}$ mice treated with vinyl carbamate (single intraperitoneal dose of 250 nmol/g body weight).

Etheno adduct repair activities in lung cancer patients

To assess the role of oxidative stress and LPO in the pathogenesis of lung cancer, we measured the levels of εA and εC in DNA (33 cases), as well as the capacity for εA and εC repair (by the nicking assay) in normal and lung tumour tissues, as well as in blood leukocytes of lung cancer patients (56 cases). Repair activities for εA and εC were also assayed in leukocytes of 25 healthy volunteers, matched with the cancer patients for age, sex and smoking habits. Up to 10-fold variations among individuals were observed in both adduct levels and repair activities. No difference in εA and εC levels between tumour and non-affected lung tissue was seen. However, leukocytes accumulated a significantly higher number of DNA adducts than the lung tissues. Repair activities for both εA and εC were significantly higher in tumour than in normal lung tissue. No significant differences in εA and εC repair activities were associated with age, sex or smoking habit. However, significantly different repair capacity was observed between two histological types of lung cancer, squamous-cell carcinoma (SCC) and adenocarcinoma (ADC), εA and εC repair activities in normal lung and blood leukocytes being significantly lower in ADC than in SCC. Moreover, in non-affected lung tissue of ADC patients, the εA/εC ratio was lower than in SCC patients. Differences have also been found between εA and εC repair activities of cancer patients and healthy volunteers. Repair capacity for εA was significantly lower in blood leukocytes of lung cancer patients than in those of healthy volunteers (p = 0.012) and even lower in those of patients with inflammation-related ADC (p = 0.00033). Repair activities for εC were the same in leukocytes of healthy controls, all lung cancer patients and SCC patients. However, individuals with ADC had significantly lower εC-repair activity (p = 0.013). These results suggest that oxidative-stress-mediated LPO may contribute to induction and/or progression of lung cancer. Decreased activity of the base excision repair (BER) pathway for εA and εC is associated particularly with inflammation-related lung ADC [466].

Formation and repair of etheno adducts and their biological consequences in mice treated with vinyl carbamate

Ethenobases can be repaired through the BER pathway. εA is excised by alkylpurine DNA *N*-glycosylase (APNG), whereas εC is excised by the mismatch-specific thymine DNA *N*-glycosylase. Using APNG knock-out mice, we examined (i) whether εA is repaired by APNG *in vivo*, and (ii) whether defective repair of εA increases susceptibility to vinyl carbamate (Vcar)-induced carcinogenesis. In juvenile mice lacking APNG, after treatment with Vcar, levels of εA in liver and lung DNA were about 14-fold higher than those of εC, indicating that εA is a major promutagenic lesion induced by Vcar. Levels of εA in DNA were higher in APNG$^{-/-}$ mice than in wild-type animals and decreased more rapidly in wild-type mice than in APNG$^{-/-}$ mice. The kinetics of formation and persistence of εC were similar in the two mouse strains. These data show that εA is repaired efficiently in mice by APNG through BER. In a second experiment, carcinogenicity of Vcar was compared in APNG$^{-/-}$ and wild-type mice. One year after treatment, the incidence of hepatocellular carcinoma was similar in the two strains. Higher levels of εA and longer persistence in hepatic DNA from the APNG$^{-/-}$ animals were again seen. Vcar also induced apoptosis (measured using the TUNEL assay) and proliferation (measured by 5-bromodeoxyuridine incorporation assay) in hepatocytes to a similar extent in wild-type and APNG$^{-/-}$ mice. This may explain why relatively slight differences in εA formation and persistence did not result in greater susceptibility of APNG$^{-/-}$ mice to hepatocarcinogenesis [25].

To determine whether the nucleotide excision repair (NER) pathway is involved in the repair of εA and εC, we compared the formation and persistence of these two adducts in hepatic DNA from wild-type mice and from XPC mice (deficient in global NER) and XPA mice (deficient in both global and transcription-coupled NER), after treatment with Vcar. Levels of both εA and εC increased rapidly in the first two hours after exposure and decreased rapidly after 8 h. No significant difference in εA and εC levels was observed between the knock-out (XPC and XPA) and wild-type strains at any time. It therefore appears that NER is not significantly involved in the repair of εA and εC in mice.

A similar experiment was carried out using MSH2 knock-out mice, which are deficient in mismatch repair (MMR). In suckling (10-day-old) mice, at earlier times after treatment, the molar ratios εA/A and εC/C in hepatic DNA were significantly higher in the knock-out strain than in the wild-type strain (Figure 42). In contrast, in similarly treated juvenile (six-week-old) mice, levels of etheno adducts in liver DNA from MSH2$^{+/+}$ and MSH2$^{-/-}$ mice did not differ. Cell proliferation was stimulated 24 h after Vcar treatment in both MSH2$^{-/-}$ and MSH2$^{+/+}$ suckling mice. DNA glycosylase activities against εA and εC [466] were similar in the liver of suckling MSH2$^{-/-}$ and MSH2$^{+/+}$ mice treated with Vcar.

Overall, these data indicate that both εA and εC residues in DNA may be processed through the mismatch repair (MMR) system in mice. They suggest the hypothesis that Vcar also reacts with the nucleotide pool, yielding ethenonucleotides which are incorporated into DNA during replication and are then subject to repair by the MMR pathway. This mechanism has also been proposed for the removal of 8-oxodGMP incorporated into DNA from the pool of oxidized deoxynucleoside triphosphates (Colussi *et al.*, 2002, *Curr. Biol.*, **12**, 912–918).

The transient formation by Vcar of elevated levels of promutagenic etheno adducts in MSH2$^{-/-}$ mice, combined with the stimulation of hepatocyte proliferation, would enhance induction of somatic mutations in the liver.

In order to obtain data for risk assessment, further experiments on Vcar-

induced DNA damage and biological effects were carried out. Suckling and juvenile wild-type mice were treated with Vcar at a range of doses. Linear dose–response relationships were obtained for the formation of εA and εC in liver DNA at 6 h after treatment. Suckling mice accumulated more εA and εC than juvenile mice. The two other ethenobases, 1,N^2-ethenoG and N^2,3-ethenoG, are now being analysed. Apoptosis of hepatocytes increased at higher doses of Vcar in both suckling and juvenile mice. Hepatocyte proliferation (measured 6 h after treatment) in suckling mice increased linearly with low doses of Vcar, but at higher doses, this early stimulation of cell proliferation disappeared. Early stimulation of hepatocyte proliferation was not observed in juvenile mice at any dose of Vcar.

DNA damage and other biological effects of trans-4-hydroxy-2-nonenal in mice

trans-4-Hydroxy-2-nonenal (HNE), a major reactive product of lipid peroxidation, exerts a variety of biological effects in cultures of mammalian cells, including genotoxicity, mutagenicity, modulation of cell proliferation, induction of apoptosis and induction of differentiation of tumour cells. HNE is thought to play a role in pathological processes such as fibrosis and atherogenesis. *In vitro*, it reacts with DNA to form propanobases and its oxidation product, 4-hydroxy-2,3-epoxynonanal, is more reactive with DNA, yielding ethenobases. Background levels of ethenobases in DNA from humans and rodents are thought to arise from endogenous 4-hydroxy-2,3-epoxynonanal. Propano- and etheno DNA bases can be mutagenic in mammalian cells. In cells, HNE also reacts with proteins and is detoxified by enzymatic conjugation to glutathione.

To obtain further information on the role of HNE in carcinogenesis, we examined whether HNE can lead to DNA damage and affect the cell cycle in mice *in vivo*. Suckling mice were pretreated with buthionine sulfoximine (to scavenge endogenous glutathione) and, 2 or 4 hours later, given an injection of HNE. A slight increase of the molar ratios εA/A and εC/C in liver DNA was observed, compared to mice not treated with HNE. No such increase was seen in mice exposed to HNE but not pre-treated with buthionine sulfoximine. HNE induced a high level of apoptosis in hepatocytes while inhibiting their proliferation. These data suggest that HNE would not be hepatocarcinogenic under our experimental conditions.

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 a 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.

Major efforts to analyse gene alterations involved in familial breast and ovarian cancer are continuing; other cancer sites that are subjects of study include the prostate and colon. Polymorphisms in genes involved in carcinogen activation and detoxification are also being examined in relation to lung, bladder and head and neck cancers.

Discovery of sequence variation in genes with genetic or biochemical ties to cancer biology

S.V. Tavtigian, D. de Silva, L. Yin, S. Pauly, D.E. Goldgar, O. Sinilnikova, C. Bonnardel; in collaboration with A. Thomas, L. Cannon-Albright, Salt Lake City, UT, USA; K. Nathanson, Philadelphia, PA, USA

There is much evidence that sequence variation in a large number of genes contributes to risk of common cancers such as breast, colon and prostate cancer. Interesting sequence variants have been found in genes whose products play roles in a variety of biochemical pathways, including DNA replication, recombination and repair; hormone synthesis and degradation; hormonal signal transduction; cell cycle progression and checkpoint control; and transcriptional regulation. Such variants may take the form of promoter variants that presumably influence the rate of transcription initiation, splice junction variants that influence splicing efficiency, 5' untranslated region (UTR) variants that influence the efficiency of translation initiation, missense variants that affect protein function, and nonsense and frameshift mutations that lead to loss of protein function. One might also expect certain 3' UTR variants to influence mRNA stability.

In view of the discovery of single nucleotide polymorphisms (SNPs) that clearly confer increased risk of common cancers, it appears desirable to detect sequence variants with allele frequencies as low as 0.5% to 1.0%, and to screen genes very thoroughly so that, if a gene contains one or more risk-conferring variants, the deleterious sequence variants themselves will be found. It also appears desirable to carry out such sequence variant discovery with a method that will reveal genotypes at all of the polymorphic positions within the sections of the genes actually screened, so as to be able to estimate haplotypes and pick tagging markers for use in later genotype association studies.

Work has been initiated in three areas: (i) developing the reagent sets required for fluorescent resequencing without relying on commercially available kits (thus

dramatically reducing costs!) [14, 184]; (ii) building a fully integrated system of laboratory automation with data-tracking and mutation detection software, to allow complete screening of 50–100 genes per year, and (iii) assembling a set of lymphoblastoid lines, derived from genetically high-risk breast cancer patients and genetically high-risk prostate cancer patients, that should, in principle, be enriched in disease-associated sequence variants. It is planned to use the resulting platform to screen candidate genes, selected on biochemical or genetic criteria, for interesting sequence variants that can be applied in extremely large scale case–control association studies such as EPIC [101, 165].

Detection and analysis of differential allelic expression in genes with genetic or biochemical ties to cancer biology

S.V. Tavtigian, D. de Silva, S. Pauly, N. Forey; in collaboration with M. Ware, S. Mazoyer, Lyon, France; A. Thomas, Salt Lake City, UT, USA

Many germline sequence variants that increase cancer risk are either frameshift (nonsense) mutations that lead to loss of protein function or missense variants that alter protein function. However, others are regulatory in nature. In some instances, promoter deletions or splice junction mutations have been found to drastically reduce expression of the normal transcript from the mutant allele. In other cases, more subtle sequence variants, often in the promoter, are suspected to cause modest but still biologically relevant over- or under-expression of the allele on which they occur. The ability to detect and analyse this phenomenon will become especially important as the combination of sequence variant discovery projects and case–control association studies begin to identify promoter, enhancer and 3' UTR sequence variants that appear to be associated with risk of disease, but for which the mode of action has not been demonstrated.

We are using the *BRCA1* and *BRCA2* genes as a test case to develop and compare fluorescence-based assays for detection of differential allelic expression. Germline mutations in the tumour-suppressor genes *BRCA1* and *BRCA2* are responsible for most familial breast cancer with or without ovarian cancer. To date, more than 600 different mutations have been identified in each of these two genes, most of which introduce premature termination codons (PTCs) into the open-reading frame, via frameshifts, nonsense mutations, aberrant splicing or genomic rearrangements. We have previously demonstrated that the majority of *BRCA1* transcripts bearing PTCs are targets of nonsense-mediated mRNA decay, a cellular process that detects and destroys transcripts bearing PTCs before they can be translated into potentially deleterious truncated proteins [367]. From the perspective of our process development project, this is a very useful system because nonsense-mediated mRNA decay naturally results in differential allelic expression.

Integrated evaluation of unclassified missense variants in disease susceptibility genes: application to the *BRCA* genes

D.E. Goldgar, S.V. Tavtigian, O. Sinilnikova, C. Bonnardel, H. Renard, O. Yaqoubi, N. Forey; in collaboration with F. Couch, Rochester, MN, USA

Interpretation of results from mutation screening of tumour-suppressor genes known to harbour mutations conferring high cancer risk, such as *APC*, *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *PTEN* and *TP53*, is becoming increasingly important in clinical practice. The interpretation of frameshift and nonsense mutations, large gene rearrangements, and obvious splice junction mutations, which are almost always deleterious, is usually quite straightforward. Similarly, each of these genes harbours common sequence variants that confer little or no risk of disease. However, a many sequence variants (usually missense substitutions) remain unclassified. Discovery of unclassified variants during clinical testing creates difficulties for clinical geneticists and genetic counsellors, as the results that must be communicated to the individuals tested and their families are uninformative and sometimes confusing. In the case of *BRCA1* and *BRCA2*, such unclassified variants account for about half of all detected variants (other than common polymorphisms) and in one survey were present in 13% of all women tested [163].

Various types of evidence may help to classify such variants as deleterious or neutral with respect to the disease of interest: these include human genetics

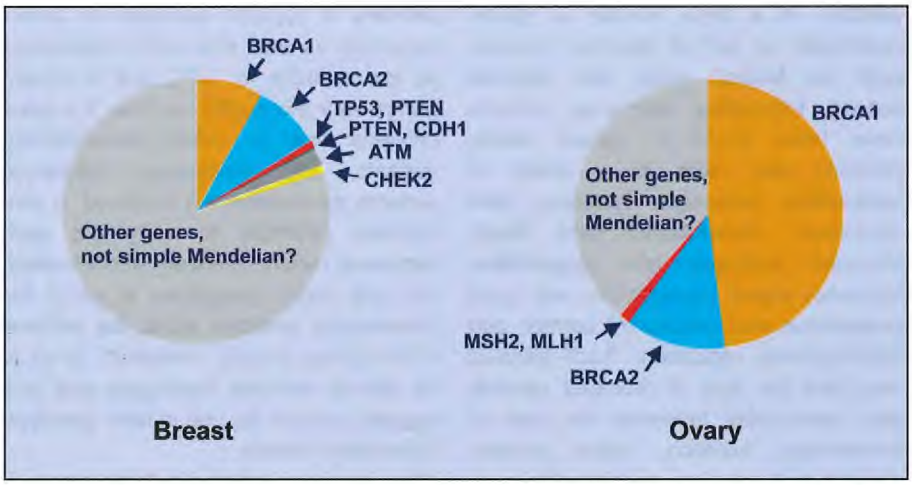

Figure 43. Genetic susceptibility accounts for some 25% to 30% of the variation in risk of breast cancer between individuals. The known susceptibility genes account for less than 25% of the genetic risk (less than about 6% of overall risk). On the other hand, known genes account for well over 50% of the genetic susceptibility to ovarian cancer. Courtesy of Douglas Easton, Cancer Research UK

data such as segregation analyses or allele frequencies in cases and controls; functional assays, often carried out in model organisms; and sequence analysis, often combined with either cross-species multiple sequence alignments or crystal structures. Each of these sources of evidence has particular strengths and limitations in addressing the general problem of causality of sequence variants. Focusing on *BRCA1* and *BRCA2*, we are carrying out two linked studies aimed at classification of these sequence variants. Similar issues arise in genetic testing for other late-onset disorders, both cancer-related (e.g., MSH1, MLH2 in hereditary colorectal cancer) and other diseases (e.g., PS1 and PS2 in early onset dementia), so our approach may eventually have quite wide applicability.

In the first study, we are using the combination of multiple sequence alignments of orthologous *BRCA1* and *BRCA2* sequences and a measure of the chemical difference between the amino acids present at individual residues in the sequence alignments to classify missense variants and in-frame deletions detected during mutation screening of these genes. In an analysis of a database of sequence variants found through full-sequence testing of *BRCA1* from 20 000 individuals, a total of 314 different missense changes and eight in-frame deletions were observed. Initially, only 21 of these missense changes were classified as deleterious and 14 as neutral or of little clinical significance. Using our new alignment-based technique, we are able to classify an additional 50 missense variants and two in-frame deletions as probably deleterious and 92 missense variants as probably neutral. An internal test of the analysis is consistent with our classification of the variants designated probably deleterious. However, it is already clear that incorporation of additional full-length orthologous *BRCA1* and/or *BRCA2* sequences into our sequence alignments will further improve the sensitivity and specificity of the analysis, and that the classification algorithm can be improved.

In the second study, in collaboration with the Breast Cancer Information Core (BIC), we are developing methods to combine several independent types of data in order to analyse unclassified sequence variants. Methods undergoing evaluation include co-segregation of these variants with disease within groups of small families; correlation between the phenotype in pooled index cases versus the phenotype in pools of families from which those index cases were drawn; a functional assay based on the formation of micronuclei in response to ionizing radiation (preliminary results have shown a highly statistically significant difference between BRCA+/– and BRCA wild-type cell lines using this assay); and the sequence alignment-based method described above.

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

D.E. Goldgar, M. Corbex, A.J. Sasco, O. Yaqoubi, C. Bonnardel, H. Renard; 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. Fourteen centres in 11 countries are participating in the study and data from the Quebec INHERIT study are now being merged into the IBCCS database. The project is integrated within the large European Breast Cancer Network. Data collection and transfer are managed using the ORACLE relational database system. Some 2000 subjects have now been enrolled in the project database and the data on first follow-up are accumulating; nearly 800 follow-up questionnaires have already been received at IARC. Thirty-one incident cancers and 18 incident ovarian cancers have been observed in these subjects.

In parallel, we have undertaken a retrospective cohort analysis on 1601 female *BRCA1/2* carriers. Two analytical approaches have been used, a Cox proportional hazards model with time-dependent covariates (where appropriate) and a matched case–control study of 323 cases who were interviewed within five years of diagnosis and 520 controls matched to these cases on age at diagnosis/censure, country of origin and gene. Preliminary analyses with both approaches have shown clear effects of parity and radiation exposure (chest X-rays), as well as a smaller protective effect of body mass index, but failed to confirm a previously suggested protective effect of tobacco use in BRCA carriers.

Mapping of non-*BRCA 1* and *2* breast cancer susceptibility loci

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

Germline mutations in the *BRCA1* and *BRCA2* genes explain only a minority of the excess familial aggregation observed for premenopausal breast cancer (Figure 43). 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. For this purpose, we are in the process of analysing the data from the genotyping of 576 DNA samples collected from 138 families meeting the criteria of three sampled cases of breast cancer diagnosed under age 60 with no identified mutation in the *BRCA1/2* genes.

Recently, two specific mutations of the *ATM* gene (7271T→G and IVS10-6T→G) were suggested to confer breast cancer risks similar to mutations of *BRCA1* or *BRCA2*. We have assessed these findings in a collaborative study of 961 families with non-*BRCA1/2*-related breast cancer from various geographical regions.

We did not detect the *ATM* 7271T→G mutation in any family, while the IVS10-6T→G mutation was detected in eight families. Mutation-positive families all originated from the Netherlands or Austria. The frequency of *ATM* IVS10-6T→G among Dutch and Austrian families with non-*BRCA1*/*BRCA2* breast cancer was similar to that of their population-matched control individuals. Bayesian analysis of linkage in the *ATM* IVS10-6T→G-positive families showed a very low overall posterior probability of causality for this mutation. We conclude that the *ATM* IVS10-6T→G mutation does not confer a significantly elevated breast cancer risk and that *ATM* 7271T→G is a rare event in familial breast cancer [486].

We have also evaluated the role of the CHK2*1100delC variant in male breast cancer. This had been reported to confer a 10-fold increased risk of breast cancer in men. However, testing this variant in 138 male breast cancer cases and 3000 controls, we found no evidence of an effect of this mutation as a risk factor [328].

Genetic susceptibility to breast and ovarian cancer

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Although mutations in the *BRCA1* and *BRCA2* genes confer high risk of breast and ovarian cancer, large variability in the age at diagnosis and cancer site is observed, even between carriers of the same mutation. Over the past two years, we have created a collection of DNA samples from individual carriers of clearly deleterious *BRCA1/2* mutations. Using this resource, we have confirmed an association of breast cancer risk and a repeat-length polymorphism in the androgen-receptor gene, and in a second study found an effect of the wild-type chromosome on ovarian cancer risk in BRCA1 carriers. We are also participating in several large international collaborative studies to examine the roles of polymorphisms in the BRCA2, RAD51 and AIB1 loci as potential modifiers of cancer risk in *BRCA* carriers.

Variability of inflammation-related genes and risk of gastrointestinal tract cancers

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Inflammation appears to be an important factor in carcinogenesis. Prostaglandins, which are major mediators of inflammation, may be involved in these effects through increasing cell proliferation, angiogenesis, carcinogen metabolism or modulation of the immune system. Two isoforms of prostaglandin synthase (also known as cyclooxygenase), *PTGS1* and *PTGS2* (*COX1* and *COX2*), have been implicated in colon and stomach carcinogenesis. *PTGS2* is expressed at high levels in colon and stomach cancers in humans and rodents. Persons who regularly use non-steroidal anti-inflammatory drugs, which act primarily by inhibiting PTGS activity, have significantly reduced risk for colon and stomach cancer.

The transcription of *PTGS2* is stimulated by interleukin-1 β (IL1B), through NFκB and polymorphisms of the *IL1B* gene have been shown to modulate risk of *H. pylori*-induced stomach cancer. Other important molecules in the regulation of inflammation are interleukin 6 (IL6), interleukin 8 (IL8) and peroxisome proliferator-activated receptor gamma (PPARG).

We have studied four polymorphisms of *PTGS2* (Figure 44) in a series of 146 cases of inflammatory bowel disease (a known risk factor for colorectal cancer) and 367 controls from the Netherlands. Two of these polymorphisms were associated with mildly increased risk of developing inflammatory bowel disease and the haplotype composed of the two at-risk alleles was associated with a strongly increased risk.

We have also studied polymorphisms of *PTGS2*, *IL1B* and several other inflammation-related genes in 375 cases of colorectal cancer and 375 controls from Spain. A mild association with one *PTGS2* polymorphism was found in this group. One polymorphism of *IL1B* showed an association with rectal cancer in homozygosity; the association became stronger when interaction with smoking was taken into account. This finding may help to explain why past studies on smoking and colorectal cancer have given conflicting results. In addition, we found moderate but significant associations with polymorphisms of *IL6*, *IL8* and *PPARG* [261]. Work is in progress to elaborate a model including all the polymorphisms that showed associations with colorectal cancer in this study, and particularly to explore their interactions.

Polymorphisms of *PTGS2*, *IL1B*, *IL6*, *IL8* and *PPARG* have also been studied in a case–control study on colon adenomas, including 232 cases and 233 controls. Case and control status was ascertained through sigmoidosopy performed at recruitment on all subjects, followed by colonoscopy to confirm presence of adenomas in cases. Statistical analysis of the genotyping data is in progress.

We are studying polymorphisms of inflammation-related genes in three studies on cancer and precancerous lesions of the stomach. The first is examining preneoplastic stomach lesions, using biological samples collected from 2200 subjects living in an area of the Venezuelan Andes where rates of *H. pylori* infection are high. The whole range of alterations from superficial gastritis to intestinal metaplasia has been observed among these subjects. We are extracting DNA from all samples in order to genotype a battery of polymorphisms related to *H. pylori* infection and inflammatory response. The second is a case–control study nested in the EPIC cohort aimed at elucidating genetic and environmental risk factors for gastric cancer (EUR-GAST; see Section 2.3). Following ascertainment of 320 cases and selection of 1280 controls, DNA has been extracted and a

biological bank has been constituted. We have performed genotyping for polymorphisms of *PTGS2* and *IL1B* on all subjects selected so far. In the third study, polymorphisms of *PTGS2*, *IL6*, *IL8* and *PPARG* have been genotyped in a series of 219 cases of stomach cancer and 302 controls from Portugal. Statistical analysis of these data, in relation to *H. pylori* strain information, is in progress.

Polymorphisms of genes related to xenobiotic metabolism and DNA repair and colorectal cancer

A. Chabrier, F. Gemignani, L. Gioia, S. Landi, F. Canzian; in collaboration with S. Chanock, Bethesda, MD, USA; V. Moreno, Barcelona, Spain

The effects of genetic variants and their interactions between each other and with environmental exposures (such as dietary exposures, tobacco and alcohol) are important for the identification of high-risk groups at the population level and for the evaluation of profiles of risk of several neoplasias at the individual level. This is particularly true of an organ such as the colorectum, which is exposed to a large number of environmental agents. Susceptibility to colorectal cancer is therefore likely to be of multifactorial nature.

A thorough search for known polymorphisms in 54 selected genes involved in various pathways of xenobiotic metabolism, DNA repair and cell-cycle control has been performed, through searches of the literature and of publicly available polymorphism databases [175]. For each polymorphism, we sought to identify 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 or with a previously reported association with cancer has been selected and used to design the MetaboChip, a genotyping DNA microarray with the arrayed primer extension technology (see Section 6.1). Multiplex PCR conditions have been set up. Validation of the microarray with a set of samples genotyped at the same 166 SNPs with reference techniques has been performed, with satisfactory results [260].

We have used the MetaboChip to genotype 375 cases of colorectal cancer and 375 controls from the Spanish population. The results confirm the association of some previously reported SNPs with risk of colorectal cancer (SNPs in *CYP2E1*, *CYP2C9*, *CYP1A1*, *CYP1A2*, *CYP1B1*, *NAT1*, *NAT2*, *GSTM3* and *UGT*). In addition, we found significant associations with polymorphisms of *DRD2*, *DRD4* and *TP53*. The possible functional role of *TP53* polymorphisms was investigated by examining the *TP53* mRNA transcripts in lymphoblastoid cell lines with different genotypes. We found reduced levels of *TP53* mRNA associated with presence of a specific allele, suggesting that the polymorphisms have a functional role.

Extensive data on lifestyle habits of the study subjects are being used to explore gene–environment interactions.

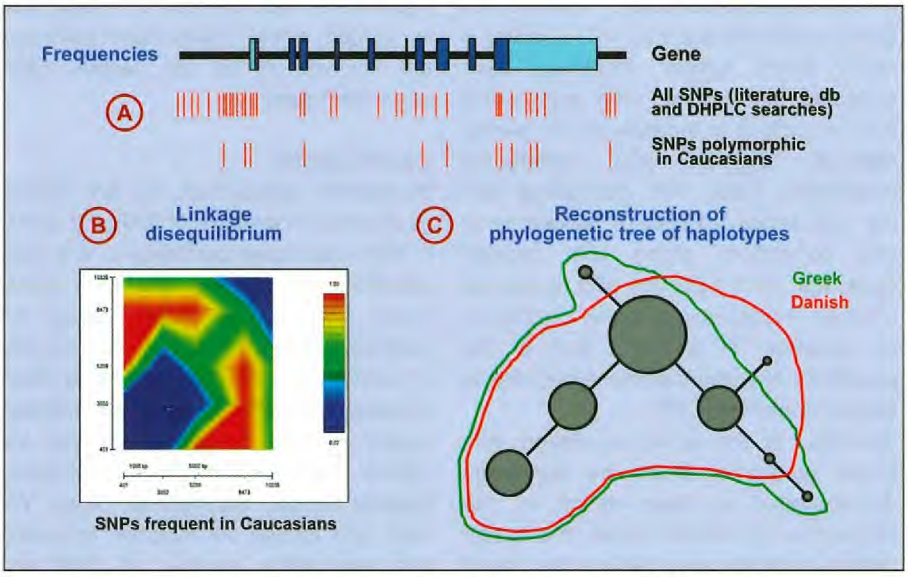

Figure 44. Characterization of genetic polymorphisms in the prostaglandin synthase 2 (*PTGS2*) gene.

A. Genomic structure of *PTGS2* (black bar: non-exonic sequence; light blue boxes: exons, untranslated parts; dark blue boxes: exons, coding parts; red lines: SNPs). A complete catalogue of polymorphisms in the gene was compiled based on data from the literature and DHPLC searches performed in the lab. SNPs present in Caucasians at a frequency of at least 5% were selected for association studies based on subjects of Caucasian descent.

B. Haplotypes reconstructed among the Caucasian SNPs demonstrate a relatively high degree of linkage disequilibrium in the gene, as graphically shown by the GOLD plot.

C. The phylogenetic relations between different haplotypes found in the gene have been reconstructed (different haplotypes are represented by circles with diameters proportional to the haplotype frequencies). Major haplotypes are present in all European populations tested, while some of the rarer ones are population-specific (examples are shown of a rare haplotype found only in Greek samples and of another found only in Danish samples).

Pooled analyses of data on genetic polymorphisms and human cancer risk

P. Boffetta, P. Brennan, R. Hung, W.J. Lee, M. Hashibe; in collaboration with S. Benhamou, Paris, France; L. Engel, N. Rothman, Bethesda, MD, USA; E. Taioli, Milan, Italy; and participants in the GSEC study

Previous studies of the role of polymorphisms of genes involved in carcinogen activation and detoxification and their interactions with environmental exposures have been hampered by small size. The International Collaborative Study on Genetic Susceptibility to Environmental Carcinogens (GSEC), coordinated by Dr E. Taioli (Milan, Italy), is pooling and analysing data from such studies. Within the framework of this study, several analyses have been conducted.

A pooled analysis of 14 case–control studies of **lung cancer** in Caucasian non-

smokers with comparable information on genetic polymorphisms included the raw data from a total of 302 cases and 1631 controls. The OR of lung cancer for the variant CYP1A1 Ile(462)Val polymorphism (Ile/Val, Val/Val) was 2.99 (95% CI 1.51–5.91); this effect was stronger for lung adenocarcinoma. There was a suggestion of a combined effect of the CYP1A1 Ile(462)Val polymorphism and GSTM1-null genotype [204].

A similar analysis for 261 young lung cancer cases and 1452 controls (up to 45 years of age at diagnosis) showed a marginally significant association between lung cancer and GSTT1-null genotype (OR = 1.2, 95% CI 1.0–1.6) and a significant association between lung cancer and the homozygous CYP1A1 Msp1 variant allele (CYP1A1*2A and *2B) genotype (OR = 4.7, 95% CI 1.2–19.0) [489].

A further pooled analysis of the original data of about 9500 subjects involved in 21 case–control studies from the GSEC data-set, including all ages and all types of smokers, found no evidence of increased risk of lung cancer among carriers of the GSTM1-null genotype nor of interaction between GSTM1 genotype and either smoking status or cumulative tobacco consumption [30].

Finally, a pooled analysis of eight studies with a total of 986 cases and 1633 controls was performed to investigate the role of microsomal epoxide hydrolase (mEH) polymorphisms in the etiology of lung cancer. A significant decrease in lung cancer risk was seen for the exon 3 His/His genotype. The OR for high predicted mEH activity, compared with low activity, was 1.18 (95% CI 0.92–1.52) [268].

Significantly increased **bladder cancer** risks associated with GSTM1-null status were found in a pooled analysis of original data from 10 studies (1496 cases and 1444 controls). There was no evidence of a multiplicative interaction between the GSTM1-null genotype and ever having smoked in relation to bladder cancer [143].

In parallel, data have been gathered from seven studies of risk of **head and neck cancer** in relation to alcohol dehydrogenase type 3 (*ADH3*) genotype and alcohol consumption. In a combined analysis with 1325 cases (758 oral cavity, 292 pharynx, 261 larynx cancers) and 1760 controls, no significantly increased risk of head and neck cancer was observed for possessing the ADH3*1/2 heterozygous genotype or the ADH3*1/1 homozygous genotype. There was evidence of interaction between ADH3*1/1 genotype and amount of alcohol consumed [87].

Down syndrome and cancer

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

The detailed study of tumour profiles in specific genetic conditions, such as Down syndrome, may constitute an epidemiological tool for suggesting molecular hypotheses. Using the French network for paediatric oncology, we performed a study aimed at identifying all cases of solid tumours in children with Down syndrome aged up to 14 years. A much lower tumour incidence than expected was found, with particularly notable deficits in tumours of the central nervous system and embryonal neoplasms [433]. This contrasted with the well known excess of leukaemia in this population, along with smaller excesses of lymphoma and germ-cell tumours. Knowledge of these conditions is important, in particular due to the sensitivity of Down syndrome patients to cancer treatment [432].

Similarly, in the adult population with Down syndrome, where we previously demonstrated a clear deficit in the occurrence of breast cancer, the sensitivity to radiation may require the use of adapted screening guidelines [431].

Genetic and functional studies of *SAP* and related genes in X-linked lymphoproliferative disease and other EBV-associated diseases

L. Yin, U. Al-Alem, W.M. Tong, C. Li, J.J. Medard, S. Pauly, M. Corbex, D.E. Goldgar, Z.Q. Wang, G. Romeo, S.V. Tavtigian

X-linked lymphoproliferative disease (XLP) is an inherited immunodeficiency characterized by selective susceptibility to Epstein–Barr virus (EBV). EBV is also implicated in nasopharyngeal carcinoma (NPC), Burkitt lymphoma (BL), Hodgkin disease, non-Hodgkin lymphoma and lymphomas in patients with immunodeficiency, including AIDS patients and organ-transplant recipients who have undergone immunosuppressive therapy (*IARC Monographs*, vol. 70, pp. 47–373, 1997). A major cause of XLP is inactivating mutations in the XLP predisposition gene *SAP* (or *SH2D1A*). Elucidation of the mechanisms underlying XLP might help to reveal the molecular basis of all these common EBV-associated tumours.

It has been established that the SAP protein interacts with the cytoplasmic domains of SLAM and several molecules of the SLAM/CD2 receptor family, belonging to the immunoglobulin superfamily (Latour & Veillette, 2003, *Immunol. Rev.*, **192**, 212–224). It is reasonable to hypothesize that alterations of SAP and its related signal transduction pathways are involved in all the various EBV-associated diseases.

Genetic studies

By genetic approaches, we are investigating the involvement of *SAP* and *SLAM* in EBV-associated pathologies. We have identified SNPs in the *SAP* and *SLAM* genes [153] and developed assays for genotyping these SNPs in a large number of individuals. We are analysing DNA samples from NPC patients and matched normal controls, in collaboration with the Cancer Center of Sun Yat-Sen University Medical School, Guangzhou, China. We have also carried out mutation screening and association studies of *SAP* and *SLAM* in BL patients, as well as analysing genome-wide LOH in BL cell lines in comparison with DNA from lymphoblastoid cell lines of the same patients [463].

Functional studies

We have investigated the function of *SAP* by characterization of *sap*-deficient mice generated at IARC. To test their susceptibility to viral infection, we infected the

mutant and wild-type mice with murine gammaherpesvirus 68 (MHV-68), which is homologous to EBV. Exacerbated proliferation of CD8+ cells and more disseminated lymphocyte infiltration were observed in the mutant mice compared with their normal littermates. As a consequence, *sap*-deficient mice displayed chronic tissue damage and haemophagocytosis. These phenotypes are reminiscent of the abnormal immune response in XLP patients, although less severe than in humans. Notably, MHV-68 reactivation was observed in *sap*-deficient mice, indicating impaired long-term control of the virus [480]. Moreover, as in XLP patients, hypogammaglobulinaemia is evident in the mutant mice both before and after viral infection. *In vitro* studies with the mutant cells revealed a primary B-cell dysfunction in immunoglobulin production. While XLP is believed to be due to a defect of T and NK cells, our results indicate that B cells may also be affected.

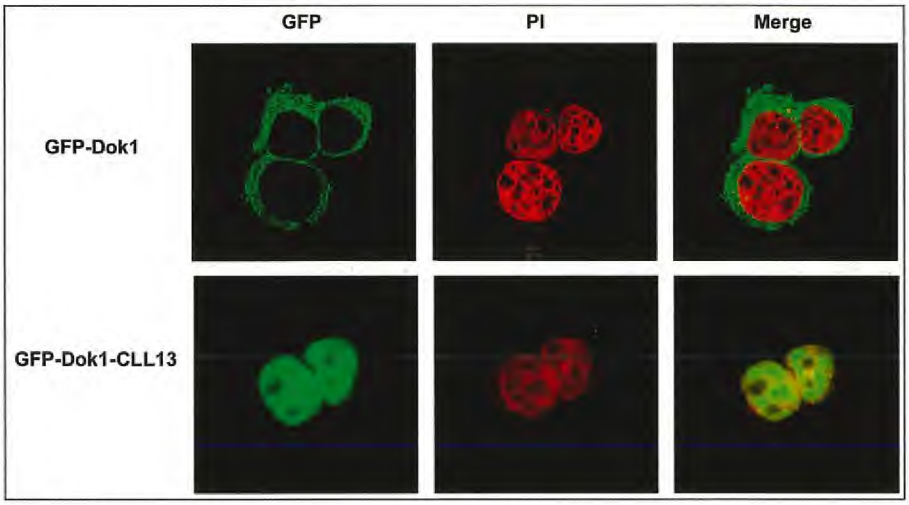

Figure 45. Mutation of Dok1 in chronic lymphocytic leukaemia (CLL) alters its function. Confocal microscopic analysis of GFP-Dok1 WT and GFP-Dok1-CLL13, a truncated mutant identified in CLL disease. While Dok1 localizes in the cytoplasm to inhibit cell proliferation, the mutant Dok1 is mislocalized and concentrates in the nucleus.

Functional studies of the SAP/SH2D1A-associated protein Dok1 and its role in human malignancies

B.S. Sylla, S.H. Lee, F. Roy, J. Michelon; in collaboration with P. Jurdic, C. Dumontet, Lyon, France; E. Kieff, Boston, MA, USA; R. Kobayashi, Houston, TX, USA

Alterations in signal transduction networks are implicated in various pathological processes, including cancer. Phosphorylation or dephosphorylation of key proteins in a given signal transduction pathway are important for cell proliferation and cell transformation. We are studying the regulation of Dok1 signalling through phosphorylation and its potential implication in human cancer.

IKKβ regulates Dok1 function through phosphorylation

Dok1 or p62 dok is an abundant Ras-GAP-associated adaptor protein that is downstream of tyrosine kinases. Dok1 is constitutively tyrosine-phosphorylated in many transformed cells or following stimulation by growth factor receptor or non-receptor tyrosine kinases. Tyrosine phosphorylation of Dok1 is also induced during B- or T-cell activation. Dok1 inhibits MAP kinase activity, down-regulates cell proliferation and suppresses cell transformation and leukaemogenesis. It also mediates cell adhesion, spreading, migration and activin-induced apoptosis, and modulates T- or B-cell receptor signalling. Phosphorylated Dok1 interacts with other signalling molecules containing SH2 domains (involved in phosphotyrosine-dependent protein–protein interactions), including SAP (also known as SH2D1A), the XLP gene product (see above). The SAP/Dok1 association may be relevant to XLP disease, as the mutant SAP protein found in XLP patients cannot interact with Dok1. Therefore, elucidating the role of these molecules would help us to understand lymphoid malignancy.

Tyrosine kinase signalling can also activate NF-κB; SAP, which is downstream of SLAM, is implicated in NF-κB activation, mediated via the tyrosine kinase pathway. Effects of Dok1 can therefore be modulated by NF-κB activation and SAP. We have shown that IκB kinase β (IKKβ), the critical component of the NF-κB activation pathway, associates with Dok1 and modulates its function through phosphorylation of specific serine residues located at the C-terminus of the protein. We showed that NF-κB inducers such as tumour necrosis factor (TNF)-α and interleukin-1 (IL-1) activate IKKβ and mediate serine phosphorylation in Dok1. Moreover, ionizing radiation induces Dok1 phosphorylation that is ATM-dependent. Furthermore, Dok1 defective for IKKβ phosphorylation has impaired capacity for inhibition of cell growth, inhibition of PDGF-induced MAP kinase activation and promotion of cell motility, whereas Dok1 with the critical serines mutated to glutamic acid enhanced cell motility. The fact that the IKKβ phosphorylation sites in Dok1 overlap with the SAP-binding site suggests a possible role for SAP in the regulation of Dok1. Our results indicate that TNF-α, IL-1 or radiation can induce IKKβ phosphorylation of Dok1 and regulate Dok1 effects downstream of tyrosine kinase activation. Overall, these data indicate that Dok1 plays an important role in the control of various cellular functions and that tyrosine kinase and IKK signalling pathways are key regulators.

Dok1 is mutated in human leukaemia

The localization of the *Dok1* gene to human chromosome 2p13, a region frequently rearranged in leukaemia, including chronic lymphocytic leukaemia (CLL), and the proposed tumour-suppressor role for Dok1, prompted us to search for Dok1

alterations in leukaemic cells. Samples from CLL and BL were analysed for mutation and altered expression of the *Dok1* gene using heteroduplex and semi-quantitative PCR approaches. Dok1 expression was found to be down-regulated in some of the samples. Moreover, a four-nucleotide GGCC deletion in the coding region was found in one CLL patient. This mutation causes a frameshift leading to protein truncation at the carboxyl-terminus, with the acquisition of a novel amino acid sequence. In contrast to the wild-type Dok1 protein, which has cytoplasmic/ membrane localization, the mutant Dok1 is a nuclear protein containing two functional nuclear localization signals (Figure 45). Whereas overexpression of wild-type Dok1 inhibited PDGF-induced MAP kinase activation, such inhibition was not observed with the mutant Dok1. This is the first example of a Dok1 mutation in B-CLL and the data suggest that Dok1 may play a role in leukaemogenesis.

Animal models for human multiple endocrine neoplasia type 1 (MEN1)

P. Bertolino, W.-M. Tong, D. Galendo, Z.-Q. Wang; in collaboration with A. Aguzzi, Zürich, Switzerland; P.L. Herrera, Geneva, Switzerland; C.-X. Zhang, Lyon, France

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary syndrome characterized by the occurrence of multiple endocrine tumours of the parathyroid, pancreas and anterior pituitary. In order to study the biological function of the MEN1 gene product (menin) and establish animal models to study its role in tumorigenesis, the *Men1* gene was disrupted in mice. *Men1*-null mutant embryos died at days 11.5–13.5, with defects in the development of the neural tube, heart and liver. Chimerism analysis revealed that cells lacking menin do not seem to have a cell-autonomous defect. It is clear that menin plays an important role in the embryonic development of multiple organs [33].

We further evaluated the proposed role for *Men1* in tumour suppression. Heterozygous *Men1* mutant mice developed the same range of major endocrine tumours as is seen in MEN1 patients, affecting the parathyroid, pancreatic islets, pituitary and adrenal glands, as well as the thyroid, and exhibiting multistage tumour progression with metastatic potential. In particular, extra-pancreatic gastrinoma, pancreatic glucagonoma and mixed hormone-producing tumours in islets were observed. There was also a high incidence of gonadal tumours of endocrine origin, i.e., Leydig cell tumours and ovarian sex-cord stromal cell tumours in heterozygous *Men1* mutant mice. Hormonal disturbance, such as abnormal parathyroid hormone and insulin levels, was also observed in these mice. These tumours were associated with loss of heterozygosity of the wild-type *Men1* allele, suggesting that menin is involved in suppressing the development of these endocrine tumours. All these features are reminiscent of MEN1 symptoms in humans and establish heterozygous *Men1* mutant mice as a suitable model for this disease [34].

To seek direct evidence on the causal role of menin in suppressing tumour development and to overcome the embryonic lethality phenotype, we generated 'conditional' *Men1* knock-out mice in which the *Men1* gene is disrupted specifically in pancreatic β-cells. These mice began to develop hyperplastic islets at as early as two months and insulinomas at six months of age. The islet lesions exhibited features of multistage tumour progression, including β-cell dedifferentiation, angiogenesis and altered expression of both E-cadherin and β-catenin. Additionally, disturbance of blood insulin and glucose levels correlated with tumour development, mimicking the human MEN1 symptoms [35].

The mice with a heterozygous *Men1* mutation or with a tissue-specific deletion of menin have proven to be a powerful tool for the study of the mechanisms of tumorigenesis related to MEN1 disease and may be useful in the testing of chemotherapeutic agents.

4.3 *Role of oxidative stress in carcinogenesis*

Oxidative stress caused by biological, chemical and physical factors has been associated with increased risk of human cancer at various sites. Mammalian cells induce and/or activate several oxidant-generating enzymes that produce high concentrations of diverse free radicals and oxidants. These reactive species can damage DNA, RNA, lipids and proteins, leading to increased mutations and altered function of enzymes and proteins, thus contributing to the multistage carcinogenesis process. Control of oxidative stress is being explored as an approach to chemoprevention of human cancers.

Oxidative stress and stomach cancer

Oxidative stress in gastric mucosa of asymptomatic humans infected with Helicobacter pylori*: effect of bacterial eradication*

H. Ohshima; in collaboration with B. Bancel, L.M. Patricot, B. Pignatelli, Lyon, France; C.P. Felley, E. Felley-Bosco, Lausanne, Switzerland

H. pylori infection is a risk factor for stomach cancer (*IARC Monographs*, vol. 61, pp. 177–240, 1994). Levels of inducible nitric oxide synthase (iNOS) and interleukin-8 (IL-8) are elevated in approximately 50% of patients with *H. pylori*-related diseases, but it is not clear whether oxidative stress is also present in *H. pylori*-infected asymptomatic humans. We have studied the expression of iNOS, superoxide dismutase (Mn-SOD) and catalase, and IL-8 production in *H. pylori*-infected asymptomatic humans, and investigated the effect of eradication of *H. pylori*. Biopsies of corpus and antrum of asymptomatic *H. pylori*-positive and -negative humans served for determination of the gastritis score and *H. pylori* status; immunostaining of iNOS, catalase and Mn-SOD was significantly associated with *H. pylori* infection and

was localized to inflammatory cells. IL-8 concentrations were greater in the *H. pylori*-positive than *H. pylori*-negative biopsies and decreased after bacterial eradication. Staining for iNOS and catalase was also decreased after *H. pylori* eradication. These results indicate that oxidative stress occurs in asymptomatic patients and can be modulated by *H. pylori* eradication [147].

Polymorphisms in the iNOS gene promoter region and gastric cancer susceptibility

M. Tatemichi, H. Tazawa, T. Sawa, I. Gilibert, M.D. Friesen, S. Michel, H. Ohshima; in collaboration with T. Katoh, Miyazaki, Japan

Polymorphisms of genes encoding for inflammatory cytokines such as interleukin-1β (IL1β) have recently been shown to be associated with gastric cancer susceptibility. We have previously observed an association between inflammatory cytokines and induction of iNOS in gastric mucosa infected with *H. pylori*, and the possible involvement of iNOS activity in gastric cancer. Several studies have found associations between polymorphisms of the promoter region of the iNOS gene and susceptibility to infectious diseases such as malaria. We are investigating polymorphisms of pentanucleotide repeat number in the promoter region of iNOS, which have been shown to associate with promoter activity. In addition, polymorphisms of the promoter region of IL1β and the protein-coding region of TNF-α are being analysed in 176 Japanese gastric cancer patients and 187 controls.

Opisthorchis viverrini infestation and cholangiocarcinoma in Thailand

Nitrated and oxidized plasma proteins as biomarkers of oxidative stress

I. Gilibert, S. Baflast, T. Takahashi, H. Ohshima; in collaboration with P. Srivatanakul, Bangkok, Thailand; M. Miwa, Tsukuba, Japan

Infection with *Opisthorchis viverrini* has been associated with increased risk of cholangiocarcinoma (CCA) in north-eastern Thailand (*IARC Monographs*, vol. 61, pp. 121–175, 1994). Chronic inflammation caused by the infection may play an important role in development of CCA. We have developed immuno-dot and western-blot assays to measure nitrated (nitrotyrosine-containing) and oxidized (carbonyl-containing) proteins in plasma samples as markers of nitrative and oxidative stress, respectively (Pignatelli *et al.*, 2001, *Cancer Res.*, **61**, 778–784). The method has been extended to measure other types of protein modification, including 4-hydroxy-2-nonenal and malondialdehyde adducts as markers of lipid peroxidation [344]. These methods have been applied to plasma samples collected in areas of high risk for liver cancer in Thailand. Samples from subjects with precancerous conditions have significantly elevated levels of nitrated and oxidized proteins as well as of 4-hydroxy-2-nonenal adduct, compared with those from healthy subjects (Figure 46). Using proteomics techniques (two-dimensional protein gel electrophoresis and mass spectrometric analysis of spots), we are analysing the nature of these modified proteins.

In addition, in order to develop a new early detection method for *O. viverrini*-associated CCA, we are comparing the patterns of expression of plasma proteins in healthy subjects and in CCA patients using a two-dimensional protein map. Our results show that the expression patterns are different between normal subjects and those with CCA. Proteins that are expressed specifically in cancer patients, but not in normal subjects, are being isolated and characterized.

Polymorphisms of genes encoding for myeloperoxidase (MPO), Mn-SOD, iNOS, IL-1β and TNF-α

M. Tatemichi, I. Gilibert, A. Hautefeuille, H. Ohshima; in collaboration with C. Malaveille, Lyon, France; M. Miwa, Tsukuba, Japan; P. Srivatanakul, Bangkok, Thailand

Chronic inflammation caused by *O. viverrini* infection can induce and/or activate various oxidant-generating enzymes. These enzymes produce high concentrations of various free radicals and oxidants, leading to tissue and DNA damage. Genetic polymorphism of genes encoding for such oxidant-generating enzymes and enzymes that defend against oxidative damage may play an important role in determining individual susceptibility to inflammation-associated cancer. DNA samples collected from normal subjects and those with CCA or HCC in northern Thailand are being analysed for polymorphisms of genes coding for MPO, iNOS, Mn-SOD and some cytokines such as IL1β and TNF-α.

Role of inducible nitric oxide synthase in carcinogenesis

Role of iNOS in spontaneously developing tumours of TP53-deficient mice

M. Tatemichi, H. Tazawa, S. Wada, I. Gilibert, M.-P. Cros; N. Lyandrat, H. Ohgaki, H. Ohshima; in collaboration with L.A. Donehower, Houston, TX, USA

TP53-deficient mice spontaneously develop lymphomas, mainly of thymic origin, although the molecular mechanism remains largely unknown. As several interaction effects between p53 and iNOS have been reported, we hypothesized that iNOS activity in the thymus is causally linked to lymphomagenesis in *TP53*-deficient mice. To investigate this hypothesis, we have created double mutant mice for the *TP53* and iNOS genes. iNOS homozygous disruption caused partial inhibition of the development of thymic lymphomas in $TP53^{-/-}$ mice and almost complete inhibition in $TP53^{+/-}$ mice. On the other hand, surprisingly, a lack of the iNOS gene strongly predisposed *TP53*-deficient mice for development of non-thymic T-cell lymphomas, suggesting that iNOS activity may have some protective potential against non-thymic T-cell lymphomagenesis in *TP53*-deficient mice.

In order to study further the molecular mechanism for the role of iNOS in tumorigenesis in *TP53*-deficient mice, we are studying the expression and activity of some cytokines, cyclooxygenase-2 and haem oxygenase-1, all of which play important roles in tumorigenesis.

Role of chronic inflammation induced by implantation of plastic plates in tumorigenesis in TP53-deficient mice

H. Tazawa, M. Tatemichi, I. Gilibert, M.-P. Cros, N. Lyandrat, M. Mounawar, T. Sawa, H. Ohshima

We are studying whether chronic inflammation induced by subcutaneous implantation of plastic plates affects tumorigenesis in *TP53*-deficient mice, which spontaneously develop lymphomas and sarcomas. Plastic plate-induced inflammation dramatically reduced latency of sarcoma induction in $TP53^{+/-}$ mice. Subcutaneous tumours developed in half of $TP53^{+/-}$ mice (n = 38) around implanted plastic plates, but none developed in the absence of plastic plates. Thus chronic inflammation clearly promotes tumorigenesis in *TP53*-deficient mice. We are currently investigating the molecular mechanism underlying this effect.

Effects of nitric oxide on UV-induced p53 phosphorylation and apoptosis

R. Fukunaga, K. Fukunaga, S. Wada, M. Tatemichi, T. Takahashi, H. Ohshima; in collaboration with Y. Taya, Tokyo, Japan

We have reported that excess nitric oxide (NO) may impair functions of p53 by modifying its conformation and/or amino acid residues. We have investigated the effects of NO on UV-induced p53 phosphorylation and apoptosis. As previously reported, UV-irradiated MCF-7 cells strongly phosphorylated p53 at various serine residues, including serine-46, that has recently been shown to play an important role in induction of apoptosis. On the other hand, when cells were UV-irradiated in the presence of an NO-releasing compound (SNAP, 200 μM), the level of serine-46 phosphorylation in p53 was significantly reduced and UV-induced apoptosis was also reduced. This inhibition of serine-46 phosphorylation in p53 occurred independently of cyclic GMP generation and without affecting activities of p53 kinases such as the PI3K family, p38 MAPK and HIPK2 [166]. We are also studying the effect of NO on serine phosphorylation of several other sites, including Ser-392 which plays an important role in the function of p53, especially the stability of the p53 tetramer. Our results suggest that NO may inhibit UV- or other toxicant-induced p53-dependent apoptosis pathways and may enhance carcinogenesis by affecting functions of p53 protein through post-translational modification.

The role in carcinogenesis of NO-mediated post-translational modifications, including tyrosine nitration and S-nitrosylation, in p53 and other tumour-suppressor proteins or oncogene products is under investigation.

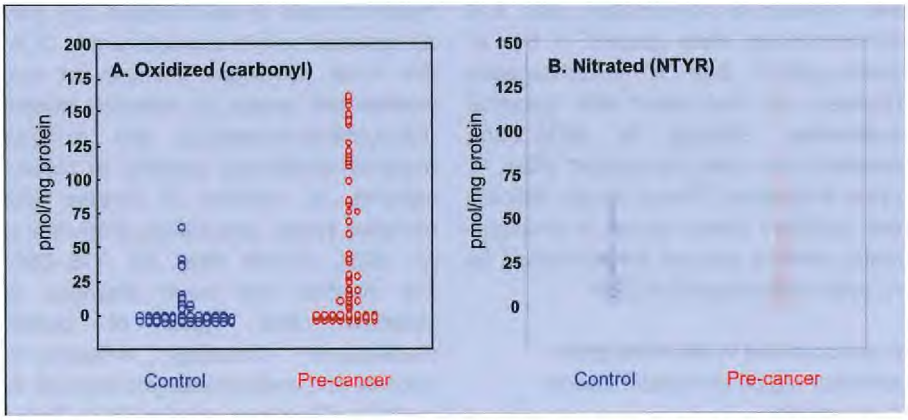

Figure 46. Increased oxidized and nitrated plasma proteins in patients with pre-cancerous liver lesions in Thailand

Apoptosis and DNA damage induced by reactive nitrogen species

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

Nitroxyl anion (NO^-), the one-electron reduction product of NO, is formed by various biochemical and chemical reactions and may play an important role in many pathological conditions through generation of highly toxic hydroxyl radicals. We have shown that NO^- is generated from NO in mitochondria under anaerobic conditions and that this may account for NO-mediated inhibition of complex I and complex II activities, which are important components of the electron transport system in mitochondria. We have also found that xanthine oxidase in the presence of its substrate (hypoxanthine or xanthine) can convert NO into NO^- under anaerobic conditions. Xanthine oxidase and iNOS have been shown to play an important role in ischaemia-reperfusion injury. Taken together, our results suggest that NO^- generated from NO in mitochondria or by xanthine oxidase may be responsible for various physiological conditions such as inflammation and neurodegenerative diseases.

DNA and protein damage by reactive nitrogen and oxygen species

Formation of 8-nitroguanosine in cellular RNA as a biomarker of exposure to reactive nitrogen species

T. Suzuki, T. Sawa, H. Ohshima; in collaboration with T. Akaike, H. Maeda, Kumamoto, Japan; M. Masuda, Kyoto, Japan; J.-L. Ravanat, Grenoble, France

Reactive nitrogen species such as peroxynitrite, nitrogen oxides and nitryl chloride have been implicated as causes of diverse pathophysiological conditions including inflammation, neurodegenerative and cardiovascular diseases and cancer. Peroxynitrite reacts with guanine or calf-thymus DNA *in vitro* to form 8-nitroguanine. 8-Nitroguanosine in RNA is much more stable than 8-nitro-2'-deoxyguanosine in DNA, which rapidly depurinates to release 8-nitroguanine. Both 8-nitroguanosine and 8-oxoguanosine were formed in calf-liver RNA following exposure to various reactive nitrogen species such as synthetic peroxynitrite. They were also formed in RNA by reactive species formed from nitric oxide and superoxide anion generated concomitantly from 3-morpholino-sydnonimine (SIN-1) and those formed with MPO or horseradish

peroxidase in the presence of nitrite and hydrogen peroxide. 8-Nitroguanosine was detected by HPLC with an electrochemical detector in enzymatic hydrolysates of RNA isolated from human lung carcinoma cells incubated with synthetic peroxynitrite. Our results indicate that 8-nitroguanosine in cellular RNA can be measured as a marker of damage caused by endogenous reactive nitrogen species in tissues and cells [297].

Using a monoclonal antibody against 8-nitroguanine, it has been found that 8-nitroguanine is formed in RNA of murine macrophage-like RAW 264 cells activated with lipopolysaccharide and interferon-γ, and in the lungs of wild-type mice, but not iNOS-deficient mice, infected with influenza virus [2], and also in the liver of hamsters infected with *O. viverrini* (Pinlaor *et al.*, 2003, *Biochem. Biophys. Res. Commun.*, **309**, 567–571). Immunohistochemical staining of 8-nitroguanine in various tissues from humans and experimental animals is now being performed.

Generation of nitrosating species by myeloperoxidase in the presence of nitric oxide

T. Sawa, S. Ohnishi, M.D. Friesen, H. Ohshima

MPO, a haem enzyme secreted from activated neutrophils in inflamed tissues, produces the highly toxic oxidant hypochlorous acid (HOCl). In addition, it generates various reactive nitrogen and oxygen species such as hydroxyl radical (•OH), singlet oxygen and nitrogen dioxide ($•NO_2$), and contributes to inflammatory tissue damage involved in development of cancer. Recently, it was suggested that MPO oxidizes NO to form nitrosonium cation (NO^+). In inflamed tissues, NO is overproduced due to intensive expression of iNOS. We are studying the action of NO on MPO-mediated tissue damage. Using tyrosine as a model biological substrate, we found that MPO in the presence of NO and hydrogen peroxide (H_2O_2) efficiently generates 4-hydroxyphenyllactic acid, a deaminated product of tyrosine. This is consistent with the chemical reactivity of NO^+; NO^+ reacts with the α-amino group of tyrosine to form its diazonium intermediate, and this intermediate is hydrolysed to the corresponding alcohol. NO^+ is considered to be mutagenic because it efficiently produces mutagenic nitrosamines in the reaction with secondary amines. A major endogenous source of NO^+ is the stomach, where ingested nitrite is converted to NO^+ in the acidic environment. Our data imply that co-expression of MPO and iNOS in inflamed tissues might be an alternative pathway to form NO^+. Cooperative actions of MPO and iNOS in carcinogenesis are being further explored using transgenic animal models.

Nitration and nitrosation of tryptophan by reactive nitrogen species

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

Tryptophan is an important target amino acid for protein damage caused by reactive nitrogen species. We have studied the reaction of *N*-acetyl-L-tryptophan with several reactive nitrogen species. With peroxynitrite, products were 1-nitroso-*N*-acetyl-L-tryptophan, 6-nitro-*N*-acetyl-L-tryptophan and one that was tentatively identified as 1-nitro-*N*-acetyl-L-tryptophan. SIN-1 (an NO- and superoxide-releasing compound), Angeli's salt (an NO^--releasing compound) and spermine NONOate (an NO-releasing compound) generated the nitroso derivative but not the nitro derivatives. An $MPO–H_2O_2–Cl^-$ system in the presence of nitrite (NO_2^-) generated the nitro derivatives but not the nitroso derivative. Among these three products, 6-nitro-*N*-acetyl-L-tryptophan was the most stable under physiological conditions and may be suitable as a biomarker of protein damage caused by peroxynitrite or the $MPO–H_2O_2–Cl^–NO_2^-$ system. A method to measure 6-nitro-tryptophan in proteins using HPLC with electrochemical detection is being developed.

Nitrated, oxidized and halogenated plasma proteins as biomarkers of oxidative stress

I. Gilibert, S. Baflast, T. Takahashi, T. Sawa, H. Ohshima; in collaboration with I. Kato, Z. Djuric, Detroit, MI, USA; J. Virtamo, Helsinki, Finland

We have developed immuno-dot and western-blot assays to measure nitrated (nitrotyrosine-containing) and oxidized (carbonyl-containing) proteins in plasma samples as markers of nitrative and oxidative stress, respectively [344]. Analyses are being carried out in plasma samples collected from Finnish smokers during the ATBC chemoprevention trial with β-carotene and α-tocopherol, as well as samples from a US study of dietary habits and breast cancer risk. In addition, the relationships between polymorphisms of genes coding for enzymes involved in oxidative stress (e.g., MPO, Mn-SOD) and levels of modified proteins in smokers are being studied.

Tyrosine residues in proteins react with HOCl or an $MPO–H_2O_2–Cl^-$ system to generate 3-chlorotyrosine. Polyclonal antibodies against 3-chlorotyrosine-containing proteins have been raised and are being characterized. Immunoassays for 3-chlorotyrosine are being developed as a biomarker of neutrophil-induced protein damage.

Products formed by reaction of 2'-deoxyguanosine with HOCl or an $MPO–H_2O_2–Cl^-$ system

T. Suzuki, M.D. Friesen, H. Ohshima

HOCl, generated by MPO from H_2O_2 and Cl^-, plays an important role in host defence and inflammatory tissue injury. Among the four naturally occurring nucleosides, we found that 2'-deoxyguanosine (dGuo) reacted with HOCl more easily than the others, forming spiroiminodihydantoin nucleoside (dSph), a diimino-imidazole nucleoside (dDiz), an amino-imidazolone nucleoside (dIz) and 8-chloro-2'-deoxyguanosine (8-Cl-dGuo) as reaction products [483, 485]. Nicotine enhanced the formation of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG) by HOCl [484]. In order to identify more polar products, we carried

out the reaction of the 3',5'-di-*O*-acetyl derivative of 2'-deoxyguanosine with an MPO–H_2O_2–Cl^- system under mildly acidic conditions. New products identified included 3',5'-di-*O*-acetyl derivatives of a guanidinohydantoin nucleoside (dGh), an iminoallantoin nucleoside (dIa) and a diamino-oxazolone nucleoside (dZ) [482]. These new products may correspond to important DNA lesions generated by MPO.

Analysis of 8-chloro-2'-deoxyguanosine, a biomarker of HOCl-mediated DNA damage, by ^{32}P-postlabelling

S. Ohnishi, A. Barbin, T. Sawa, M.D. Friesen, H. Ohshima; in collaboration with M. Masuda, Kyoto, Japan; H. Nakabeppu, Fukuoka, Japan; T. Osawa, Y. Kawai, Nagoya, Japan; H. Kasai, Kitakyushu, Japan; J.-L. Ravanat, Grenoble, France

The DNA damage caused by HOCl is especially localized at guanine sites in the DNA fragments obtained from the human *p53* tumour-suppressor gene and the c-Ha-*ras*-1 protooncogene (Ohnishi *et al.*, 2002, *Cancer Lett.* **178**, 37–42). In the reaction of deoxyguanosine (dG), HOCl caused various kinds of modification, including formation of 8-chloro-dG (8-Cl-dG). 8-Cl-dG is quite stable and may be usable as a specific biomarker for HOCl-mediated DNA damage caused by inflammation. We have prepared monoclonal antibodies against 8-Cl-dG. Using an 8-Cl-dG immuno-affinity column for purification and a ^{32}P-postlabelling method, we can separate 8-chloro-2'-deoxyguanosine 3'-monophosphate from a mixture containing 10 000 times more of nucleoside 3'-monophosphates. We are now improving this method for highly sensitive and quantitative analysis.

We are also studying the biological significance of the 8-Cl-dG adduct in DNA. We recently found that 8-chloro-dGTP is hydrolysed by hMTH1, the human MutT homologue [164]. This enzyme hydrolyses various oxidized nucleotides, such as 8-hydroxy-dGTP, 2-hydroxy-dATP and 8-hydroxy-dATP, to the corresponding nucleotide monophosphate, and acts as a nucleotide sanitization enzyme to prevent the incorporation of these modified nucleotides into DNA (Fujikawa *et al.*, 1999, *J. Biol. Chem.*, **274**, 18201–18205). Our finding that 8-Cl-dGTP is a substrate of the hMTH1 protein suggests that 8-Cl-dGTP may be produced in human cells. Studies on mutagenic effects and repair of 8-Cl-dG in DNA are under way.

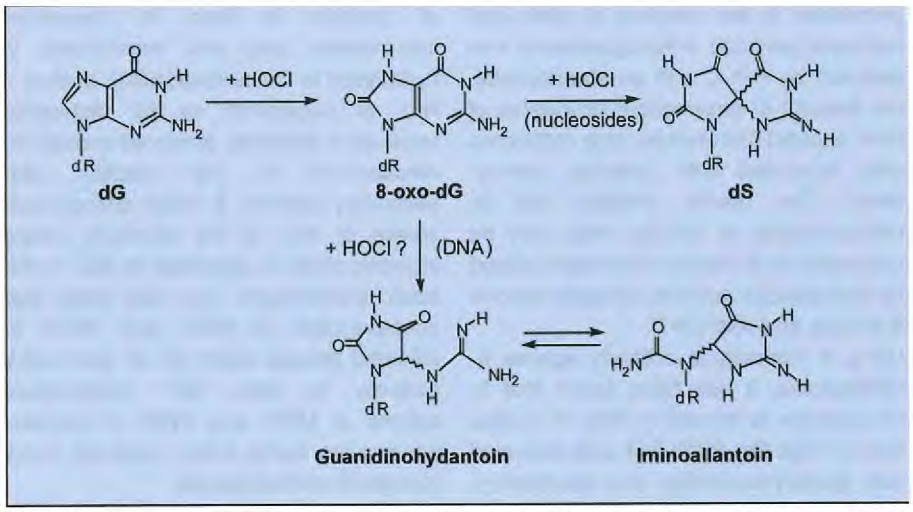

Figure 47. Oxidation products of 2'-deoxyguanosine (dG) and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG). dR stands for 2-deoxyribose.

Effects of epigallocatechin gallate on HOCl-mediated formation of 8-oxo-7,8-dihydro-2'-deoxyguanosine, a biomarker of oxidative DNA damage

T. Suzuki, H. Ohshima; in collaboration with M. Masuda, Kyoto, Japan; N. Nakano, Sendai, Japan

The tea polyphenol (–)-epigallocatechin gallate (EGCG), which can scavenge a variety of reactive oxygen species, enhances the yield of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG) up to 20-fold in the reaction of 2'-deoxyguanosine with HOCl, compared to that without EGCG. Low concentrations of EGCG inhibited HOCl-mediated oxidation of 2'-deoxyguanosine to 8-oxo-dG to a limited extent, but efficiently inhibited further oxidation of 8-oxo-dG to spiroimino-dihydantoin nucleoside, resulting in accumulation of 8-oxo-dG in the reaction mixture. Conversely, EGCG dose-dependently inhibited an increase of 8-oxo-dG levels in calf-thymus DNA incubated with HOCl. However, addition of HOCl to DNA pre-oxidized with an oxidant-generating system ($CuCl_2$, ascorbate, H_2O_2) led to extensive loss of 8-oxo-dG due to its further oxidation. EGCG effectively inhibited this HOCl-mediated loss of 8-oxo-dG in the oxidized DNA, resulting in an apparent increase in 8-oxo-dG levels in the oxidized DNA over the levels found without EGCG. The conversion of 8-oxo-dG into other oxidized lesions will inevitably affect recognition by DNA repair enzymes as well as the rates of mutations and DNA synthesis. Thus our results suggest that as a biomarker of oxidative DNA damage, not only 8-oxo-dG but also the products of its further oxidation should be measured (Figure 47).

Modifications of nucleosides and proteins by ozone

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Ozone is a major air pollutant. Recently it has been reported that antibodies catalyse singlet oxygen ($^1O_2$)-induced water oxidation to generate an ozone-like oxidant and H_2O_2. This ozone-like oxidant can efficiently kill bacteria in the presence of H_2O_2, possibly via formation of $HO_3^\bullet$ and $HO_2^\bullet$ radicals. Activated human neutrophils also generate a similar ozone-like oxidant. In order to find a biomarker for ozone-induced DNA

and protein damage, we have carried out the reactions of nucleosides, isolated DNA and proteins (lysozyme, serum albumin) with ozone in the presence of other oxidants such as H_2O_2, nitrite and HOCl. Our results indicate that ozone is a strong oxidant, generating a variety of hitherto unknown modifications of DNA bases and amino acids including spiroiminodihydantoin nucleoside and tryptophan-indole derivatives, respectively. These new modifications can be measured as markers of ozone-induced damage.

4.4 Role of cell–cell interaction 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.

Tumour-suppressor function of connexin 32

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The family of connexin gap junction proteins has 20 members. The tumour-suppressing role of connexins is well established and several lines of evidence show that individual connexins possess highly variable capacity to suppress different types of tumour [519]. Alteration of connexin function in tumours is believed to arise by genetic [138] and epigenetic [31, 244] mechanisms. Previously we found that in human colon tumours, connexin 43 (Cx43) was specifically mutated at advanced stages of the tumours, while connexin 32 (Cx32) was not found genetically altered in these tumours. In order to assess the anti-tumorigenic potency of individual connexins in different types of tumour, we used a genetically modified mouse model in which Cx32 is mutated. Cx32-deficient mice exhibited increased susceptibility to spontaneous or chemically-induced hepatocarcinogenesis.

In order to investigate whether the lack of Cx32 predisposes mice to chemically induced carcinogenesis of the digestive tract organs, groups of Cx32 knock-out and wild-type mice of both sexes were treated with 1,2-dimethylhydrazine (DMH), which usually induces a high incidence of colon and liver tumours in mice. After 90 weeks, ~40% of the mice deficient in Cx32 had developed tumours in the glandular part of the stomach. No such tumours were found in DMH-treated wild-type mice. In accordance with earlier findings, DMH also increased the incidence of liver tumours in Cx32-deficient mice, but no significant difference in the incidence of colon tumours was observed in Cx32 knock-out mice compared with their wild-type counterparts.

This finding prompted us to investigate possible alterations of Cx32 in human stomach cancer. Immunohistochemical analysis of several human gastric neoplasms revealed steady expression of Cx32 in tumour cells. However, the Cx32 was aberrantly translocated from the lateral plasma membranes into the cytoplasm of tumour cells, suggesting a loss of capacity to couple cells. Direct sequencing of the *Cx32* gene amplified from tumour tissues did not reveal any mutations. In the same (stomach) tumours, expression of Cx43 was lost in most cells, unlike in human colon tumours. This loss of Cx43 expresion was not due to mutational alterations in the coding region of this gene.

These results provide additional evidence that individual connexins play different roles in carcinogenesis in different tissues and show that connexins demonstrate marked species specificity in the suppression of tumour growth.

4.5 Role of TP53 in carcinogenesis

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.

ΔNp53, a new isoform of the p53 protein with regulatory roles in normal cell-cycle progression

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We previously identified a new isoform of the p53 protein, ΔNp53, which is assembled by initiation of translation at codon 40 and thus lacks the N-terminus that contains the sequence-specific transactivation domain. This isoform behaves as a dominant inhibitor of full-length p53. We have now found that ΛNp53 is the product of a new mRNA species, p53I2, generated by alternative splicing that retains intron 2. Presence of intron 2 sequences introduces a stop codon upstream of codon 40, resulting in the use of an internal AUG as the main initiation codon. Studies in cultured cells have shown that ΛNp53 does not follow the same variations in response to stress as full-length p53. However, in normal

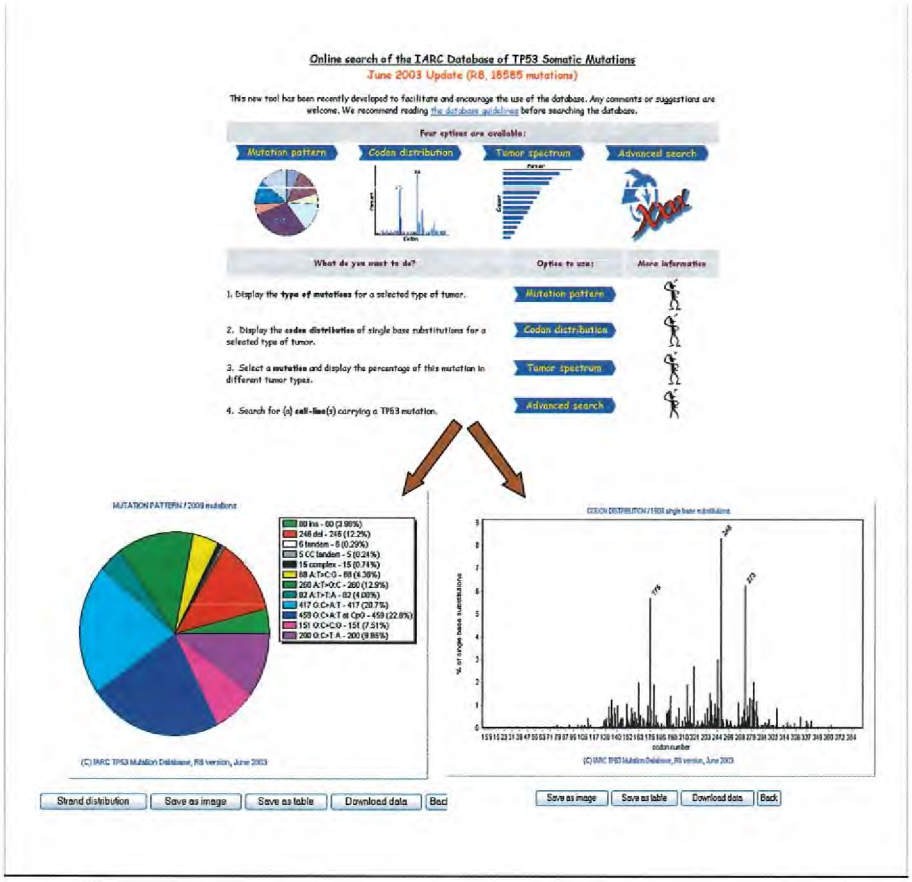

Figure 48. The IARC *TP53* web site provides information on TP53 genetic variations in human cancer through a database that can be searched and analysed online (top). Various graphical outputs can be displayed showing the proportion of various types of mutation in selected tumours (bottom left) as well as their position in the coding sequence (bottom right).

tissues, ΔNp53 is expressed at a relatively high level and is sometimes the predominant form of the protein. This led us to investigate a possible role of ΔNp53 in the control of a normal physiological cellular function rather than in the response of cells to genotoxic stress. It has recently been shown that, apart from its role in arresting cell growth in response to genotoxic stress, p53 could also be activated by unprogrammed growth stimuli to mediate G1 arrest in cells overexpressing oncogenes or subjected to excess stimulation by growth factors. This mechanism is now considered to play a major role in carcinogenesis, since it represents a safeguard of normal cells against excessive proliferation. Using cultured normal human fibroblasts, we have found that levels of ΔNp53 protein increase in cells that are engaged in the G1 to S transition of the cell cycle. To confirm that ΔNp53 participates in G1/S transition by neutralizing p53-mediated suppression in response to excess growth stimuli, we micro-injected an expression vector for ΔNp53 into diploid fibroblasts arrested in G1 by serum starvation. The results showed that ΔNp53 cooperates with the E2F1 transcription factor to promote entry into S-phase by overcoming a p53-dependent checkpoint activated by unprogrammed growth stimuli. Thus, these studies identify ΔNp53 as an important component of normal cell-cycle regulation. It is important to note that ΔNp53 is the exact functional and structural counterpart of the ΔN forms of p63 and p73, two members of the p53 protein family. Thus, regulation by ΔN isoforms appears to be a conserved feature of all family members.

Role of oxidation–reduction in the control of the p53 tumour-suppressor protein

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The DNA-binding activity of the p53 tumour-suppressor protein is tightly dependent on its three-dimensional structure, which is maintained by a zinc atom coordinated on histidine and cysteine residues. Redox regulation of reactive thiols is essential for zinc binding and proper protein folding. We have identified a redox-active drug, amifostine, that modulates the redox status of thiols in p53 and stabilizes the protein in the active conformation. Amifostine activates p53 through a DNA-damage independent pathway that involves phosphorylation of p53 by the c-Jun-N-terminal kinase. We have now obtained *in vitro* evidence that amifostine induces p53-dependent cell-cycle arrest and confers protection against cytotoxic DNA damage in cells that express wild-type p53 but not mutant forms. These observations provide a molecular basis for the chemo- and radio-protective effects of amifostine, a drug used clinically to limit damage to normal tissues of patients in some therapeutic protocols.

We are now determining the cellular factors that allow p53 to maintain its active form, notably by keeping the zinc atom within the protein, and how destabilization of the protein leads to the development of abnormal cells. We have identified thioredoxin (Trx) as a protein that may play a role in the control of p53 protein conformation. A small ubiquitous protein, Trx is a regulator of many redox-dependent reactions, including the activation of transcription factors such as AP1 or NFκB. We have shown that Trx is

involved in p53 control in response to carcinogenic agents: it interacts with p53 and promotes its activation, consistent with the idea that redox regulation is important for optimal binding to p53 to specific DNA sequences. We are now developing an RNAi-based approach to detail the role of Trx in the behaviour of p53 in cancer cells. These experiments are helping to elucidate the cellular factors that control p53 activation, and may open new possibilities for developing drugs that modulate p53 activation in response to chemotherapeutic agents.

IARC database of *TP53* mutations in human cancer

M. Olivier, P. Kleihues, H. Ohgaki, D.E. Goldgar, P. Hainaut; in collaboration with A.L. Børresen-Dale, Oslo Norway; R.A. Eeles, Sutton, UK; M. Hollstein, Heidelberg, Germany; M. Khan, C.C. Harris, Bethesda, MD, USA; A. Martin, Reading, UK; G. Pfeifer, Duarte, CA, USA; M. Resnick, Research Triangle Park, NC, USA

The IARC *TP53* database (http://www.iarc.fr/p53) is a compilation of data on human *TP53* genetic variations reported in the peer-reviewed literature [348]. The database can be searched and analysed online and users can retrieve data in graphic and tabular formats (Figure 48). With over 18 500 somatic mutations and 1000 citations, the database is recognized as a major source of information on *TP53* mutations in human cancer.

The main focus of the database is to provide a central resource for research on mutation patterns and the identification of carcinogen fingerprints. One well documented example of a carcinogen fingerprint is the excess of G→T transversions at specific positions in the coding sequence of *TP53* in lung cancer from smokers that appeared to be directly caused by tobacco carcinogens. In a detailed analysis of *TP53* mutation data in lung cancers and other tobacco-associated cancers, we have confirmed the molecular signature of tobacco smoke components (polycyclic aromatic hydrocarbons, PAHs) in lung cancer from smokers, whereas in other tobacco-related cancers, different mutation patterns were observed [368]. These patterns probably reflect the fact that other carcinogens in addition to tobacco are involved in the pathogenesis of these cancers (alcohol in oesophageal and oral carcinomas, aromatic amines in bladder cancer).

Data on germline *TP53* mutations have recently been re-organized into a database of information on cancer families with Li–Fraumeni and related syndromes, allowing better assessment of the type and occurrence of tumours associated with a *TP53* germline mutation (Figure 49) [349].

Another application of the *TP53* database is the search for correlations between mutations and tumour phenotype or behaviour. Information from published studies that investigated the value of *TP53* mutation as a diagnostic and prognostic factor in cancer was added to the database in September 2002. These studies show that the presence of a *TP53* mutation is generally associated with poor prognosis. Because these results are often of borderline significance due to small sample size, we are collaborating with the European Breast Cancer Study Group to investigate the prognostic value of specific types of *TP53* mutation in breast cancer, using the largest series of European patients assembled to date (over 2000 patients). Clinical and *TP53* mutation data are now being collected and integrated into a new database.

Although there is experimental evidence that all p53 mutant forms are not functionally equivalent, data on the

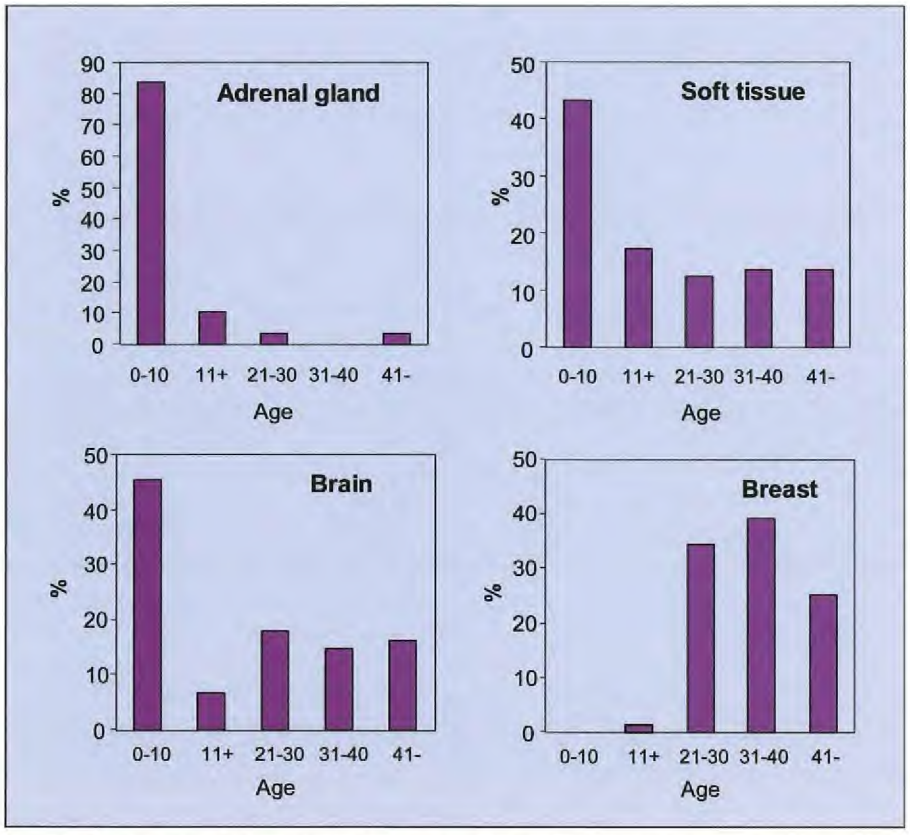

Figure 49. Age distribution of the most frequent cancers arising in *TP53* germline mutation carriers. Only tumours from individuals who were confirmed or obligate *TP53* mutation carriers and who had a family history of cancer (Li–Fraumeni and Li–Fraumeni-like syndromes or other family history) are included. The total tumour number is 148 for breast, 62 for brain, 59 for bone, 81 for soft tissues and 30 for adrenal gland.

functional activity and clinical impact of each of the 3000 different mutants reported in the database are still lacking. To address this problem, we are using a new approach, based on computerized structure-prediction models, to define the structural impact of all mutations reported to date. The results show that only 70% of the mutations can be predicted to have structural effects that would influence the DNA-binding capacity of p53 [295]. This suggests that 'unexplained' mutants may retain partial wild-type function, or that the mutations may inactivate protein activities other than DNA binding. These properties have been tested in human cell systems or yeast-based assays. Functional information on 200 different mutants was added to the database in June 2003. However, these mutants represent less than 10% of the mutants reported in the database. To promote a concerted international effort on the structural and functional characterization of p53 mutants, an international workshop focusing on mutant p53 was held at IARC in June 2003. Standard assays to test p53 activities were discussed and it was decided that functional data should be deposited in the database to provide a functional classification of p53 mutants. This information will help in analysis of correlations between mutation effects and pathological or clinical observations.

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.

Women queuing for cervical cancer screening in Nepal

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. Any such intervention therefore needs to be subjected to very careful scrutiny at all stages of 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 initiated.

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 is an electronic publication on current human cancer prevention studies. For the purpose of inclusion in the Directory, cancer prevention studies are defined as those aiming to reduce incidence of, or mortality from cancer or to modulate intermediate end-points of cancer incidence or mortality. The Directory contains brief descriptions of projects carried out in 34 countries. The majority (60%) are randomized intervention trials covering areas of primary prevention, chemoprevention and secondary prevention. The uterine cervix and breast are by far the leading cancer sites involved, being the subject of respectively 29% and 25% of the studies, followed by colon and rectum (19% each). Other sites of interest are lung, head and neck, and skin. A listing of biological material banks is also provided, as well as links to population-based cancer registries (members of the International Association of Cancer Registries and of the European Network of Cancer Registries). In order to update the information in the Directory, the principal investigators of the projects currently in the database have been contacted to determine the current status of their projects and potential new contributors have been invited to report on their work.

The Gambia Hepatitis Intervention Study

E. Bah, P. Hainaut, K. Szymanska, E. Gormally, E. Caboux, S. Michel, D.M. Parkin; in collaboration with M.P. Carrieri, Marseille, France; A. Hall, London, UK; G. Kirk, Bethesda, MD, USA; R. Montesano, Lyon, France; O. Sam, Banjul, The Gambia; S. Viviani, Bern, Switzerland; H. Whittle, S. McConkey, M. VanderSande, Fajara, The Gambia; C.P. Wild, Leeds, UK

The Gambia Hepatitis Intervention Study (GHIS) is a long-term, population-based trial aimed at determining the effect of childhood hepatitis B virus (HBV) vaccination in protecting against chronic liver disease and liver cancer (hepatocellular carcinoma; HCC) in an African country with high incidence of liver cancer. After completion of vaccination (1990) and evaluation of protection against chronic HBV carriage in children (1999), the study

Figure 50. Gambia Hepatitis Intervention Study staff

has now entered a phase of long-term follow-up through countrywide, population-based cancer registration. This follow-up includes three components: development of a national cancer registry, support for clinical and laboratory-based diagnosis of cancer and record-linkage studies aimed at developing strategies for accurate matching between the cancer registry and the initial vaccination database. Over the past two years, significant efforts have been made to improve the coverage and completeness of cancer registration and to promote better cancer diagnosis, in particular through support to the National Histopathology Service based at the Royal Victoria Hospital in Banjul. Current efforts focus on re-assessing the assumptions of the initial GHIS study design, using extensive new data on incidence of HCC, prevalence of chronic infection with HBV and HCV, risk of HCC attributable to HBV, vaccine efficacy and attrition within the GHIS cohort. This re-assessment will allow better prediction of the duration of long-term follow-up, and determination of adequate strategies to ensure efficient record linkage.

In parallel with this follow-up, a number of studies are in progress to better characterize the interactions between aflatoxin exposure, HBV infection and the occurrence of molecular alterations in the pathogenesis of liver cancer. A case–control study was carried out in the field between 1997 and 2000, with 216 incident HCC cases and 408 frequency-matched controls with no apparent liver disease. Molecular analysis of the specimens has been completed. In liver cancer biopsies, mutations were detected in about 50% of the cases, 40% being ser249 mutations (see Section 3.3). Analysis of DNA extracted from plasma revealed a 90% concordance between the presence of a ser249 mutation in circulating free DNA and in liver biopsies. The ser249 *TP53* mutation was detected in 3.5% of controls, 15% of cirrhotics and 40% of HCC cases, with adjusted risk estimates for cirrhosis and HCC of 4.8 and 20.2, respectively. Positivity for hepatitis B surface antigen (HBsAg) along with a ser249 *TP53* mutation was observed in 45/183 (24.6%) HCC cases, compared with only 1 (0.3%) control participant; the combined effect on HCC risk approximated a multiplicative interaction. Overall, these findings suggest a multiplicative effect on HCC risk resulting from chronic, active HBV infection and the mutational effect of aflatoxin on the *TP53* gene.

In parallel, we investigated genetic polymorphisms of carcinogen-metabolizing (*GSTM1*, *GSTT1*, *HYL1*2, CYP2D6*) and DNA repair (*XRCC1*) enzymes. Although the prevalence of variant genotypes was generally low, in multivariate analysis, the *GSTM1*-null genotype and the *XRCC1*-399 AG genotype were significantly associated with increased HCC risk. Homozygosity or heterozygosity for the G allele in the *XRCC1*-399 locus conferred increased HCC risk, especially among younger study participants. The effect on HCC risk with GSTM1 was most prominent among HBsAg-negative subjects and those with the highest groundnut consumption. When all four suspected aflatoxin-related high-risk genotypes were combined [*GSTM1*- and *T1*-null, *HLY*2* (HY/HH) and *XRCC1* (AG/GG)], a significant 19-fold increased risk of HCC was observed. These findings suggest that genetic modulation of carcinogen metabolism and DNA repair can alter susceptibility to HCC, and that these effects may be modified by environmental, ethnic and age-related factors.

Chemoprevention trial on precancerous lesions of the stomach in Venezuela

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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 study was conducted in Tachira state, Venezuela, in a population at high risk of stomach cancer.

Subjects in the trial were randomized to treatment with anti-oxidant vitamins—vitamin C (750 mg/d), vitamin E (600 mg/d) and β-carotene (18 mg/d)—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. A single pathologist (G. Lopez) reviewed all the biopsies of subjects with at least one follow-up visit to provide a consistent histological diagnosis for the analysis.

Preliminary results show that subjects in the treated group had substantially increased plasma levels of β-carotene and vitamin E, indicating high compliance. Plasma levels of vitamin C were not significantly increased. The rate ratio for progression of precancerous lesions was 0.92 (95% CI 0.74–1.15) and for regression was 1.09 (95% CI 0.90–1.30) for the treated group versus the placebo group. Thus, although the results are consistent with a modest decrease in progression and increase in regression of gastric lesions, they are not sufficient evidence for a beneficial effect of anti-oxidant vitamins on precancerous gastric lesions. This trial does not provide information on the effect of *Helicobacter pylori* eradication, which was attempted in an early phase but interrupted on account of high failure rates.

A spin-off project has been initiated using baseline data from this study to examine the effects of genetic polymorphisms on gastric cancer risk. The polymorphisms to be studied are suspected to modulate the

host response to infection with *H. pylori* (see project: Prevalence surveys of *H. pylori*), which is extremely common in this population (94% prevalence). The two main groups of polymorphisms being studied are those in receptors to *H. pylori* lipopolysaccharide and in the related cytokines.

Accelerated evaluation and introduction of HPV vaccines against cervical cancer in developing countries

S. Franceschi, M. Plummer, G. Clifford; in collaboration with S. Pagliusi, T. Aguado, Geneva, Switzerland

Early findings from trials by Merck and GlaxoSmithKline have shown that prophylactic vaccines against HPV have very high efficacy, at least in the short term. They have given added urgency to the evaluation and deployment of suitable HPV vaccines in areas of the world where cervical cancer is most common and, particularly, where screening programmes will be very difficult to mount and maintain [159, 377]. In collaboration with WHO Vaccines and Biologicals, we are developing an approach that includes phase 1 and 2 trials, to establish the safety and immunogenicity of an HPV vaccine based on virus-like particles (VLPs) in five or six sites in Asia (possibly India, the Republic of Korea, the Philippines, Thailand and Viet Nam). Phase 3 randomized efficacy trials may be initiated within one year of starting phase 1 and 2 trials and should include, in the pooled analyses of all study sites, approximately 30 000 women. In addition to a large multi-centric phase 3 trial, the WHO/IARC project includes:

1. Bridging studies: smaller immunogenicity trials in developing countries not included in the efficacy trial or in special populations (e.g., populations where HIV, malaria or nutritional deficiency may limit HPV vaccine efficacy).
2. Post-licensing trials: large and simple community-based intervention trials where, for instance, young men might be vaccinated, too.
3. Phase 1 trials of second-generation vaccines against HPV, yet to be chosen among different candidates (e.g., mucosal VLP vaccines, chimeric VLP vaccines, L1 pentamers, naked DNA, etc.) which may offer advantages over VLP vaccines in developing countries.
4. Special trial designs that can allow joint evaluation of HPV-based screening programmes and anti-HPV vaccination. The methodology of intervention trials has been reviewed [377].

5.2 *Evaluation of cancer-preventive agents*

H. Vainio, F. Bianchini, J. Thévenoux, A. Rivoire. The following members of other units have contributed to the programme: W. Al-Delaimy, P. Brennan, J. Cheney, V.J. Cogliano, P. Ferrari, S. Franceschi, M.D. Friesen, Y. Grosse, J. Hall, R. Kaaks, T. Norat, H. Ohshima, C. Partensky, D.M. Parkin, P. Pisani, E. Riboli, A.J. Sasco, T. Sawa, B. Secretan, N. Slimani, K. Soldan, K. Straif, E. Suonio, J.E. Tyczynski, E. Weiderpass

Breast cancer screening

A substantial volume of information on breast cancer screening has accumulated over the last thirty years and regional and national screening programmes have been established in a number of countries. IARC convened an international group of 24 experts from 11 countries on 5–12 March 2002 to evaluate all relevant published studies. The group included both known supporters and critics of published studies of breast cancer screening. The full report was published in September 2002 as volume 7 of the *IARC Handbooks of Cancer Prevention*, entitled *Breast Cancer Screening*.

The conclusion of the Working Group was that there is *sufficient evidence* from randomized trials that mammographic breast cancer screening directed towards women aged 50–69 years reduces mortality from breast cancer by 25%. There is only *limited evidence* for an effect in women aged 40–49 years, in whom the reduction, if real, is estimated to be 19%. This figure could be lower depending on the extent to which it may have been due to further examinations which occurred after the women attained 50 years. No conclusion could be reached regarding the efficacy of screening by mammography in women younger than 40 or older than 69 years of age.

There is little evidence on which to base

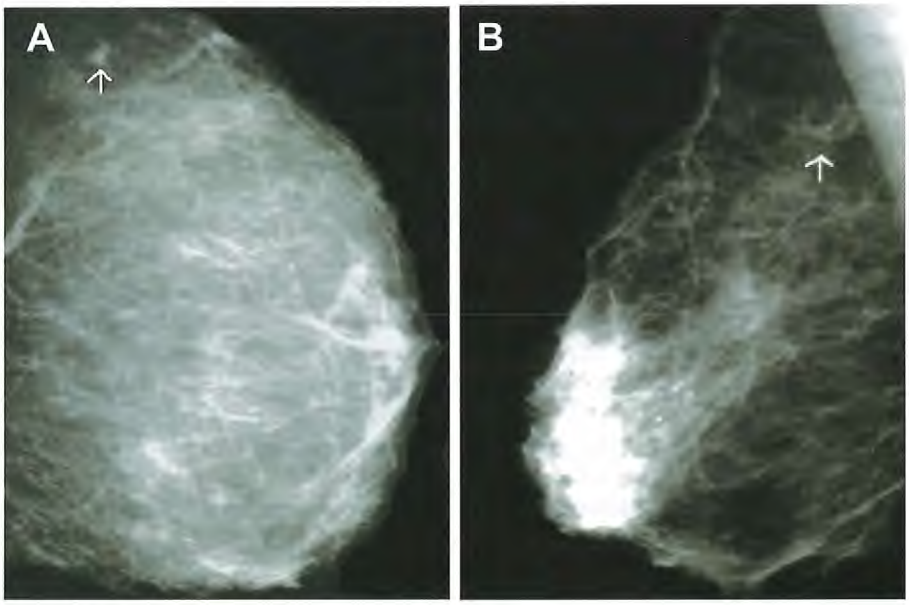


Figure 51. Screening mammograms of early breast lesions

recommendations on the frequency with which women should be offered mammographic screening. In most trials, women were invited to be screened at intervals of about 24 months.

There is *inadequate evidence* to indicate whether screening by clinical breast examination, whether alone or in addition to mammography, can reduce mortality from breast cancer and *inadequate evidence* to indicate whether breast self-examination can reduce mortality from breast cancer.

The available evidence for the effectiveness of programmes of breast screening by mammography (as opposed to randomized trials), with or without clinical breast examination, indicates a reduction in mortality from breast cancer of up to 20% in the long term among women aged 50–69 years.

False-positive results generate anxiety, additional physician visits and diagnostic tests, and some excision biopsies, as well as possible overtreatment for breast cancer. In women aged 50–69 years of age, the increase in risk for breast cancer due to exposure to X-rays is substantially outweighed by the benefits of mammography.

Costs per year of life saved in programmes for biennial mammographic screening of women aged 50–69 years have been estimated as varying from 3000 to 8000 euros, similar to the cost-effectiveness of other cancer-screening programmes.

Fruit and vegetables

A group of 21 experts from 11 countries was convened on 4–11 March 2003 in Lyon to evaluate the cancer-preventive activity of fruit and vegetables, and compile the eighth volume of the *IARC Handbooks of Cancer Prevention*.

Fruit and vegetables have always been a major component of the human diet in most, though not all, parts of the world. For this purpose, fruit and vegetables are defined as plant foods consumed by humans, excluding cereal grains, seeds and nuts. There is much diversity, between and within countries, both in the total amount of fruit and vegetables consumed and in the relative amounts of these two categories. In general, consumption is highest in more affluent, better educated, urban-dwelling populations. In recent decades, there has been a steady, worldwide, increase in availability of fruit and vegetables, and in year-round availability, although some regions have lagged behind.

Fruit and vegetables contain many nutrients, as well as other bioactive compounds that may influence many aspects of human biology and related disease processes. The clearest evidence of a cancer-protective effect of eating more fruit is for stomach, lung and oesophageal cancers. Higher intake of vegetables probably reduces the incidence of cancer of the oesophagus and colon-rectum. The Working Group estimated that about one in ten cancers in western populations is due to insufficient intake of fruit and vegetables. For some sites (including the oesophagus and lung), despite the relatively high agreement of the study results, doubt remains as to whether the protective effects reported might be generated by residual confounding due to smoking and alcohol drinking or socioeconomic factors. In addition, the possibility of recall and selection bias in the case–control studies, and of confounding in both cohort and case–control studies could not be excluded. On the other hand, measurement error, inadequate consideration of exposure timing and inadequate intake range could be attenuating stronger protective associations.

The results of this evaluation should encourage all governments and other organizations to continue efforts to increase fruit and vegetable intake as an important objective of programmes to improve nutrition so as to reduce the burden of cancer and other chronic diseases.

Figure 52. Canada's Food Guide to Healthy Eating (rainbow). The advice is to eat 5–10 portions of fruits and vegetables per day.

Cruciferous vegetables, isothiocyanates and indoles

Observational studies have provided some evidence for a protective role of vegetable consumption against cancer (see above). The evidence for protection has often been assigned to cruciferous vegetables such as broccoli and cabbage. An evidence-based evaluation of the cancer-preventive potential of cruciferous vegetables, and their component isothiocyanates and indoles derived from degradation of glucosinolates, was made by a group of experts which met in Lyon on 18–25 November 2003. The outcome of this meeting is to be published as volume 9 of the *IARC Handbooks of Cancer Prevention*.

Overall, cruciferous vegetable intake appears to account for 10–15% of total vegetable intake, ranging from 5% to almost 25% in the countries with the highest consumption.

Most epidemiological data on cancer risk in relation to cruciferous vegetable intake came from studies of all vegetables; in interpreting the evidence, it was recognized that results were often based on subsidiary analyses, and confounding with total vegetable intake was possible. Eating cruciferous vegetables is associated with reduced risk of cancer, particularly of the stomach and lung. The observed effect is of the same order of magnitude as that for total vegetables.

Cruciferous vegetables at levels relevant to human intake or higher also inhibit neoplastic and preneoplastic responses in experimental animals, mainly when given simultaneously with carcinogens or throughout the experiment.

Both naturally occurring and synthetic isothiocyanates have cancer-preventive effects in most experimental animal cancer models, the extent depending on the compound, the experimental conditions and the animal species. The evidence is particularly strong for phenylethyl-, benzyl- or 3-phenylpropylisothiocyanate. Nevertheless, some studies show no cancer-preventive effect and some show effects that could be interpreted as adverse.

Indoles (specifically indole-3-carbinol and its derivative diindolylmethane) also prevent cancer development in experimental animals, mainly when administered before or concurrently with a carcinogen.

Whole cruciferous vegetables, isothiocyanates and indoles modulate the activity of several biotransformation enzymes and the formation of DNA adducts, generally accepted intermediate markers of cancer-preventive effects. Other cellular mechanisms, including inhibition of cell proliferation and induction of apoptosis, may also be relevant for tumour suppression.

5.3 *Studies of screening for cancer*

Screening is a means of achieving early detection of certain cancers and pre-cancerous 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.

Detection of cervix cancer in developing countries

R. Sankaranarayanan, D.M. Parkin, C. Mahe, E. Lucas, R. Muwonge, S. Arrossi, S. Franceschi; in collaboration with *Angola* M. de Ganda Manuel, Luanda; *Burkina Faso,* B. Sakande, M. Nacoulma, Ouagadougou; *Canada,* P. Drouin, Montreal; *Cuba,* L. Fernandez, Havana; *France,* L. Frappart, B. Fontanière, M. Marien, J. Liaras, P. Mathevet, Lyon; *Guinea,* N. Keita, M. Koulibaly, Conakry; *India,* R. Rajkumar, P. Cherian, J. Cherian, Ambillikai; B.M. Nene, K. Jayant, A. M. Budukh, P.S. Chauhan, Barshi; K. Dinshaw, S. Shastri, R. Chinoy, R. Kelkar, S.G. Malvi, Mumbai; P. Basu, U. Chattopadhyay, Kolkata; G. Shyamalakumary, Ernakulam; R. Anand, Chennai; U. Reddy, P. Bidinger, Hyderabad; R. Sharma, Jaipur; R. Wesley, P. Sebestian, T. Somanathan, M.K. Nair, Trivandrum; *Laos*, P. Alongkone, A. Phuthone, Vientiane; *Mali*, A. Dolo, S. Bayo, Bamako; *Mauritania*, I. Sidi, Nouakchott; *Niger*, N. Madi, S. Hassan, Niamey; *Nigeria*, J. Thomas, A. Omgbodun, Ibadan; *Peru*, J. Jeronimo, Lima; *Republic of Congo*, C. Gombe, J. Malanda, A.P. Filipe Jr, Brazzaville; *South Africa*, L. Denny, Capetown; *Tanzania*, T. Ngoma, Dar es Salaam; *Thailand*, S. Koonsaeng, P. Srivatanakul, S. Deerasami, Bangkok; *UK*, S. Sundar, Oxford; *USA*, P. Blumenthal, L. Gaffikin, Baltimore, MD; A. Pollack, K. Beattie, T. Wright, New York; J. Sherris, V. Tsu, A. Bishop, J. Sellors, Seattle, WA; S. Robles, S. Corbier, Washington DC

Supported by the Bill and Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention

IARC is a member of the Alliance for Cervical Cancer Preventiom (ACCP; http://www.alliance-cxca.org), a group of five international organizations with a shared goal of working to prevent cervical cancer in developing countries.

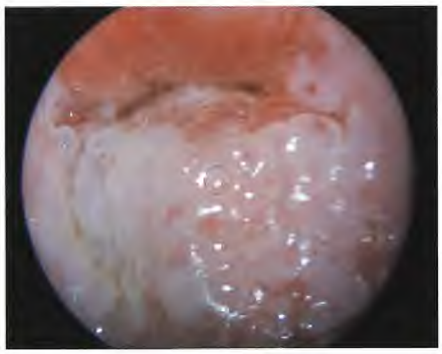
Different approaches to early detection and prevention of cervical cancer are being evaluated in studies in several locations in Angola, Burkina Faso, Republic of Congo, Guinea, India, Mali, Mauritania, Nepal, Niger and Tanzania, with support from ACCP. The early detection methods being evaluated include visual inspection with acetic acid without (VIA) and with magnification (VIAM), visual inspection with Lugol's iodine (VILI), conventional cytology and HPV DNA testing using hybrid capture II (HC II).

Figure 53. Medical officer reassuring a woman treated for CIN in the Kolkata cervical cancer early detection study

Table 7. Interim results from cervical cancer screening trial in Osmanabad district, India

	VIA	Cytology	HPV testing
Invited women	30 345	27 904	28 309
Screened	23 807 (78.5%)	22 244 (79.7%)	21 943 (77.5%)
Test-positive	3477 (14.6%)	1659 (7.5%)	2261 (10.3%)
Women with CIN 1 on reference standard	824 (3.5%)	353 (1.6%)	409 (1.9%)
Women with CIN 2–3 on reference standard	184 (0.8%)	228 (1.0%)	200 (0.9%)
Women with invasive cancer	77 (0.3%)	74 (0.3%)	57 (0.3%)

Cross-sectional studies in 11 locations in six countries to investigate the accuracy of these tests in detecting cervical intraepithelial neoplasia grades 2–3 (CIN 2–3) and invasive cervical cancer in terms of sensitivity, specificity and predictive value have been completed. Overall, these studies involved 54 982 women aged 30–64 years. All the recruited women were subjected to a battery of tests and the reference standard, namely colposcopy with or without directed biopsy. Since all the women received the reference investigations, these studies permit unbiased direct estimates of test parameters. The pooled sensitivity, specificity, positive and negative predictive value for VIA were 77.7%, 84.8%, 9.2% and 99.5%, respectively, and for VILI were 92.4%, 85.1%, 10.8% and 99.8%, respectively. The pooled sensitivities for cytology and HPV testing were 58.8 and 58.1% respectively; the respective specificities were 93.8 and 91.8%. VILI appears to be a more sensitive visual screening test. New cross-sectional studies have been initiated in Congo, Guinea and India to assess the performance of VILI sequentially followed by VIA.



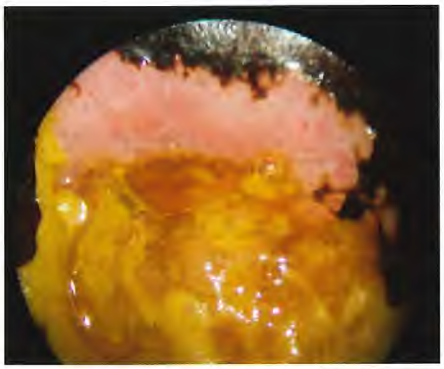


Figure 54. Photographs showing positive VIA and VILI screening test outcomes

The comparative efficacy and cost-effectiveness of once-a-lifetime VIA (provided by nurses), conventional cytology and HPV testing in detecting cervical neoplasia and in reducing incidence of and mortality from cervical cancer is being evaluated in a cluster randomized controlled intervention trial in Osmanabad district, Maharashtra, India. This study involves 130 000 women aged 30–59 years living in 502 villages in 52 primary health centres, randomized to one of the above screening tests or to a control group. Recruitment was completed in October 2003. Preliminary results for women tested to date are given in Table 7.

The impact of a single round of VIA screening on cervical cancer incidence and mortality is being assessed in a cluster randomized trial in Dindigul District, south India. Women aged 30–59 years were randomized to VIA screening (57 clusters, 48 225 women) by nurses or to a control group (56 clusters, 30 167 women). Recruitment of women has been completed and the initial analysis is complete. 30 577 eligible women were screened between May 2000 and April 2003 and 9.8% were VIA-positive. CIN 1 was diagnosed in 1778 women and CIN 2–3 lesions were found in 222. Overall, 97 and 34 incident cervical cancer cases were observed in the intervention and control arms, respectively. The age-standardized cervical cancer incidence rates were 92.4 per 100 000 person-years in the intervention and 43.1 per 100 000 in the control arms. In the screened arm, 35.0% of cases were in stage I as opposed to none in the control arm. The preliminary findings from this study indicate that a VIA-based screening programme is feasible, safe and acceptable to a population in rural settings, and that it results in early detection of cervical neoplasia.

The impact of health education in improving stage distribution, adherence to treatment and reducing cervical cancer mortality is being evaluated in a non-randomized controlled trial involving 200 000 women in Solapur district, India. Analysis of the results of this intervention has started.

The efficacy of single- versus double-freeze cryotherapy in controlling CIN is being addressed in a multicentre randomized clinical trial in India and Nepal. In the context of the above programmes, around 3000 CIN cases have been treated with cryotherapy and around 1000 cases with loop electrosurgical excision procedure (LEEP). These women are actively followed up to establish the effectiveness and long-term complications of these treatments carried out by nurses or mid-level clinicians in field conditions.

Figure 55. A bus used as a mobile clinic for cervical cancer screening in Barshi, India

Cervical cancer prevention training centres to train master trainers in various aspects of cervical cancer prevention, particularly in screening and diagnosis and management of cervical precancerous lesions, have been organized in Kolkata, Trivandrum, Barshi (India), Conakry (Guinea), Luanda (Angola) and Dar es Salaam (Tanzania). These centres are expected to catalyse the growth in trained personnel in the region.

A beginners' manual on colposcopy and management of CIN and a training manual on VIA and VILI have been published [411, 440].

Oral cancer screening in developing countries

R. Sankaranarayanan, D.M. Parkin and P. Pisani; in collaboration with L. Fernandez Garrotte, J. Lence, R. Camacho, Havana, Cuba; K. Ramadas, B. Mathew, G. Thomas, B. Kuruvilla, T. Somanathan, P. Sebastian, M. Pandey, E. Abraham, M.K. Nair, Trivandrum, India

A community-based cluster randomized trial in Trivandrum district, India, is addressing whether screening by visual oral inspection leads to reduction in incidence of and mortality from oral cancer. Subjects aged 35 years and above in 13 clusters in the district were randomized to the intervention (screening) group (7 clusters, 78 969 subjects) to receive three rounds of screening by oral visual inspection by trained health workers at three-year intervals or to a control group (6 clusters, 74 739 subjects). Two rounds of screening were completed between 1995 and 2002, during which 69 896 (88.5%) subjects were screened at least once and 59.7% of the 4408 screen-positive subjects were further investigated.

In the intervention group, 344 404 person-years were accrued and in the control group 329 326 person-years up to June 2002. In the intervention group, 149 incident oral cancer cases and 65 deaths from oral cancer were observed, and in the control group 106 incident cases and 62 deaths from oral cancer. The programme sensitivity for detection of oral precancerous lesions and cancer was 81.5% and the programme specificity was 84.8%; the programme positive predictive value was 39.6%. In the intervention group, 47.1% of the cases were in stages I–II, as opposed to 24.7% in the control group. The three-year survival rate was 57.5% in the intervention and 38.8% in the control group ($p < 0.05$). The age-standardized oral cancer mortality rates were 21.1 per 100 000 person-years in the intervention and 21.3 per 100 000 in the control group. After completion of two rounds of screening, oral cancer mortality rates were similar in both study groups. The third round is now in progress. Oral cancer incidence and mortality among the study groups are monitored by cancer registration, linkage with the mortality register and active follow-up.

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

Supported by the US Army Medical Research and Material Command under Contract DAMD17-94-J-4327

The prognosis of breast cancer is now good, provided that the disease is detected at an early clinical stage and cases receive optimal treatment. Clinical examination of the breast (CBE) appears to be an applicable screening option in countries in economic transition, where incidence rates are on the increase but resources do not permit mass screening by mammography. However, its value in reducing mortality from breast cancer has not been established. This study was set up to assess whether mass screening by CBE performed by trained para-medical personnel is feasible in an urban population of a low-income country and whether it can reduce mortality from breast cancer by at least 25%.

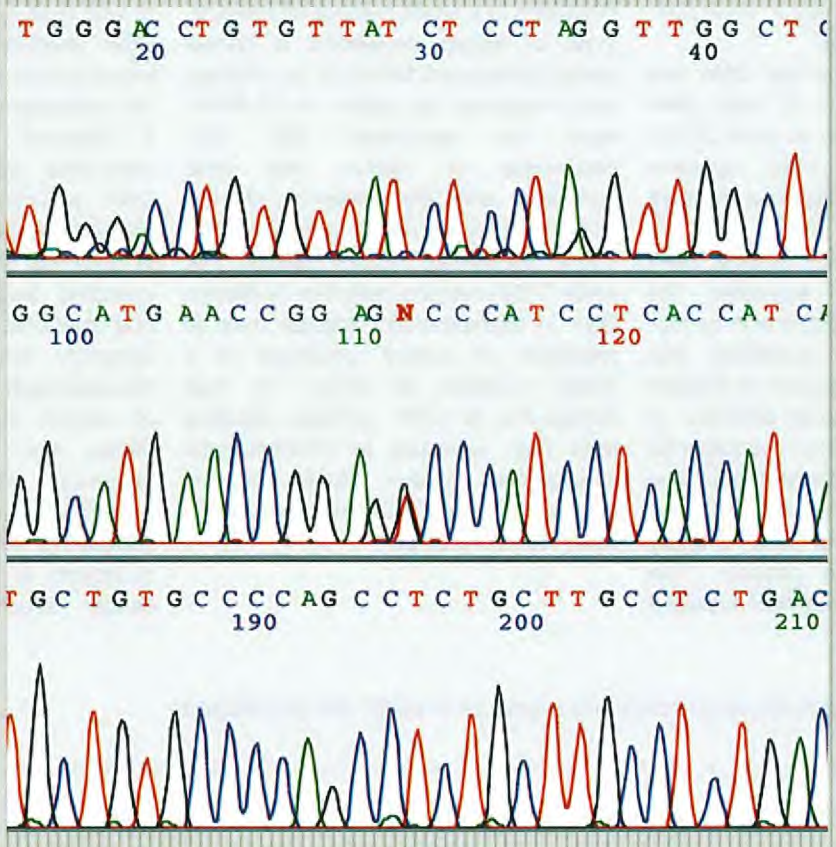
In this randomized controlled trial of the effect of five annual CBEs performed by trained nurses or midwives, the target population comprised women aged 35–64 years, resident in 12 selected municipalities of the National Capital Region of Manila. The units of randomization were the 202 health centres within these municipalities. During 1995, nurses and midwives were recruited and trained in performing CBE. The first round of screening took place in 1995–1997 (30 months). Incident breast cancer cases in 1995–98 were identified by the two local population-based registries.

In the single round of examinations, 151 168 women were interviewed and offered CBE; 92% complied (138 392) and 3483 were detected positive for a lump and referred for diagnosis. Of these, only 1220 women (35%) completed diagnostic follow-up, while 42.5% actively refused further investigation even with home visits, and 22.5% were not traced. Of the 57 cases that occurred among screen-positive women, only 34 were diagnosed through the intervention and 84 cases occurred among screen-negative women. The sensitivity among positive women who completed the diagnostic process was 41.6% but the actual sensitivity of the programme (including cases that occurred among women with incomplete follow-up) was 24.8% and the positive predictive value was 1.6%. Screen-detected cases were non-significantly less advanced than the others.

Breast cancer cases in the Philippines present at advanced stages and have an unfavourable outcome. CBE undertaken by health workers appears an attractive compromise with a good cost-effectiveness ratio suitable for a country with limited resources, but in practice the sensitivity of the screening programme was very low. Moreover, despite a high level of participation with the screening examination, compliance with clinical investigation in women detected as positive was very poor. The reasons for this paradox are unclear and need further investigation. The outcome of this trial is a reminder that it is not only the technical efficacy of a screening procedure that needs to be considered when introducing community screening in developing countries; specific culturally related health-belief issues also need to be taken into account.

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.



DNA sequencing plot, showing a mutation in the *TP53* gene

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.

Plasma DNA as a marker of exposure or of disease in prospective studies

E. Gormally, E. Caboux-Derepierre, G. Tchoua, P. Hainaut; in collaboration with E. Brambilla, Grenoble, France; P. Merle, Lyon, France; C. Trepo, Lyon, France; M. Peluso, Florence, Italy; P. Vineis, Turin, Italy; N. Tonisson, Tartu, Estonia

Small amounts of tumoural DNA are detectable in the form of free DNA fragments in the plasma of most cancer patients. This DNA often contains alterations (mutations) identical to those found in the primary tumour. We are investigating (1) whether plasma DNA represents a good surrogate for detection of genetic alterations in tumour tissues; and (2) the possibility that plasma DNA may be a source of relevant biomarkers for early cancer detection or for monitoring exposure to environmental carcinogens. First, we performed parallel analyses on pairs of DNA specimens extracted from plasma and primary tumours of the same patients. The molecular alterations analysed included *TP53* and *KRAS* mutations as well as hypermethylation of *CDKN2a*. While good correlations were found between plasma and liver tumour DNA, mutations were not found in plasma paired with lung tumours, indicating that not all cancers release DNA into plasma at the same rate, so that plasma DNA may not be a universal surrogate for all types of cancer. Second, we have evaluated the significance of plasma DNA in a prospective study nested within EPIC, the GENAIR study (see Section 2.3). GENAIR is designed to clarify the relationship between exposure to air pollution and environmental tobacco smoke (ETS) and cancer (lung, larynx/pharynx, oral and bladder cancers, leukaemia and chronic obstructive pulmonary disease) in non-smokers or ex-smokers who have ceased smoking for more than 10 years. The study involves detailed exposure assessment and analysis of numerous polymorphisms in candidate susceptibility genes. A pilot study on over 500 plasma DNA samples revealed *TP53* point mutations in a small number of subjects, most of whom developed a cancer during subsequent follow-up. In contrast, point mutations at codon 12 of *KRAS* were not associated with later occurrence of cancer, but were correlated with the presence of high levels of bulky adducts in genomic DNA. These preliminary results indicate that while *TP53* mutation detection in plasma DNA in asymptomatic subjects may be predictive of cancer, presence of a *KRAS* mutation at codon 12 may correspond to DNA damage resulting from high exposure to environmental carcinogens. Further studies are in progress to extend these observations to other types of cancer.

Development of a sensitive microarray method for detection of *TP53* mutations

F. Le Calvez, E. Caboux-Derepierre, P. Boffetta, P. Brennan, P. Hainaut; in collaboration with A.L. Børresen-Dale, Oslo, Norway; N. Tonisson, A. Metspalu, Tartu, Estonia

Detection of mutations in the *TP53* gene has applications in fields ranging from molecular epidemiology (mutation patterns may reveal clues to mutagenic mechanisms) to early cancer detection and clinical management of cancer. Most published studies have been limited to the analysis of, at best, a few hundred cancer specimens, due to the lack of sensitive and affordable high-throughput methods for precise identification of mutations. In collaboration with an Estonian company, we have developed a new microarray based on the APEX (arrayed primer extension) technology for the rapid and sensitive detection of mutations in exons 2 to 9 of *TP53*. APEX involves the immobilization onto a solid support of short oligonucleotides corresponding to wild-type sequences, hybridization of PCR products of tumour DNA, and incorporation of four distinct fluorescent dye terminators (each corresponding to a different nucleotide) into oligonucleotide primers by a thermostable DNA polymerase (Figure 56). This method has proved extremely sensitive in detecting all types of *TP53* mutation, including point mutations, insertions and deletions. In contrast to other, more common microarray-based methods, this approach does not require spotting of mutant oligonucleotides and thus allows the use of smaller, less expensive DNA chips. We have extensively validated this approach by comparing its efficiency in detecting mutations in a large series of lung cancer specimens collected in the

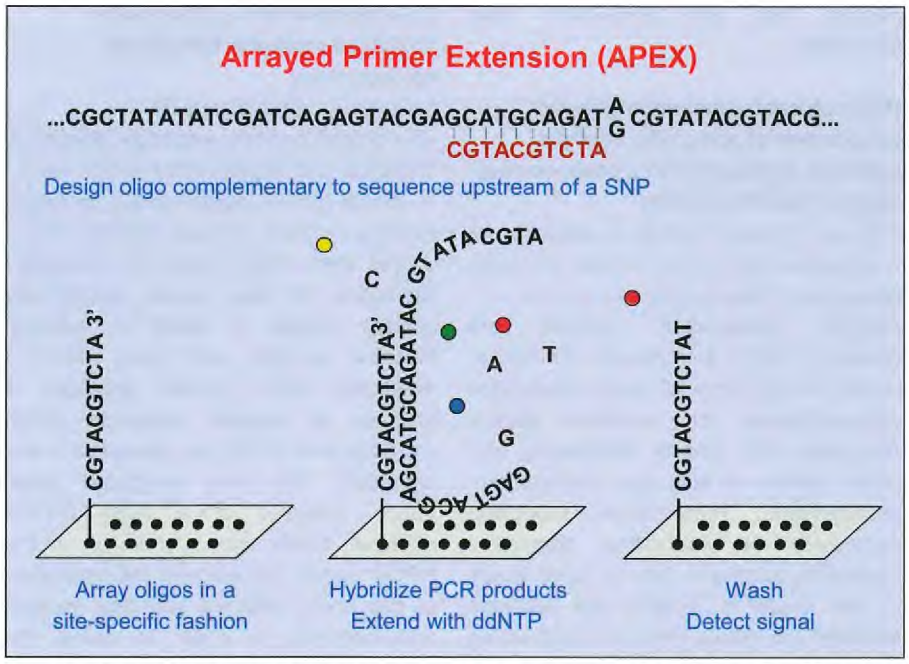


Figure 56. Scheme of the molecular mechanism of arrayed primer extension (APEX). Following identification of a single nucleotide polymorphism (SNP), a suitable oligonucleotide is designed and synthesized (upper panel). Oligonucleotides, each corresponding to a different SNP, are linked to the surface of a glass slide according to a predefined grid (lower left panel). Each oligo thus corresponds to a spot on the slide, of known position. PCR products obtained from sample DNA are hybridized onto the arrayed oligos. Fluorescently labelled ddNTPs and a DNA polymerase are added to the mix and used to perform single-base extensions of the arrayed oligos (lower centre panel). Finally, the slides are washed to eliminate unincorporated ddNTPs and read with a four-colour scanner which detects the fluorescent signals from the extended oligos (lower right panel)

context of a molecular epidemiology study on non-smokers and ex-smokers. We are now developing an extended array containing sequences of *TP53* and several other cancer-related genes such as *KRAS* and *CDKN2a*. Our goal is to generate an instrument capable of providing a routine screening system for detection of *TP53* mutations in large series of DNA specimens extracted from either tumours or surrogate tissues.

6.2 *Epidemiological methods*

Extraction of the maximum amount of sound information from epidemiological results requires that appropriate data collection methods should have been used and that suitable and powerful statistical methods are applied for the analysis. New methods are often developed to deal with new types of problem that arise in specific studies; some such work is mentioned in the descriptions of the studies themselves (see, for example, Section 2.3) and more fundamental methodological work is described below.

Statistical methods for cancer epidemiology

M. Plummer, S. Franceschi; in collaboration with V. Bagnardi, Milan, Italy

Current work on development of statistical methods is concentrated in three areas: interval censored data, multi-state models and floating absolute risk.

Cancers associated with infectious agents are frequently associated with a series of precancerous states that may be identified histologically: this is true of cervical cancer (see Section 3.4: Risk factors for acquisition and persistence of HPV infection in women) and gastric cancer (see Section 5.1: Chemoprevention trial on precancerous lesions of the stomach in Venezuela). Progression and regression of the precancerous states is monitored by panel studies, in which subjects are examined at periodic follow-up visits. Such studies give rise to two difficulties in statistical analysis: firstly, the disease outcome may have multiple states rather than being a simple case/control dichotomy, and secondly the data are interval censored, because the time of transition between two disease states is not known exactly, but is known only to have occurred between two visits. The aim of this project is to develop statistical methods that allow such studies to be correctly analysed [312].

A second project concerns floating absolute risk, a method of presenting relative risk estimates for polychotomous risk factors that avoids the problems caused by the choice of reference

category [317]. This methodology has been put on a rigorous basis, so that improved confidence intervals may now be calculated for floating absolute risks, and their interpretation has been clarified [376].

Statistical software

M. Plummer; in collaboration with D. Bates, Madison, WI, USA; B. Carstensen, Gentofte, Denmark; J. Chambers, D. Temple Lang, Murray Hill, NJ, USA; P. Dalgaard, Copenhagen, Denmark; R. Gentleman, Cambridge, MA, USA; K. Hornik, F. Leisch, Vienna, Austria; S. Iacus, Milan, Italy; R. Ihaka, P. Murrell, Auckland, New Zealand; T. Lumley, Seattle, WA, USA; M. Maechler, Zürich, Switzerland; G. Masarotto, Padua, Italy; D. Murdoch, London, Canada; B. Ripley, Oxford, UK; L. Tierney, Iowa, IA, USA

The aim of this project is to provide software implementations of advanced statistical methods that are not available in standard packages (such as SAS and Stata). Initial software development is typically driven by the needs of a specific epidemiological project. This leads to the development of custom software: examples include software for analysis of interval censored survival data [312] and for creating summary plots in meta-analyses [321, 378]. The eventual aim is to create reusable software that may also be used by other researchers.

The project focuses on the R language for data analysis and graphics (http://www.r-project.org), a free implementation of the S language developed at AT&T Bell laboratories. R is uniquely customizable and has a large library of user-contributed extensions (http://cran.r-project.org). Participation in the R project involves development of the base R distribution and its dissemination. Future plans include an annual course on statistical practice in cancer epidemiology using R, which will form the basis of a book.

Another program currently under development is JAGS, a re-implementation of the BUGS language for analysing Bayesian graphical models. Such models can combine various sources of complexity, such as measurement error, random effects, missing data and hierarchical data structures.

Hierarchical modelling in genetic association studies with multiple markers: application to a case–control study of bladder cancer

P. Brennan, R. Hung, P. Boffetta; in collaboration with C. Malaveille, Lyon, France; S. Porru, F. Donato, Brescia, Italy; J. Witte, San Francisco, CA, USA

Genetic association studies are generating large amounts of information, usually in the form of single nucleotide polymorphisms for candidate genes. Analysing such data is challenging, and raises issues of potential false positive associations. Hierarchical modelling represents an interesting alternative approach, adding in two or more levels in the model to specify the relations between the genes being studied. Using data from a case–control study of bladder cancer in Brescia, Italy (see Section 3.6), we used hierarchical modelling to control overestimation of effects and false positive associations. The data were first analysed with the conventional approach of estimating each main effect individually. We then employed hierarchical modelling by adding a second-stage model that incorporated information on the potential function of the genes along different pathways (e.g., detoxification of carcinogens, DNA repair). We used an empirical Bayes approach, estimating the residual effects of the genes from the data. When this was set to zero, we used a semi-Bayes approach, in which we pre-specified the residual effects. Pre-specifying the second-stage covariates led the estimates to shrink to the mean of each pathway. Extreme but unstable values experienced the greatest shrinkage. Similar results were observed for the interaction between genetic factors and environmental exposures (tobacco smoking, occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons).

Development and evaluation of analytical methods for genetic epidemiology

D.E. Goldgar, J. Witte, D. Thompson

This project explores important analytical, statistical and experimental design issues in cancer genetic epidemiology for which existing methods are not optimal. Some of this work relies largely on computer-simulation of data under appropriate genetic models in order to evaluate different sampling and gene detection strategies, while another approach is analysis of specific data-sets which currently exist or will be generated in our laboratory. We have completed penetrance analyses of a large (~1700 member) family with a mutation in the *BRCA1* gene, focusing on the estimation of risk using different statistical models and methods, in order to define the inherent variability in such estimates. We have also examined 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 [450]. These studies will also help family cancer clinics set guidelines for family history in deciding who should be eligible for genetic testing.

We have developed a statistical approach for assessing causality of sequence variants in relevant cancer predisposition genes through analysis of co-segregation of the variants in affected families [503]. We have investigated optimal strategies for determining the optimal choice of SNPs in performing genetic association studies using a haplotype-tagging approach [504]. In a study of the possible gain in efficiency for genetic case–control studies through incorporation of data on family history of the disease of interest in cases and controls, we concluded that an approximate 20% gain in power can be achieved by incorporating such information in a genetic model. We have implemented a computer program which should be widely usable for analysing genetic polymorphisms in case–control studies of cancer and other chronic disease.

6.3 *Statistical methods and bioinformatics*

The newly established Unit of Biostatistics and Bioinformatics is carrying out cancer research projects focusing on the use of biomic (cellular, molecular and other) data. The development of procedures for the management and analysis of microarray and other laboratory data is a primary focus of this work.

Laboratory and microarray data analysis

E. Lazaridis, H. Ohgaki, H. Huang; in collaboration with C. Sotiriou, M. Buysse, Brussels, Belgium; G. Potamias, M. Reczko, Heraklion, Greece

Supported by the European Commission

In the context of the Breast cancer genomics Trans-BIG Network of Excellence project (see Section 3.10), work has been initiated on creating and deploying informatics and analysis systems for the consensus management and analysis of microarray and supporting data derived from biological samples provided by collaborating facilities in nearly 20 countries. Work has also started on the development of software for analysing microarray data as well as the collection, archiving and testing of appropriate biological samples for the PROGNOCHIP project (see Section 3.10). In addition, development and application of microarray analysis tools to distinguish oligodendroglioma and low-grade astrocytomas is in progress (see Section 3.5).

EPICURE

E. Lazaridis, E. Cardis

EPICURE is a package of FORTRAN programs for risk modelling and for the creation of multi-way tables frequently used in large epidemiological studies. It includes programs for logistic regression, Cox regression and Poisson regression. The package has been revised to work on a Linux multiprocessor computer, more than doubling the speed of large simulations.

Development systems

E. Lazaridis, S. Cuber

For the infusion of informatics tools into the Agency to have long-term and substantial impact on the research environment requires that a computational infrastructure appropriate for support of informatics research and services be created. The development of an informatics toolkit at the Agency is proceeding in stages. The first of these stages was to design and build a hardware and software web services platform for research and development studies. Development systems consisting of four tightly integrated computers have been purchased and assembled into a network. A test of the network design resulted in a proposal to build a computational grid at the Agency, which was funded by the Governing Council in 2003.

Computational grid for cancer research

E. Lazaridis, S. Cuber, G. Suchet

Some recent applications of distributed computing have focused on the modelling of protein structures or protein folding. A computational grid has been designed for the Agency to support the execution of large computational tasks in analytic and bioinformatics studies that may include protein modelling, Monte Carlo simulations and nonparametric statistical modelling. In addition, this computational grid is designed to provide web services to Agency staff and external scientific collaborators. A theoretical design was established based on work described above, and used to prepare specifications for vendors.

Provision of computational tools

E. Lazaridis, G. Suchet, S.V. Tavtigian; in collaboration with A. Thomas, Salt Lake City, UT, USA

Specialized tools for data analysis that have been developed within individual units at IARC could be made more widely accessible and useful with straightforward database connectivity and an intuitive web interface. In addition, researchers increasingly need easy access to software tools from external sources. This study aims to identify such tools and rebuild them for use in a web services context. Analytic Server (Insightful Corp.) software has been installed and tested on the development systems, to support integration of customized analysis routines. A specifications document is being written to support the development of in-house routines on the Analytic Server.

BLAST (Basic Local Alignment Search Tool) is a popular software for comparing various kinds of genomic sequences. RepeatMasker is a standard software tool used in computational genomics to identify repetitive elements and low-complexity sequences. MaskerAid is a drop accelerator that increases the speed of Repeatmasker about 30-fold while maintaining its sensitivity. BLAST facilities have been integrated into the development systems, along with the RepeatMasker and MaskerAid software packages, and are now undergoing in-house testing.

The GDE (genomic data environment) software package in support of bioinformatics studies is being adapted to a web-enabled interface. A visiting scientist has written a program (SnpScreen) for carrying out mutation screening from sequencing waveforms; this program is now being recast as a web service to allow wide distribution.

Electronic document management

E. Lazaridis, K. Lenormand, H. Miido, S. Grant, V.J. Cogliano

The Agency collects mountains of paper documents in both research and administrative processes. For example, a vast document library has been collected in the carcinogen evaluation programme (see Section 2.1). If the text of these documents were available in electronic

format for searching with artificial intelligence (data-mining), new information might be gleaned that was previously overlooked. A system based on a scanner and document server has been set up, allowing documents to be scanned, stored and managed by a web-enabled database, and is being tested.

To assess the feasibility and efficacy of storing and maintaining library information in Extensible Markup Language (XML) format, this study includes a demonstration of the transformation of current records in the library from the MARC format to the XML standard now employed by the US National Institutes of Health. It also tests the feasibility of translating scientific data into XML formats, and storing, retrieving and employing such data in a networked environment. Software has been developed to convert record-sets from MARC, EndNotes and Reference Manager to XML format. The EndNotes converter is now undergoing testing.

Database migration and standardization

E. Lazaridis, M. Olivier, E. Caboux-Derepierre, S. Monnier

A standard system is being developed for data management across the Agency. The MySQL database system is being tested for this purpose. The work involves the conversion of many existing databases, improving the connectivity, functionality and maintainability of Agency data. A process for transferring data from Access into MySQL is being tested.

Routing and electronic signature

E. Lazaridis

Many Agency research and administrative activities involve routing of information, which may originate anywhere in the Agency. For example, official correspondence is often routed through several units before mailing. Biological samples managed by the sample archives must be tracked as they move from freezer to laboratory and back. This project is building tools for verifiably signing electronic records in a routing process. An initial system for ordering laboratory supplies, in which orders are routed for approval between various units and administrative offices, is already being tested.

Image data management

E. Lazaridis, S. Cuber

This study aims to design and test a new-generation system that addresses the issue of storage and management of images resulting from molecular biology studies, and additionally provides better linkage of image data with analytical software for sensitivity testing of imaging algorithms. Methods for extracting data collected in molecular biology studies as images and methods for analysing the resulting data have tended to be difficult to integrate. Tools for image management in a MySQL database context have been written and are undergoing testing. The original aim of this study was to adapt and employ technology originally developed for the analysis of microarray images to a wide variety of experimental contexts; however, substantial effort was needed to first convert existing code from Oracle to MySQL database systems. These tools will be used in the microarray research studies mentioned above.

Analytic server graphics

E. Lazaridis, M. Olivier

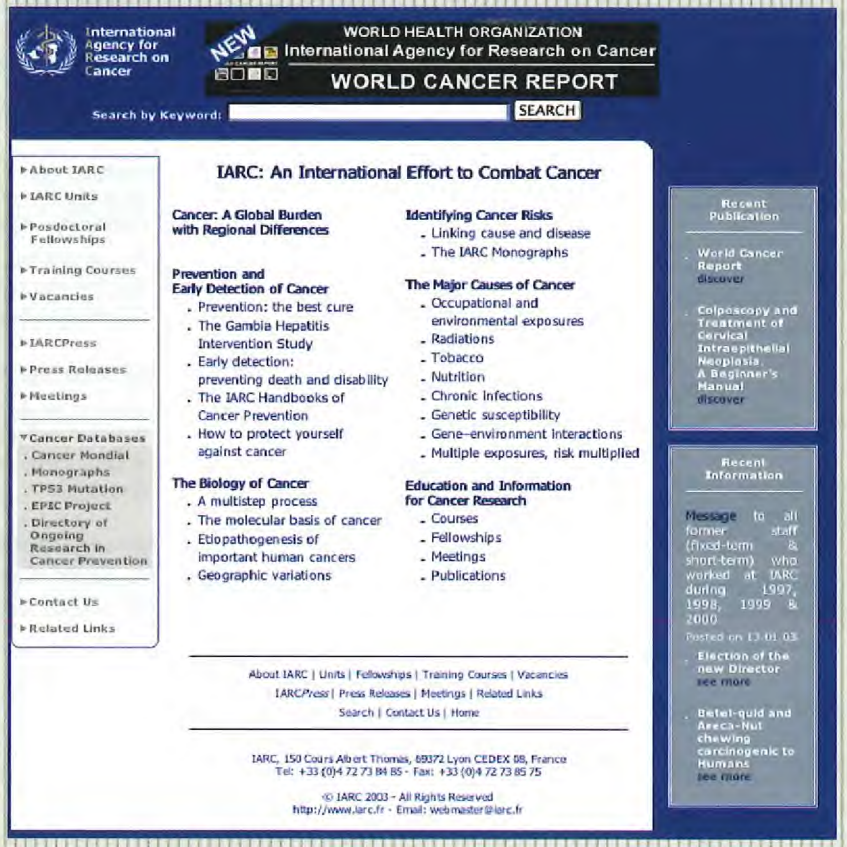
Presentation of analytical results is a very important component of research activities. This study seeks to demonstrate the efficacy in application of a networked graphical interface through an analytic server engine. Analytic Server (Insightful Corp.) software has been installed and tested on the development system, to support wide access to standardized graphics functions. A specifications document for implementing these graphics is being developed. This study is of particular relevance to the *TP53* database (Section 4.6) and management of the Agency's information system for sample archives.

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 increasingly 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.



The new Internet home page of IARC

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". The Communications Unit manages 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. It aims to present 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 unit thus provides the scientific units with 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 six volumes had been published by the end of 2003, with considerable success. These provide authoritative and profusely illustrated descriptions of tumours for histological and genetic typing of human tumours. An electronic version is in preparation.

The IARCPress sales service has continued to increase its turnover, through major marketing efforts by direct mailing and displays at scientific meetings. The IARCPress office in Washington, DC, assists with promotional activities and sales in North America, as well as generally enhancing the visibility of IARC throughout the continent. The number of books sold annually by IARCPress (Lyon and Washington combined) doubled between 2001 and 2003.

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 is accessible on the Internet and a CD-ROM carrying most volumes of the Monographs is available (see below).

Three new volumes were published during the period under review:

Volume 80, *Non-ionizing Radiation*, Part 1: *Static and Extremely Low Frequency Electric and Magnetic Fields*

Volume 81, *Man-made Vitreous Fibres*

Volume 82, *Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*

IARC Scientific Publications

Three new volumes were published:

Cancer in Africa: Epidemiology and Prevention (IARC Scientific Publications No. 153)

Cancer Incidence in Five Continents, Vol. VIII (IARC Scientific Publications No. 155)

Nutrition and Lifestyle: Opportunities for Cancer Prevention (IARC Scientific Publications No. 156)

IARC Handbooks of Cancer Prevention

This programme is fully described in Section 5.2. Three new volumes were published:

Volume 6. *Weight Control and Physical Activity*

Volume 7. *Breast Cancer Screening*

Volume 8. *Fruit and Vegetables*

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 were published in the current biennium:

Pathology and Genetics of Tumours of Soft Tissue and Bone

Pathology and Genetics of Tumours of the Breast and Female Genital Organs

Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs

IARC Reports

The series of IARC Technical Reports was renamed IARC Technical Publications. Five new volumes were published:

Evaluation of Clinical Care by Cancer Registries (IARC Technical Publication No. 37)

Cancer in Portugal (IARC Technical Publication No. 38)

Predictive Value of Rodent Forestomach and Gastric Neuroendocrine Tumours in Evaluating Carcinogenic Risks to Humans (IARC Technical Publication No. 39)

Standards and Guidelines for Cancer Registration in Europe (IARC Technical Publication No. 40)

A Practical Manual on Visual Screening for Cervical Neoplasia (IARC Technical Publication No. 41)

One IARC Internal Report was produced:

Report of an Ad-Hoc IARC Monographs Advisory Group on Priorities for Future Evaluations (IARC Internal Reports No. 03/001)

Non-serial publications

The *World Cancer Report*, published in early 2003, provides a comprehensive

review of all aspects of cancer research, covering occurrence, causes, mechanisms, prevention and treatment of the disease. A French edition is in preparation. *Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginners' Manual* was published to help health care personnel, particularly in developing countries, to obtain skills in an essential technique for diagnosis of cervical lesions leading to cancer.

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/). The web site has been completely redesigned and updated to ensure optimal impact, navigability and information content, in view of the ever-growing importance of this form of communication. A publications-ordering module has been introduced. Forthcoming events, fellowships, job vacancies and new publications are routinely announced on the web site. 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 4.5). A large amount of epidemiological data can be accessed through the CANCER-Mondial web site (see below).

Volumes 1–80 plus Supplement 7 of the IARC Monographs are available as Version 2.0 of a CD-ROM from GMA Industries, Inc. (Annapolis, Maryland, USA) and also on-line at http://www.gmai.com. This contains the full corrected text in modern format, with corrigenda to original printed volumes replacing original text where needed. The text is fully searchable and the references have been updated.

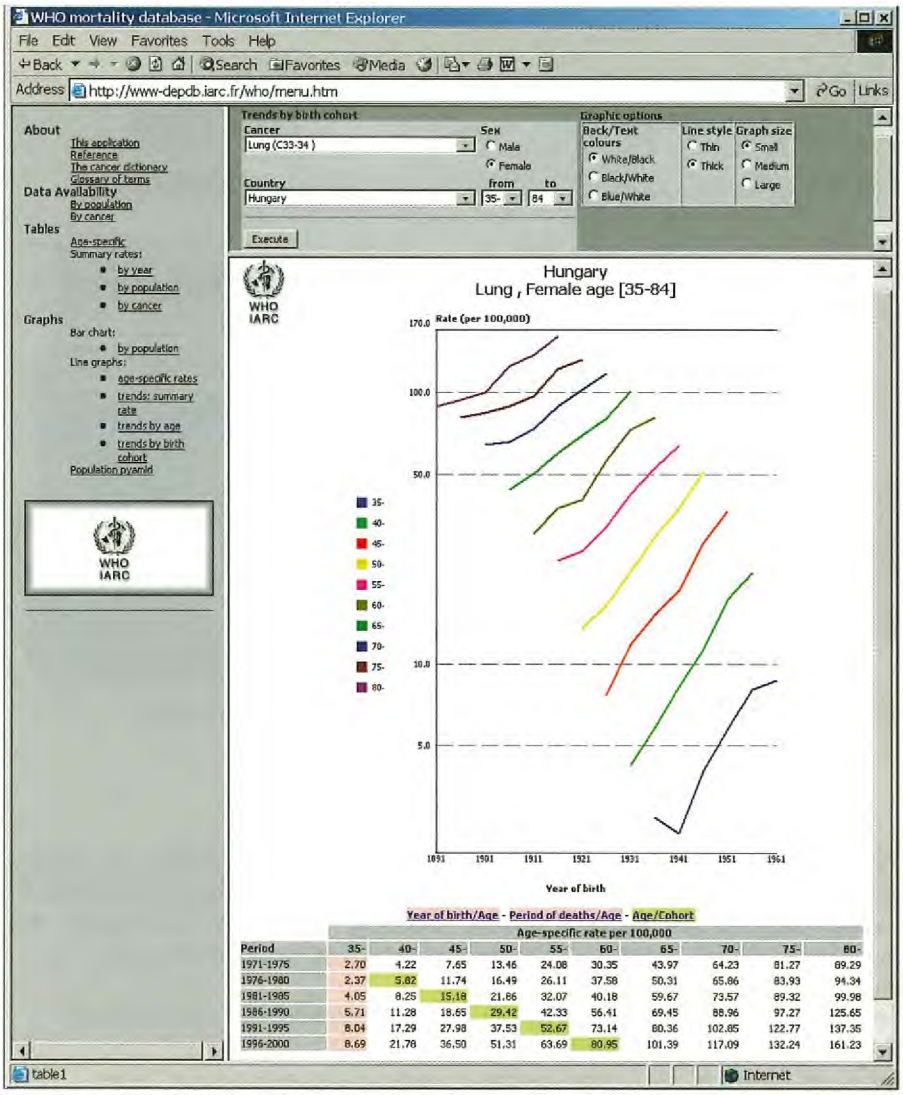


Figure 57. Graph of lung cancer mortality in Hungary, created using the GLOBOCAN 2002 software

Epidemiological data

J. Ferlay, M.T. Valdivieso

GLOBOCAN 2000, the fifth volume of the CancerBase series, provides estimates of 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 and grouped as desired. In addition, GLOBOCAN 2000 allows estimation of future cancer burden using user-specified trends and population projections included in the package. The original GLOBOCAN 2000 database has been updated to provide estimates for the year 2002 (Figure 57). The new database and its corresponding software GLOBOCAN 2002 are available for registered users through the Internet (http://www-dep.iarc.fr/globocan/download.html).

To complement the databases published in the CancerBase series, statistical and epidemiological data are accessible through the Internet using the CANCER-*Mondial* web site (http://www-dep.iarc.fr). The design and structure of the web site have been revised and it now provides access to the simplified, updated versions of the GLOBOCAN 2002 and EUCAN CD-ROMs, with limited statistics and options, and to the cancer mortality database, containing data extracted from the WHO mortality databank. The data in the latter can be extracted using a simple menu-driven interface, then presented as a variety of tables and graphs (Figure 57).

Figure 58. The CANCERMondial home page and the pages of specific projects hosted on the web site

In addition, CANCER*Mondial* hosts the home pages of the International Association of Cancer Registries (IACR, Section 1.1), the European Network of Cancer Registries (ENCR, Section 1.1), the Comprehensive Cancer Monitoring Programme in Europe (CaMon, Section 1.2), the Automated Childhood Cancer Information System (ACCIS, Section 1.3), the Directory of On-going Research in Cancer Prevention (Section 5.1) and the IARC component of the Alliance of Cervical Cancer Prevention (ACCP, Section 5.3) (Figure 58). A new server has been dedicated to database access in order to provide a smooth and fast service. The continued increase in the numbers of connections proves that this service is still very much appreciated around the world.

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 in the world with training in aspects of cancer research ranging from biostatistics and epidemiology to mechanisms of chemical and viral carcinogenesis so that they can return to their own country to implement and develop programmes in cancer research or cancer control. The majority (64%) of the 520 fellowships awarded since 1966 have come from western Europe, Japan, North America, Israel, Australia and New Zealand, while 18% came from eastern Europe and 18% from Africa, Asia and South America (see below). Host laboratories have been mainly located in western Europe (50%) and North America (48%). The programme is one of the few to provide training in epidemiology, and the 108 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 2002–03 biennium to review applications; the members of the Committee were:

Dr M. Hollstein (2002) (*Chairperson, 2002*)
German Cancer Research Center
Heidelberg, Germany

Dr L. Luzzatto (2002, 2003)
Istituto Nazionale per la Ricerca sul Cancro
Genoa, Italy

Dr K. Nilsson (2002, 2003) (*UICC Representative*)
Uppsala University Hospital
Uppsala, Sweden

Dr T.E. Pangestu (2002, 2003) (*Representative of WHO*)
Division of Evidence and Information for Policy
World Health Organization
Geneva, Switzerland

Fellows from :		Fellows to :
France	58	37
IARC, Lyon	–	58
Japan	45	3
Italy	38	4
United States	31	253
Israel	27	–
Russian Federation	25	–
United Kingdom	25	102
PR China	25	1
India	21	1
Australia	18	3
Other countries	207	85
Total:	520	547*

Figure 59. IARC fellows 1966–2003: countries of origin and host countries

*Twenty-seven fellows had two host countries

Dr E. Olah (2003)
National Institute of Oncology
Budapest, Hungary

Dr P. Peeters (2003)
Julius Center for Health Sciences and Primary Care
Utrecht, The Netherlands

Dr A. Puisieux (2002, 2003)
Centre Léon Bérard
Lyon, France

Dr Z. Ronai (2002, 2003)
Mount Sinai School of Medicine
New York, NY, USA

Dr K. Sikora (2002, 2003)
Hammersmith Hospital
London, United Kingdom

Dr J. Svoboda (2002)
Institute of Molecular Genetics
Prague, Czech Republic

Dr P. Swann (2002, 2003) (*Chairman, 2003*)
University College London
London, United Kingdom

Dr K. Wakabayashi (2002, 2003)
National Cancer Center Research Institute
Tokyo, Japan

Table 8. Distribution of research training fellowships awarded by discipline

Scientific discipline	No. of fellowships		
	2002	2003	**1966–2003**
Epidemiology/biostatistics	2	2	**110**
Cell biology	3	3	**105**
Chemical carcinogenesis	–	–	**69**
Viral carcinogenesis	1	1	**61**
Cell genetics/molecular biology	1	2	**79**
Biochemistry	–	1	**37**
Others	2	1	**59**
Total	9	10	**520**

The Agency representatives were Dr D.E. Goldgar, Dr E. Riboli (2002) and Dr E. Weiderpass (2003).

In 2002, among a total of 63 candidates, 29 were evaluated by the full Selection Committee and nine finally given an award; in 2003, among a total of 50 candidates, 27 were evaluated by the full Selection Committee and 10 fellowships finally awarded. The distribution of fellowships awarded by discipline is given in Table 8, 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.

Visiting Scientist Award

In 2002, this Award was given to Dr John Witte (Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland, OH, USA), who spent a year in the Unit of Genetic Cancer Epidemiology, and in 2003 to Dr Tony Fletcher (Environmental Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, UK), who will spend one year in the Unit of Environmental Cancer Epidemiology.

Postdoctoral fellowships at IARC

Z.-Q. Wang, H. Ohgaki and E. El Akroud

Since its inception in 1998, the IARC in-house postdoctoral fellowships programme has offered fellowships to junior scientists from all over the world and has proved effective in attracting young scientists of high quality to the Agency.

In 2002, from a total of 34 eligible applications from 15 countries, postdoctoral fellowships were awarded to Dr Rutao Cui from the Beijing Friendship Hospital, Capital University of Medical Sciences, Beijing, People's Republic of China, tenable in the Unit of Molecular Carcinogenesis, Dr Min Dai from the College of Public Health, Henan Medical University, Zhengzhou, People's Republic of China, tenable in the Unit of Field and Intervention

Table 9. Fellowships awarded in 2002 and 2003

Name	Institute of origin	Host institute
2002		
BUSUTTIL, V.E.M.G.	INSERM U526 Faculté de Médecine Pasteur Nice, France	La Jolla Institute for Allergy and Immunology Division of Cell Biology San Diego, CA, USA
CABRITA, M.A.	University of Alberta Cross Cancer Institute Department of Oncology Edmonton, Canada	University of Basel Institute of Biochemistry Basel, Switzerland
CHAVARRO, J.E.	Universidad Nacional de Colombia Facultad de Medicina Departamento de Salud Pública y Tropical Bogotá, Colombia	Harvard School of Public Health Department of Epidemiology Boston, MA, USA
DALLE LUCHE, D.	Universidade de São Paulo Instituto de Ciencias Biomedicas - 2 São Paulo, Brazil	University of North Carolina School of Medicine Department of Pathology and Laboratory Medicine Chapel Hill, NC, USA
DUGAST-DARZACQ, C.M.M.-L.	Centre National de la Recherche Scientifique (CNRS) Laboratoire de Biologie Moléculaire Eucaryote Toulouse, France	Albert Einstein College of Medicine Department of Molecular Genetics New York, NY, USA

Table 9 (contd)

Name	Institute of origin	Host institute
LE CROM, S.	Ecole Normale Supérieure INSERM U368 – Laboratoire de Biologie Moléculaire du Développement Paris, France	Université de Montréal Faculté de Médecine Département de Biochimie Montreal, Canada
MAEDA, A.	Kyoto Prefectural University of Medicine Department of Preventive Medicine Kyoto, Japan	City of Hope National Medical Center and Beckman Research Institute Division of Molecular Biology Duarte, CA, USA
MATSUO, K.	Aichi Cancer Center Research Institute Division of Epidemiology and Prevention Nagoya, Japan	Harvard School of Public Health Department of Epidemiology Boston, MA, USA
SAUROJA, I.A.	University of Turku Central Hospital Department of Oncology and Radiotherapy Turku, Finland	Dana Farber Cancer Institute Harvard Medical School Department of Cancer Biology Boston, MA, USA
2003		
AYOUB, N.	The Hebrew University Hadassah Medical School Department of Molecular Biology Jerusalem, Israel	Medical Research Council (MRC) Cancer Cell Unit Hutchinson/MRC Research Centre Cambridge, UK
BILTON, R.L.	University of Adelaide Discipline of Biochemistry Department of Molecular Biosciences Adelaide, Australia	Institut de Recherche CNRS-INSERM-UNSA CNRS UMR 6543 Nice, France
CIOCE, M.	European Institute of Oncology Department of Experimental Oncology Milan, Italy	University of Dundee School of Life Sciences Dundee, Scotland, UK
DE NICOLO, A.	University of Padua Department of Oncology and Surgical Sciences (Oncology Section) Padua, Italy	Dana Farber Cancer Institute Harvard Medical School Department of Cancer Biology Boston, MA, USA
DHILLON, P.	Fred Hutchinson Cancer Research Center Program in Epidemiology Seattle, WA, USA	Indian Council of Medical Research National Cancer Registry Programme Bangalore, India
DI FIORE, B.	University of Rome "La Sapienza" National Research Council (CNR) Centre of Evolutionary Genetics c/o Department of Genetics and Molecular Biology Rome, Italy	The Wellcome Trust/Cancer Research UK Institute of Cancer and Developmental Biology Cambridge, UK
KUCHINSKAYA, E.	Research and Clinical Institute for Radiation Medicine and Endocrinology Minsk, Belarus	Universita degli Studi di Pisa Dipartamento di Endocrinologia e Metabolismo, Ortopedia e Traumatologia Medicina del Lavoro Pisa, Italy
MILLS, K.E.	Cook, Australia	Heidelberg University Otto Meyerhof Zentrum Department of Molecular Virology Heidelberg, Germany
NGOAN, L.T.	Hanoi Medical School Faculty of Public Health Hanoi, Viet Nam	Johns Hopkins University Bloomberg School of Public Health Department of Epidemiology Baltimore, MD, USA
ROSENQUIST, M.	University of Uppsala Rudbeck Laboratory Uppsala, Sweden	Harvard Medical School Department of Pathology Boston, MA, USA

Studies, Dr Paolo C. Maiorka from the University of São Paulo, Faculty of Veterinary Medicine & Zootechny, São Paulo, Brazil, tenable in the Unit of Molecular Pathology, Dr Shiho Ohnishi from Mie University School of Medicine, Mie, Japan, tenable in the Unit of Endogenous Cancer Risk Factors, Dr Srinivas Patnaik from the Institute of Life Sciences, Bhubaneswar, Orissa, India, tenable in the Unit of Gene–Environment Interactions, Dr Min Shen from Tongji Medical College, Wuhan, People's Republic of China, tenable in the Unit of Environmental Cancer Epidemiology, and Dr Deborah Thompson from the University of Cambridge, Cambridge, UK, tenable in the Unit of Genetic Cancer Epidemiology.

In 2003, 52 eligible applications were received from 22 countries, and an IARC postdoctoral fellowship was awarded to Dr Garnett P. McMillan from the University of New Mexico, Albuquerque, NM, USA, tenable in the Unit of Epidemiology for Cancer Prevention, Dr Rebecca Cleveland from the University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, tenable in the Hormones and Cancer Group, Dr Anne-Sophie Gabet, from the Centre Léon Bérard, Lyon, France, tenable in the Unit of Infection and Cancer, Dr Yanhui Lu from the Fu Wai Hospital and Cardiovascular Institute, Beijing, People's Republic of China, tenable in the Genome Analysis Group, and Dr Wookee Min from Oxford University, Oxford, UK, tenable in the Unit of Gene–Environment Interactions. These fellows contribute significantly to IARC's research activities while receiving good training and experience, thus enhancing the prospects for their future scientific career.

The members of IARC in-house postdoctoral fellowship committee were: Dr Z.-Q. Wang (Chairman, until March 2002), Dr H. Ohgaki (Chairperson, from April 2002), Dr P. Boffetta (2002, 2003), Dr P. Hainaut (2002, 2003), Dr E. Weiderpass (2002, 2003), Dr F. Canzian (2003) and Dr R. Kaaks (2003).

7.3 *Training courses*

During 2002 and 2003, eight courses were held within the core programme, hosting 321 participants, of whom a third were financially supported by IARC. This brings the total number of courses organized since the start of the programme in 1968 to 116 and the total number of attendees to 4800. In addition, the Unit of Descriptive Epidemiology organizes a range of courses on cancer registration and descriptive epidemiology.

Figure 60. Course on cancer epidemiology, Trivandrum, India, September 2003

International courses on cancer epidemiology

International courses on cancer epidemiology have always been the cornerstone of the courses programme. They constitute an important tool in implementing IARC's mission to provide education in cancer epidemiology in areas of the world where opportunities for training are scarce. The courses are organized annually; in this biennium, they focused on the Middle East and southern Asia. The courses are organized as two-week modules, based since 1999 on the book *Cancer Epidemiology – Principles and Methods* by Isabel dos Santos Silva, of the London School of Hygiene and Tropical Medicine, which is distributed to course participants to allow them to continue to study on their own after the course.

Izmir, Turkey, 15–26 April 2002

The course, organized in collaboration with the Izmir Cancer Registry, was attended by 46 participants from 22 countries. The teaching team comprised three IARC staff, two local and three

international faculty members. Lectures on basic concepts of epidemiology were complemented by computer-based practical sessions with the Stata software, GLOBOCAN, EUCAN and Cancer Incidence in Five Continents data-sets. Financial assistance from the United States National Cancer Institute (NCI) and IARC helped 29 participants to attend. The course director was Paul Brennan (IARC).

Trivandrum, India, 1–12 September 2003
The course was organized in collaboration with the Regional Cancer Centre in Trivandrum and the Indian Council of Medical Research (ICMR). The course hosted 50 participants mostly from India. The majority of the participants received financial assistance provided by the ICMR, the Alliance for Cervical Cancer Prevention (ACCP), the NCI and IARC. The faculty included two members from IARC, three international members and three local members. Isabel dos Santos Silva was the course director. The course covered basic cancer epidemiology with a special focus on the cancer problem in India, and included a cancer registration workshop and a grant proposal simulation.

Advanced courses
Advanced courses are typically one-week courses focusing on specific topics within cancer epidemiology. They are designed for active cancer researchers who wish to deepen their understanding or shift the focus of their work. The courses have a strong interdisciplinary character, bringing together faculty and participants with different research interests from all around the world. Some topics included have been nutrition, radiation and molecular epidemiology.

Fifth international course on molecular epidemiology
New York, United States, 29 April–5 May 2002
The fifth international course on molecular epidemiology was attended by 29 participants, five of whom were supported by IARC. The faculty included 19 members from five countries. The course directors were Marianne Berwick from New York, Paolo Boffetta from IARC and Paolo Vineis from Turin.


Figure 61. Course on genetic epidemiology, Veyrier-du-Lac, France, June 2003

International course on radiation epidemiology
IARC, Lyon, 17–21 June 2002
This course was organized in conjunction with the Karolinska Institute, Sweden, to present aspects of radiation research from the perspective of the cancer epidemiologist. The course directors, Elisabeth Cardis from IARC and Per Hall from the Karolinska Institute, were helped by five external faculty members and one from IARC. 36 participants from 12 countries attended the course, of whom five were funded by IARC.

Advances in cancer epidemiology
IARC, France, 18–22 May 2003
The course focused on four fields in which major epidemiological work is being carried out: nutrition, infections, genetic factors and environmental factors. Rather than presenting a traditional review, speakers addressed the gaps in current knowledge, highlighted controversies and explored alternative approaches for epidemiological and interdisciplinary research. Paolo Boffetta (IARC) was the course director, with a faculty of five members from various countries and seven from IARC. The NCI provided funding for six of the 23 participants.

International course on genetic epidemiology – focus on biostatistics and bioinformatics
Veyrier-du-Lac, near Annecy, France, 9–13 June 2003
This course covered emerging epidemiological concepts and statistical techniques, bringing together researchers with practical experience in either epidemiology or biostatistics. The course dealt with four major topics: linkage analysis, association studies, genomics and bioinformatics. Paul Brennan, David Goldgar, Emmanuel Lazaridis and John Witte (all at IARC) directed the course. The faculty was complemented by two more IARC members and three external members. The course welcomed 52 participants from 23 countries, and was hosted by the Fondation Mérieux. The NCI provided funding to help seven participants to attend.

International course on molecular epidemiology
Singapore, 21–26 September 2003
This course was attended by 35 participants from eight countries. It was designed as part of a new genetic and molecular epidemiology (GAME) Ph.D. programme initiated by the National University of Singapore and the Karolinska Institute, Sweden, with the participation of IARC. Most of the participants were enrolled in the GAME programme, but the course also attracted a number from elsewhere. IARC provided financial support for six of these participants. The

faculty included 17 members from five countries. The course directors were Kee-Seng Chia (Singapore), Paolo Boffetta (IARC) and Paolo Vineis (Turin).

International course on epidemiological research in nutrition and cancer
IARC, Lyon, 8–13 December 2003
This course was organized by IARC together with the MRC Dunn Human Nutrition Unit, Cambridge. It focused on the planning, conduct and critical interpretation of studies on the role of nutritional factors in cancer etiology. The course directors were Elio Riboli and René Lambert (IARC) and Sheila Bingham (Cambridge). The teaching board included five external faculty members and four from IARC. The teaching board included five external faculty members and seven from IARC. 48 participants from 27 countries attended the course, of whom 12 were funded by IARC.

Courses on cancer registration and descriptive epidemiology

IARC summer school on cancer registration and applications in epidemiology
The seventh Summer School took place in Lyon on 6–24 May 2002, and the eighth on 26 May to 13 June 2003. The courses followed the structure of the previous ones in this series, with minor modifications to the programme. Following the first three weeks of formal training at IARC, the participants spent three days at cancer registries in Europe and in India to gain practical experience of registration activities. The course organizer was Jerzy Tyczynski. In 2002 there were 17 participants from Argentina, China, Gabon, Iran, Iraq, India, Malaysia, Peru, Mauritania, South Africa, Tanzania, Thailand and Turkey. In 2003 there were 20 participants from Argentina, Belarus, China, Egypt, Honduras, Iran, India, Jamaica, Kenya, Republic of Korea, Saudi Arabia, Senegal, Spain, Thailand and Viet Nam.
The course participants were supported by grants from the US National Cancer Institute, the UICC, the Regional Offices of WHO (AFRO and EMRO), IARC, IACR, ACCP, ENCR and the International Atomic Energy Agency (IAEA).

European Network of Cancer Registries courses
ENCR organizes training courses of five types, covering general registration, statistical methods, coding, EUROCIM use (with a special emphasis on the time trends analysis module), and automation in cancer registration.
One course on cance registration was held in 2002 in Lyon, France (course organizer: Jerzy Tyczynski, IARC). Twenty-eight participants from 15 countries attended. In 2003, a course was held in Cluj, Romania, mainly aimed at the south-east European cancer registries, and 39 participants (plus two observers) from Bulgaria, Cyprus, Romania, Serbia and Montenegro, and Turkey attended. The course organizer was Daniela Coza, of the Institute of Oncology in Cluj.
Courses on statistical analysis methods have been held annually in Lyon since 1997. The theme in 2002 was geographical analysis methods (course director: Eero Pukkala, Helsinki, Finland). It was attended by 28 participants from 16 European countries and two observers from Canada and Colombia. In 2003, the theme of the course was time trends analysis (course organizer: Freddie Bray, IARC). Twenty-nine participants (and five observers) from 18 countries attended.
Five courses on ICD-O coding were held: in the UK (London, February 2002), Spain (Granada, July 2002), Germany (Stuttgart, April 2003), Italy (Naples, April 2003) and Norway (Oslo, September 2003). The faculty consisted of April Fritz (NCI, Bethesda, USA) and Sharon Whelan (IARC). Paola Pisani (IARC) was in charge of the course in Naples.
Courses on the use of the new EUROCIM software (version 4.0) were held in Spain (Talavera de la Reina, April 2002) and Italy (Trieste, July 2002). The organizer of both courses was Freddie Bray (IARC). The course in Spain was attended by 20 participants from Spanish registries, while the course in Trieste was attended by 16 participants mainly from Italy, but also from Croatia, Norway, Slovenia, Sweden and Yugoslavia.
The first course on automated cancer registration, organized in Lyon in July 2003, was attended by 23 participants from 11 countries. The course organizer was Lorenzo Simonato, of the University of Padua, Italy.

CanReg4/ICD-O-3 courses
Cancer registrars using the registry software CanReg (see Section 1.1) were trained in the use of the new CanReg4

Figure 62. Summer school on cancer registration and applications in epidemiology, Lyon, May 2003

program and of ICD-O-3. During 2002–03, courses were held in Thailand (for south-east Asian registries), Lyon (one for registries in English-speaking Africa and one for those in French-speaking Africa), Saudi Arabia (for the Middle East), Ecuador (for Latin America), China, Tunisia (for north African registries), the Republic of Korea, India and the Philippines. The courses were financed by the US National Cancer Institute, the UICC, the Regional Offices of WHO (especially AFRO), IACR, IARC and IAEA.

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 15th EEPE course, held on 24 June–12 July 2002, was attended by 88 students from 19 countries. The 16th course was held on 23 June–11 July 2003, attended by 93 participants from 11 countries. The course director was Rodolfo Saracci, from IARC and the National Research Council in Pisa, Italy.

Figure 63. CanReg-4/ICD-O-3 training course in Seoul (Republic of Korea)

Cancer genetics courses

These courses provide training in genetics relevant to cancer prevention, using an international approach and based on the experience of cancer genetic clinics. The 7th IARC–Menarini course in cancer genetics held in Bertinoro di Romagna, Forli, Italy, on 28 August–1 September 2002, attracted 63 mainly European participants. The course directors were Giovanni Romeo (Bologna) and Peter Devilee (Leiden). The 8th IARC–Menarini course, also in Bertinoro di Romagna, was held on 5–9 September 2003. It was directed by Peter Devilee (Leiden), Pier-Luigi Lollini (Bologna) and Giovanni Romeo (Bologna) and a total of 50 students attended.

Biostatistics and bioinformatics

Two half-day courses were organized by Emmanuel Lazaridis (IARC) during the Annual Meeting of the American Statistical Association in August 2002, on statistical methods for microarray studies and on Molecular biology and bioinformatics studies for analysts.

IARC Technical Transfer Awards

Promising participants are selected during IARC courses and invited to spend a period of several months in one of IARC's units. The stay usually leads to a long-lasting collaboration between IARC and the home institute. Two awards were made in 2002, to Raika Durusoy and Vladimir Drozdovitch. Raika Durusoy, from the Ege University of Izmir, participated in the cancer epidemiology course held in Izmir, Turkey, in 2002, and worked subsequently in the Unit of Environmental Cancer Epidemiology. Vladimir Drozdovitch, selected at the international course on radiation and cancer in Lyon in June 2002, worked in the Unit of Radiation and Cancer. Dr Veena Ganesh Kamath, a participant at the international course on cancer epidemiology in Trivandrum, received an award in 2003, to work in the Unit of Descriptive Epidemiology from April to June 2004.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

Scientific Council
Chairman
Dr L.K. Borysiewicz

Governing Council
Chairman
Dr J. Larivière

Director-General, WHO
Dr G.H. Brundtland
Dr J.-W. Lee (from July 2003)

Director
Dr P. Kleihues

Research Units

Carcinogen identification and evaluation

Dr V.J. Cogliano

Chemoprevention

Dr H. Vainio

Descriptive epidemiology

Dr D.M. Parkin

Environmental cancer epidemiology

Dr P. Boffetta

Epidemiology for cancer prevention

Dr A.J. Sasco

Field and intervention studies

Dr S. Franceschi

Genetic cancer epidemiology

Dr D.E. Goldgar

Genetic cancer susceptibility

Dr S.V. Tavtigian

Infection and cancer

Dr M. Tommasino

Molecular pathology

Dr H. Ohgaki

Nutrition and cancer

Dr E. Riboli

Radiation and cancer

Dr E. Cardis

Research Groups

Genome analysis

Dr F. Canzian

Hormones and cancer

Dr R. Kaaks

DNA repair

Dr J. Hall

Research Services

Communications

Dr N. Gaudin

Library

S. Grant

Computer services

M. Smans

Administration and Finance

Director, Administration and finance

V. Hay

Budget and finance

R. Thomas

Personnel

R. Alloin

Administrative services

G. Guillerminet

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 2003. 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

Visiting scientist
Dr B.W. Stewart, Australia

Administrative assistant
Ms E. Rivière

Secretary
Ms C. Bassier

P. Kleihues, P. Boyle

Biostatistics and Bioinformatics

Chief
Dr E. Lazaridis

Trainee
Ms G. Suchet

Technical assistance
Mr S. Cuber

Secretaries
Ms L. Marnat
Ms S. Millon

Rationale

Technological advances and the expanding global reach of IARC research programmes are leading to fundamental shifts in the conduct of molecular biology studies, epidemiological research and cancer control programmes. Automated laboratories are generating ever greater quantities of data. The regular use of large genomic databases and molecular modelling programs in biological research is becoming commonplace. The analysis of complex interactions between biology and environment requires sophisticated data collection, data management and computational solutions. Problems ranging from the management and analysis of laboratory data in-house to the conduct of surveys in distant parts of the world pose major analytic and informatic challenges.

Objectives

The Unit, created in 2002, seeks to facilitate the IARC research programme by investigating, developing and deploying state-of-the-art and visionary informatics, analysis and communications methods and tools. The Unit provides assistance in areas of mathematics, statistics and computer science, to identify and address common informatics and analytical needs of cancer research scientists. It carries out demonstration studies with collaborating units in three major areas of expertise: biostatistics, bioinformatics including computational biology, and web services. Demonstration studies that show promise are then refined for use across related studies or various units. The Unit organizes and participates in training and scientific outreach programmes locally and internationally.

Selected publications

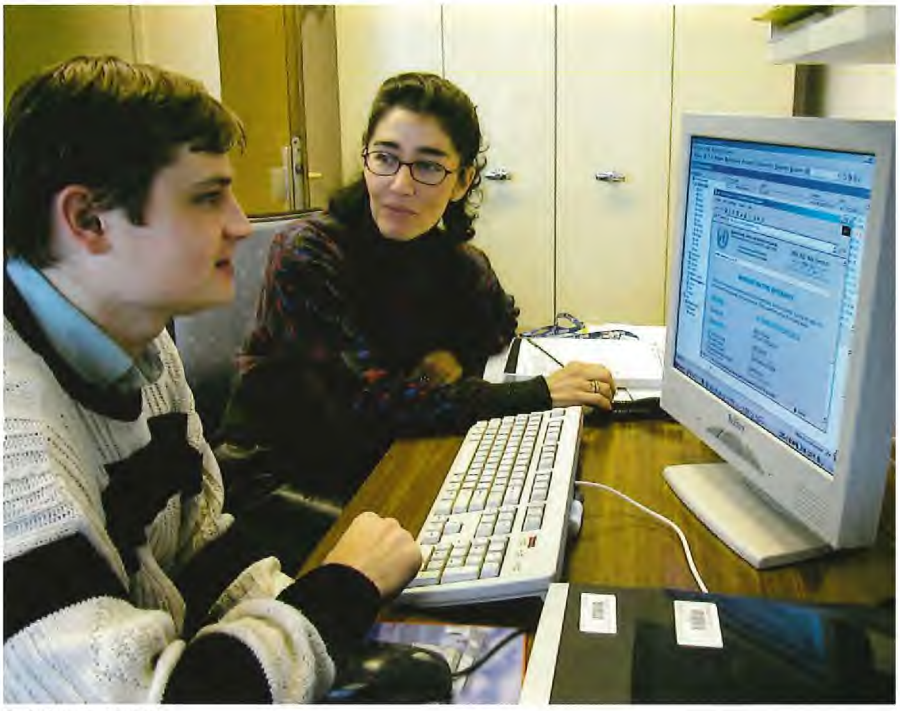
Bloom GC, Gieser P, Lazaridis EN (2002) Linking image quantitation and data analysis. *Methods in Molecular Biology: Biostatistical Methods*, **184**, 15–27

Gieser P, Bloom GC, Lazaridis EN (2002) Introduction to microarray experimentation and analysis. *Methods in Molecular Biology: Biostatistical Methods*, **184**, 29–49

Lazaridis EN, Bloom GC (2002) Statistical contributions to molecular biology. *Methods in Molecular Biology: Biostatistical Methods*, **184**, 1–14

Lazaridis EN, Sinibaldi D, Bloom G, Mane S, Jove J (2002) A simple method to improve probe set estimates from oligonucleotide arrays. *Math. Biosci.*, **176**, 53–58

Lazaridis EN, Szabo A, Yakovlev A (2002) Statistical research in molecular biology: some thoughts and recommendations. *Math. Biosci.*, **176**, i



S. Cuber, L. Marnat

Carcinogen Identification and Evaluation

Chief of Unit
Dr V.J. Cogliano
Dr J. Rice

Scientists
Dr R.A. Baan
Dr C. Cohet
Dr F. El-Ghissassi
Dr Y. Grosse
Dr N. Mironov
Ms C. Partensky
Dr B. Secretan
Dr K. Straif
Dr E. Suonio

Visiting scientist
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Technical assistance
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Ms M. Lézère
Ms J. Mitchell

Secretaries
Ms E. Perez
Ms M. Mainaud
Ms Z. Schneider

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 *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, which have 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.

Selected publications

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 80, *Non-ionizing Radiation*, Part 1: *Static and Extremely Low Frequency Electric and Magnetic Fields*; Vol. 81, *Man-made Vitreous Fibres*; Vol. 82, *Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*

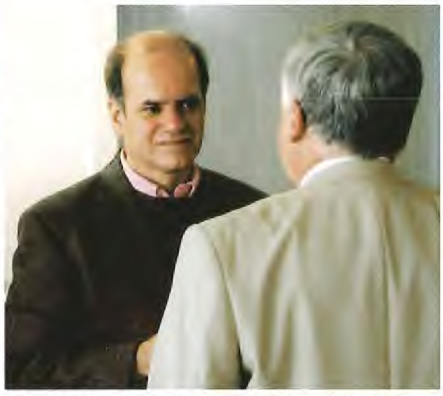
Rice JM, Wilbourn JD (2000) Tumors of the nervous system in carcinogenic hazard identification. *Toxicol. Pathol.*, **28**, 202–214

Rice JM, Boffetta P (2001) 1,3-Butadiene, isoprene and chloroprene: reviews by the IARC monographs programme, outstanding issues, and research priorities in epidemiology. *Chem. Biol. Interact.*, **135–136**, 11–26

Sun Y, Taeger D, Weiland SK, Keil U, Straif K. (2003) Job titles and work areas as surrogate indicators of occupational exposure. *Epidemiology*, **14**, 361–377

IARC Working Group (2003), *Predictive Value of Rodent Forestomach and Gastric Neuroendocrine Tumours in Evaluating Carcinogenic Risks to Humans* (IARC Technical Publications No. 39)

B. Secretan, R.A. Baan



V.J. Cogliano, in discussion with his predecessor

Chemoprevention

Chief of Unit
Dr H. Vainio

Scientist
Dr F. Bianchini

Visiting scientist
Dr S. Verma, Canada

Technical assistance
Ms A. Rivoire

Secretary
Ms J. Thévenoux

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.

H. Vainio

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.

Selected publications

Vainio H, Miller AB (2003) Primary and secondary prevention in colorectal cancer. *Acta Oncologica* (in press)

Bianchini F, Vainio H (2003) Wine and resveratrol: mechanisms of cancer prevention? *Eur. J. Cancer Prev.*, **12**, 417–425

Bianchini F, Kaaks R & Vainio H (2002) Overweight, obesity and cancer prevention. *Lancet, Oncol.*, **3**, 565–574

Vainio H (2002) The need for preventive drugs and vaccines in global cancer control: a challenge for public health and for industry. *Toxicol. Ind. Health*, **18**, 84–90

Bianchini F, Vainio H (2001) *Allium* vegetables and organosulfur compounds: do they help prevent cancer? *Environ. Health Perspect.*, **109**, 893–902

Descriptive Epidemiology

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Ms I. Battaglia
Ms E. Bayle
Ms O. Bouvy
Ms C. Déchaux
Ms P. Dégoulange
Ms S. Dunderdale
Ms I. Haeve-Emery
Ms S. Haver-Legros
Ms S. Sibert-Dardenne

Rationale

Descriptive epidemiology makes use of existing information systems to study the risk of cancer – in terms of incidence, mortality or prevalence – in relation to the characteristics of individuals or their environment. The aim is to help in the understanding of the causes of cancer, and their relative importance to the burden of the disease in different populations. This permits the planning of rational cancer control programmes and the evaluation of their effectiveness. In addition, the study of cancer survival provides information on the consequences of a cancer diagnosis in terms of illness and risk of death.

R. Sankaranarayanan, E. Bayle, delivering a nitrous oxide cylinder and cryotherapy equipment in Vientiane, Lao People's Democratic Republic

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 activities is in 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 – are also being evaluated.

Selected publications

Basu P, Sankaranarayanan R, Mandal R, Roy C, Das P, Choudhury D, Datta K, Karamakar S, Tsu V, Chakrabarti RN, Siddiqi M, Calcutta Cervical Neoplasia Early Detection Study (CEDS) Group (2000) Evaluation of down-staging in the detection of cervical neoplasia in Kolkata, India. *Int. J. Cancer*, **100**, 92–96

Parkin DM, Bray F, Devesa S (2001) Cancer burden in the year 2000: the global picture. *Eur. J. Cancer*, **37**, S4–S66

Vizcaino AP, Moreno V, Lambert R, Parkin DM (2002) Time trends incidence of both major histological types of oesophageal carcinomas in selected countries, 1973–75. *Int. J. Cancer*, **99**, 860–868

Parkin DM, Ferlay J, Hamdi-Chérif M, Sitas F, Thomas JO, Wabinga H, Whelan SL (eds) (2003) *Cancer in Africa: Epidemiology and Prevention* (IARC Scientific Publications No. 153), Lyon, IARCPress

Sankaranarayanan R, Wesley R, Thara S, Dhabad N, Chandralekha B, Sebastian P, Chithrathara K, Parkin DM, Nair MK (2003) Test characteristics of visual inspection with 4% acetic acid (VIA) and Lugol's iodine (VILI) in cervical cancer screenin in Kerala, India. *Int. J. Cancer*, **106**, 404–408

DNA Repair

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Technical assistance
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Secretary
Ms M. Wrisez

Rationale
Mutations in genes encoding proteins involved in the detection and repair of DNA damage are associated with cancer-prone conditions, such as ataxia telangiectasia (AT) and Nijmegen breakage syndrome. The presence of variants in such genes also influences cancer risk, with a number of single-nucleotide polymorphisms (SNPs) being associated with increased risk in the general population. Molecular analyses of these variants will provide valuable insights into how the expression and physiological functions of these proteins are modified and in particular their role in the cellular response to ionizing radiation and the risk of developing radiation sensitivity seen in some cancer patients after radiotherapy.

Objectives
The main objectives of the Group are to:
1. determine genotype/phenotype relationships using a variety of biological endpoints in carriers of *ATM* variants in order to address the basis of the increased cancer risk, in particular for breast and prostate cancer, found in association studies and AT families.
2. assess the role of variants in other DNA damage detection and repair proteins in the cellular response to ionizing radiation and increased cancer risk.
3. examine the expression profiles of such proteins in breast and prostate tumours and investigate the underlying molecular mechanisms that control variations in expression profiles.

Selected publications

Fernet M, Angèle S, Dörk T, Hall J (2003) Variation in radiation-induced apoptosis in ataxia telangiectasia lymphoblastoid cell lines. *Int. J. Radiat. Biol.*, **79**, 193–202

Mauget-Faÿsse M, Vuillaume M, Quaranta M, Moullan N, Angèle S, Friesen MD, Hall J (2003) Idiopathic and radiation induced ocular telangiectasias: the involvement of the ATM gene. Invest. *Ophthalmol. Visual Sci.*, **44**, 3257–3262

Angèle S, Treilleux I, Brémond A, Tanière P, Hall J (2003) Altered expression of DNA double-strand break detection and repair proteins in breast carcinomas. *Histopathology* (in press)

Moullan N, Cox DG, Angèle S, Romestaing P, Gérard J-P, Hall J (2003) Polymorphisms in the DNA repair gene XRCC1, breast cancer risk and response to radiotherapy. *Cancer Epidemiol. Biomarkers Prevention* (in press)

Angèle S, Romestaing P, Moullan N, Vuillaume M, Chapot B, Friesen M, Jongmans W, Cox DG, Pisani P, Gérard JP, Hall J. (2003) ATM haplotypes and cellular response to DNA damage: association with breast cancer risk and clinical radiosensitivity. *Cancer Res.* (in press)

B. Chapot, M. Fernet, N. Moullan

Endogenous Cancer Risk Factors

Chief of Unit
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Dr T. Sawa

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Dr K. Fukunaga, Japan
Dr R. Fukunaga, Japan
Professor H.F. Mower, USA
Dr S. Ohnishi, Japan
Dr T. Suzuki, Japan
Dr T. Takahashi, France
Dr M. Tatemichi, Japan
Dr H. Tazawa, Japan
Dr S. Wada, Japan
Dr R. Wang, China
Dr R. Yoshida, Japan

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Mr N. Baratin
Ms C. Josserand
Ms A. Lin
Ms M. Mounawar
Ms J. Olliver

Technical assistance
Ms I. Gilibert

Secretary
Ms P. Collard

Rationale
Chronic inflammation caused by biological, chemical and physical factors has been associated with increased risk of human cancer at various sites. Inflamed tissues can generate endogenous risk factors that may contribute to the development of cancer. These factors include production of reactive species of oxygen, nitrogen and halogens that can damage DNA, RNA, lipids, and proteins, leading to increased mutations and altered functions of enzymes and proteins and thus contributing to the multistage process of carcinogenesis.

Rear: N. Baratin, S. Baflast, I. Gilibert, T. Takahashi, M. Tatemichi
Front: P. Collard, A. Barbin, S. Wada, H. Ohshima, S. Ohnishi, T. Sawa, R. Wang, H. Tazawa

Objectives
The Unit studies the role of chronic inflammation in carcinogenesis at the molecular and cellular levels and in experimental animals. It also characterizes structural and functional modifications of nucleic acids and proteins by reactive oxygen, nitrogen and halogen species and by aldehydes derived from lipid peroxidation and evaluates their usefulness as biomarkers of cancer risk in animal models and human samples. Levels of oxidative damage are correlated with cancer risk in humans, particularly in relation to genetic polymorphisms of enzymes involved in the production of oxidants and defence against oxidative damage. Biomarkers are also measured to evaluate the efficacy of prevention trials with various agents.

Selected publications

Barbin A, Ohgaki H, Nakamura J, Kurrer M, Kleihues P, Swenberg JA (2003) Endogenous deoxyribonucleic acid (DNA) damage in human tissues: a comparison of ethenobases with aldehydic DNA lesions. *Cancer Epidemiol. Biomark. Prev.*, **12**, 1241–1247

Barbin A, Wang R, O'Connor PJ, Elder RH (2003) Increased formation and persistence of 1,N^6-ethenoadenine in DNA is not associated with higher susceptibility to carcinogenesis in alkylpurine-DNA-*N*-glycosylase knockout mice treated with vinyl carbamate. *Cancer Res.*, **63**, 7699–7703

Masuda M, Nishino H, Ohshima H (2002) Formation of 8-nitroguanosine in cellular RNA as a biomarker of exposure to reactive nitrogen species. *Chem.-Biol. Interact.*, **139**, 187–197

Ohshima H, Tatemichi M, Sawa T (2003) Chemical basis of inflammation-induced carcinogenesis. *Arch. Biochem. Biophys.*, **417**, 3–11

Suzuki T, Masuda M, Friesen MD, Fenet B, Ohshima H (2002) Novel products generated from 2'-deoxyguanosine by hypochlorous acid or a myeloperoxidase-H_2O_2-Cl^- system: identification of diimino-imidazole and amino-imidazolone nucleosides. *Nucleic Acids Res.*, **30**, 2555–2564

Environmental Cancer Epidemiology

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Dr R. Durusoy, Turkey
Dr M. Saadatian-Elahi, France
Mr A. Fazeltabar Malekshah
Dr T. Fletcher, UK
Dr M. Hashibe, USA
Dr J. Hunt, USA
Dr F. Islami, Iran
Dr S. Lewis, UK
Dr A. 't Mannetje, Netherlands
Dr D. Marchioni, Brazil
Mr D. Maximovitch
Dr B. Reckzeh, Germany
Dr S. Sartor, Brazil
Dr V. Sewram, South Africa
Dr O. Shangina, Russian Federation
Dr M. Shen, China
Dr W. Sobala, Poland
Dr K. Soldan, UK
Dr O. Van der Hel, Netherlands
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Ms S. Guillonneau
Ms R. Hung
Ms G. Scelo
Ms N. Travier

Trainees
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Ms N. Druguet
Ms S. Gros

Technical assistance
Mr F. Deloche
Mr G. Ferro
Dr O. Kelm (courses)
Ms A. Meunier

Secretaries
Ms S. Fayolle
Ms M. Geesink

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.

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 that integrate molecular biology and genetic methods in a multidisciplinary approach.

P. Brennan, R. Hung

Selected publications

Korte JE, Brennan P, Henley SJ, Boffetta P (2002) Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk. *Am. J. Epidemiol.*, **155**, 496–506

Brennan P, Lewis S, Hashibe M, Bell DA, Boffetta P, Bouchardy C, Caporaso N, Chen C, Coutelle C, Diehl SR, Hayes RB, Olshan AF, Schwartz SM, Sturgis E, Wei Q, Zavras AI, Benhamou S (2003) Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer – a HuGE review. *Am. J. Epidemiol.* (in press)

Boffetta P, Ye W, Boman G, Nyrén, O (2002) Lung cancer risk in a population-based cohort of patients hospitalized for asthma in Sweden. *Eur. Respir. J.*, **19**, 127–133

Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V, Varghese C, Boffetta P (2003) Independent and combined effects of tobacco smoking, chewing, and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int. J. Cancer*, **105**, 681–686

Kjaerheim K, Boffetta P, Hansen J, Cherrie J, Chang-Claude J, Eilber U, Ferro G, Guldner K, Olsen JH, Plato N, Proud L, Saracci R, Westerholm P, Andersen A (2002) Lung cancer among rock and slag wool production workers. *Epidemiology*, **13**, 445–453

Epidemiology for Cancer Prevention

Chief of Unit
Dr A.J. Sasco
(on secondment from INSERM)

Visiting scientists
Ms C.I. Cann, USA
Dr V. Henriques-Verjat, France
Dr E. Iacovou, Cyprus
Dr M.-K. Lim, Republic of Korea
Dr R. Little, USA
Dr G.P. McMillan, USA
Dr R. Merrill, USA
Dr P. Renaudier, France
Dr S. Yu, China

Students
Mr J. Berthiller
Mr H. Besson
Ms M. Levrier
Ms E. Martin
Ms A. Ricci
Ms C. Suget

Trainees
Ms P. Medina
Ms A. Olsson
Ms A. Pochelon

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, notably tobacco smoking, or intervening in the carcinogenic process in particular by pharmacoprevention, and secondary prevention or screening.

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 lung cancer in northern Africa, and evaluative studies measuring the impact of health education and legislation on smoking and other health-related behaviours.

Selected publications

Sasco AJ, Merrill RM, Dari I, Benhaïm-Luzon V, Carriot F, Cann CI, Bartal M (2002) A case-control study of lung cancer in Casablanca, Morocco. *Cancer Causes Control*, **13**, 609–616

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Rachet B, Abrahamowicz M, Sasco AJ, Siemiatycki J (2003) Estimating the distribution of lag in the effect of short-term exposures and interventions: adaptation of a non-parametric regression spline model. *Stat. Med.*, **22**, 2335–2363

Besson H, Renaudier P, Merrill RM, Coiffier B, Sebban C, Fabry J, Trepo C, Sasco AJ (2003) Smoking and non-Hodgkin's lymphoma: a case-control study in the Rhône-Alpes region of France. *Cancer Causes Control*, **14**, 381–389

IARC staff and national represenatatives at Worksafe meeting, IARC, May 2000 (see page 25).
Left to right: H. Wennborg (Sweden), D. Vecchio (Italy), M. Renaud, A.J. Sasco, V. Benhaïm-Luzon, G. Viano (Italy), A. Desideri (Italy), (in front) A. Olsson, L. Isotalo (Italy), M. González (Spain), I. Laamanen (Finland)

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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.

Selected publications

Franceschi S, Castellsagué X, Dal Maso L, Smith JS, Plummer M, Ngelangel C, Chichareon S, Eluf-Neto J, Shah KV, Snijders PJF, Meijer CJLM, Bosch FX, Muñoz N (2002) Prevalence and determinants of human papillomavirus genital infection in men. *Br. J. Cancer,* **86**, 705–711

Moreno V, Bosch FX, Muñoz N, Meijer CJLM, Shah KV, Walboomers JMM, Herrero R, Franceschi S for the IARC Multicentric Cervical Cancer Study Group (2002) Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multi-centric case-control study. *Lancet,* **359**, 1085–1092

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Shin HR, Lee DH, Herrero R, Smith J, Vaccarella S, Hong SH, Jung KY, Kim HH, Park UD, Cha HS, Park S, Muñoz N, Snijders, PJF, Meijer CJLM, Coursaget P, Franceschi S (2003) Prevalence of human papillomavirus infection in women in Busan, South Korea. *Int. J. Cancer,* **103**, 413–421

Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S (2003) Human papillomavirus in invasive cervical cancer worldwide: a meta-analysis. *Br. J. Cancer,* **88**, 63–73

S. Franceschi, with Drs Hai-Rim Shin and Keun Young Yoo and collaborators, visiting Haman County, Republic of Korea, an area of high risk for liver cancer

A. Kreimer, G. Randi, H. Lorenzen-Augros, M. Dai

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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.


U. Cortes, W.K. Min, V. Petrilli, S. Patnaik

Selected publications

Dubina MV, Iatckii NA, Popov DE, Vasil'ev SV, Krutovskikh VA (2002) Connexin 43, but not connexin 32, is mutated at advanced stages of human sporadic colon cancer. *Oncogene*, **21**, 4992–4996

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Kanai M, Tong W-M, Sugihara E, Wang Z-Q, Fukasawa K, Miwa M (2003) Involvement of poly(ADP-ribose) polymerase 1 and poly(ADP-ribosyl)ation in regulation of centrosome function. *Mol. Cell. Biol.*, **23**, 2451–2462

Bertolino P, Tong W-M, Herrera PL, Casse H, Zhang C-X, Wang Z-Q (2003) Pancreatic β-cell-specific ablation of the multiple endocrine neoplasia type 1 (MEN1) gene causes full penetrance of insulinoma development in mice. *Cancer Res*, **63**, 4836–4841

Dumon-Jones V, Frappart P-O, Tong W-M, Sajithal G, Hulla W, Schmid G, Herceg Z, Digweed M, Wang Z-Q (2003) *Nbn* heterozygosity renders mice susceptible to tumor formation and ionizing radiation-induced tumorigenesis. *Cancer Res.*, **63**, 7263–7269

Genetic Cancer Epidemiology

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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 at are particularly high risk for developing cancer when exposed to specific carcinogens.

Objectives
The goals of the Unit are:
1. 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 and to examine the interaction of genes with specific known environmental factors;
2. 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 or genetic factors;
3. to develop a comprehensive model for evaluation of cancer causality of DNA sequence variants of unknown clinical significance in cancer genes and to collect all relevant data for implementing and testing this model.
4. to assess the contribution of variation in both specific cancer predisposition genes and overall genetic/familial contribution to cancer incidence in the developing world;
5. to develop necessary statistical and computational tools for the genetic analysis of complex traits.

M. Corbex, D. Thompson, M. Jalbout

Selected publications
Thompson D, Easton DF, Goldgar DE (2003) A full-likelihood method for the evaluation of causality of sequence variants in family data. *Am. J. Human Genet.*, **73**, 652–655

Thompson D, Szabo C, Mangion J, Oldenburg R, Odefrey F, Seal S, Barfoot R, Kroeze-Jansema K, Teare D, Renard H, KConFab Consortium, Mann G, Hopper JL, Buys S, Andrulis I, Senie R, Daly M, West D, Ostrander E, Offit K, Peretz T, Osario A, Benitez J, Nathanson K, Sinilnikova O, Olàh E, Bignon Y-J, Ruiz P, Badzioch M, Vasen H, Futreal A, Phelan C, Narod S, Lynch HT, Ponder B, Eeles R, Meijers-Heijboer H, Stoppa-Lyonnet D, Couch F, Eccles D, Evans G, Chang-Claude J, Lenoir G, Weber B, Devilee P, Easton DF, Goldgar DE, Stratton MR (2002). Evaluation of linkage of breast cancer to the putative BRCA3 locus on chromosome 13q21 in 128 multiple case families from the International BRCAX Linkage Consortium. *Proc. Natl Acad. Sci. USA*, **99**, 827–831

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Lesueur F, Corbex M, McKay JD, Lima J, Soares P, Griseri P, Burgess J, Ceccherini I, Landolfi S, Papotti M, Amorim A, Goldgar DE, Romeo G (2002) Specific haplotypes of the RET proto-oncogene are over-represented in patients with sporadic papillary thyroid carcinoma. *J. Med. Genet.*, **39**, 260–265

Ginolhac SM, Gad S, Corbex M, Bressac-de-Paillerets B, Chompret A, Bignon YJ, Peyrat JP, Fournier J, Lasset C, Giraud S, Muller D, Fricker JP, Hardouin A, Berthet P, Maugard C, Nogues C, Lidereau R, Longy M, Olschwang S, Toulas C, Guimbaud R, Yannoukakos D, Szabo C, Durocher F, Moisan AM, Simard J, Mazoyer S, Lynch HT, Goldgar D, Stoppa-Lyonnet D, Lenoir GM, Sinilnikova OM (2003). BRCA1 wild-type allele modifies risk of ovarian cancer in carriers of BRCA1 germ-line mutations. *Cancer Epidemiol. Biomarkers Prev.*, **12**, 90–95

Genetic Cancer Susceptibility

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Rationale
One of the strongest risk factors for breast cancer, colon cancer or prostate cancer is family history. It appears that about 20–40% of the population risk for these three cancers is genetic, but high-risk mutations in known susceptibiity genes, such as *TP53*, *PTEN*, *APC*, *MLH1*, *MSH2*, *BRCA1*, *BRCA2*, seem to account for only about 5% of breast cancer and colon cancer, and a much smaller fraction of prostate cancer. Thus over 75% of the genetic basis of these three cancers remains to be explained. In the long run, one would hope that, just as discovery of the known high-risk susceptibility genes has led, in many cases, to effective strategies for reducing risk in carriers, understanding the majority of the genetic risk of these diseases will eventually lead to more widely applicable risk-reduction strategies.

C. Li, S. Pauly

Objectives
Research projects are being set up to ascertain the fractions of the genetic risk of breast cancer, colon cancer and prostate cancer that are explained by genes harbouring as yet unidentified rare but high-risk sequence variants, by more common modest-risk variants or by less common (or rare) modest-risk variants. The initial goal is to develop an automated, high-throughput laboratory system that supports both genotyping and sequence variant discovery.

Selected publications

Ferrand V, Li C, Romeo G, Yin L (2003) Absence of SLAM mutations in EBV-associated lymphoproliferative disease patients. *J. Med. Virol.*, **70**, 131–136

Yin L, Al-Alem U, Liang J, Tong W-M, Li C, Badiali M, Medard J-J, Sumegi J, Wang Z-Q, Romeo G (2003) Mice deficient in the X-linked lymphoproliferative disease gene *sap* exhibit increased susceptibility to murine gamma-herpesvirus-68 and hypo-gammaglobulinemia. *J. Med. Virol.*, **71**, 446–455

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Genome Analysis

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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.

Selected publications

Cox D, Boillot C, Canzian F (2001) Data mining: efficiency of using sequence databases for polymorphism discovery. *Hum. Mutat.*, **17**, 141–150

Gemignani F, Landi S, Vivant F, Zienolddiny S, Brennan P, Canzian F (2002) A catalogue of polymorphisms related to xenobiotic metabolism and cancer susceptibility. *Pharmacogenetics*, **12**, 459–463

Landi S, Moreno V, Gioia-Patricola L, Guino E, Navarro M, de Oca J, Capella G, Canzian F for the Bellvitge Colorectal Cancer Study Group (2003) Association of common polymorphisms in inflammatory genes interleukin (IL)6, IL8, tumor necrosis factor alpha, NFKB1, and peroxisome proliferator-activated receptor gamma with colorectal cancer. *Cancer Res.*, **63**, 3560–3566

Landi S, Gemignani F, Gioia-Patricola L, Chabrier A, Canzian F (2003) Evaluation of a micro-array for genotyping polymorphisms related to xenobiotic metabolism and DNA repair. *Biotechniques*, **35**, 816–827

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Hormones and Cancer

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Rationale
Hormones and growth factors are central to the regulation of cell proliferation, differentiation and apoptosis, and can have a key role in tumour promotion and growth. Epidemiological evidence suggests that alterations in sex steroid metabolism may be associated with risk of cancers of the breast, endometrium, ovary and prostate. In addition, risk may be related to chronic hyperinsulinaemia and alterations in the insulin-like growth factor-I (IGF-I) system. However, precise relationships of cancer risk with alterations in hormone metabolism remain to be determined.

Objectives
The main objective of the Hormones and Cancer Group is to conduct epidemiological studies on relationships between measures of endogenous hormone levels and cancer risk. In addition, we study the effects of possible genetic and lifestyle (e.g., nutritional) determinants of circulating hormone levels. Key hormones currently under investigation include the sex steroids (androgens, estrogens, progesterone), insulin, insulin-like growth factors, and IGF-binding proteins. The group has its own laboratory, with semi-automated equipment, for the high-throughput analysis of these hormones in blood and urine.

Selected publications

Palmqvist R, Hallmans G, Rinaldi S, Biessy C, Stenling R, Riboli E, Kaaks R (2002) Plasma insulin-like growth factor-I, insulin-like growth factor binding protein-3, and risk of colorectal cancer: a prospective study in northern Sweden. *Gut*, **50**, 642–646

Le Marchand L, Donlon T, Seifried A, Kaaks R, Rinaldi S, Wilkens LR (2002) Association of a common polymorphism in the *hGH-1* gene with colorectal neoplasia. *J. Natl Cancer Inst.*, **94**, 454–460

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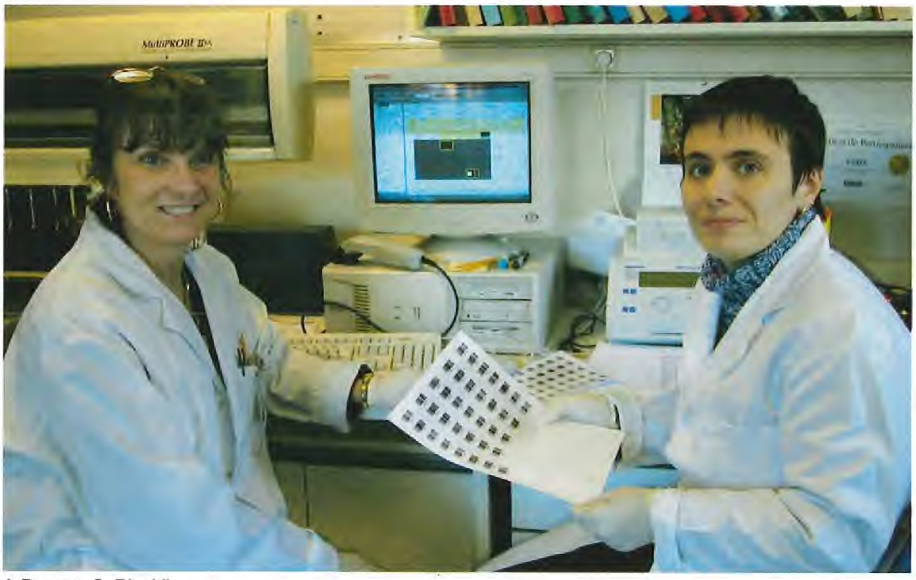
Lukanova A, Lundin E, Micheli A, Akhmedkhanov A, Ferrari P, Levitz M, Rinaldi S, Krogh V, Lenner P, Biessy C, Muti P, Riboli E, Berrino F, Hallmans G, Kaaks R, Toniolo P, Zeleniuch-Jacquotte A (2003) Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. *Int. J. Cancer* (in press)

Zeleniuch-Jacquotte A, Shore RE, Koenig KL, Akhmedkhanov A, Afanasyeva Y, Kato I, Kim MY, Rinaldi S, Kaaks R, Toniolo P (2003) Postmenopausal serum levels of estrogen, androgen, and SHBG and breast cancer: long-term results of a prospective study. *Br. J. Cancer* (in press)



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Infection and Cancer

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Rationale

Some 15–20% of cancers worldwide have been attributed to viral infections, which appear to act to promote carcinogenesis by either (*a*) generating a pathological condition that facilitates the transformation of the host cells; or (*b*) encoding oncoproteins that play a direct role in cellular transformation by altering the regulation of the cell cycle and apoptosis.

Several viruses are now known to be associated with the development of some specific human cancers. However, epidemiological studies suggest the involvement of infective agents in other human malignancies. The establishment of a causal relationship between the presence of specific infective agents and certain types of human cancer represents a key step for the development of novel therapeutic and preventive strategies.

Objectives

The newly established Unit of Infection and Cancer has two principal aims: (1) to establish an association between specific types of human cancer with particular infective agents, and (2) to characterize the cellular events induced by the infective agents and their role in neoplastic transformation. A particular focus is on studies of human papillomaviruses and their possible role in several cancers of epithelial origin.

Selected publications

Zehbe I, Voglino V, Wilander E, Delius H, Marongiu A, Edler L, Klimek F, Andersson S, Tommasino M (2001) p53 codon 72 polymorphism and various HPV 16 E6 genotypes are risk factors for cervical cancer development. *Cancer Res.*, **61**, 608–611

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Malanchi I, Caldeira S, Krützfeldt M, Giarrè M, Alunni-Fabbroni M, Tommasino M (2002). Identification of a novel activity of human papillomavirus type 16 E6 protein in deregulating the G1/S transition. *Oncogene*, **21**, 5665–5672

Caldeira S, Zehbe I, Accardi R, Malanchi I, Dong W, Giarrè M, de Villiers EM, Filotico R, Boukamp P, Tommasino M (2003). The E6 and E7 proteins of the cutaneous human papillomavirus type 38 display transforming properties. *J. Virol.*, **77**, 2195–2206

C. Thomas, C. Gand

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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.

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.

The Unit also supervises the Gambia Hepatitis Intervention Study (see page 94). This study was designed to assess the effectiveness of vaccination against HBV in preventing chronic infection and hepatocellular carcinoma.

Selected publications

Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P (2002) Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene*, **21**, 7435–7451

Pluquet O, North S, Bhoumik A, Dimas K, Ronai Z, Hainaut P (2003) The cytoprotective aminothiol WR1065 activates p53 through a non-genotoxic signaling pathway involving c-Jun N-terminal kinase. *J. Biol. Chem.*, **278**, 11879–11887

Courtois S, Caron de Fromentel C, Hainaut P (2003) p53 protein variants: structural and functional similarities with p63 and p73 isoforms. *Oncogene* (in press)

Olivier M, Goldgar, DE, Sodha N, Ohgaki H, Kleihues P, Hainaut P, Eeles RA (2003) Li Fraumeni and related syndromes: correlation between tumor type, family structure and TP53 genotype. *Cancer Res.*, **63**, 6643–6650

Tonisson N, Zernant J, Kurg A, Pavel H, Slavin G, Roomere H, Meiel A, Hainaut P, Metspalu A. (2002) Evaluating the arrayed primer extension resequencing assay of TP53 tumor suppressor gene. *Proc. Natl Acad. Sci. USA*, **99**, 5503–5508

E. Taranchon, E. Demoraes, S. Seeman

Molecular Pathology

Chief of Unit
Dr H. Ohgaki

Scientist
Dr H. Huang

Visiting scientists
Dr V.J. Amatya, Nepal
Dr N. Baeza, France
Dr Y. Edamoto, Japan
Dr S. Edmunds, UK
Dr S. Horstmann, Germany
Dr P. Maiorka, Brazil
Dr T. Nishikawa, Japan
Dr Y. Okamoto, Japan

Trainees
Mr P. Dessen
Mr B. Jourde

Technical assistance
Ms A.-M. Randon

Secretariat/database management
Mr S. Antoni
Ms S. McLornan
Ms E. Musgrave

Rationale
Carcinogenesis is a multistep process that 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, and histopathologically recognized phenotypes is a reflection of genotypes.

Objectives
The unit focuses on molecular mechanisms involved in the development of human neoplasms, in particular brain tumours, liver cancer and lung cancer. Genetic pathways leading to glioblastoma subtypes have been studied extensively. Current projects address the genetic pathways leading to astrocytic and oligodendroglial gliomas at the population level.

Selected publications

Nakamura M, Watanabe T, Yonekawa Y, Kleihues P, Ohgaki H (2001) Promoter methylation of the DNA repair gene MGMT in astrocytomas is frequently associated with G:C→A:T mutations of the TP53 tumor suppressor gene. *Carcinogenesis*, **22**, 1715–1719

Watanabe T, Nakamura M, Kros JM, Burkhard C, Yonekawa Y, Kleihues P, Ohgaki H (2002) Phenotype versus genotype correlation in oligodendrogliomas and low-grade diffuse astrocytomas. *Acta Neuropathol.*, **103**, 267–275

Baeza N, Masuoka J, Kleihues P, Ohgaki H (2003) AXIN1 mutations but not deletions in medulloblastomas. *Oncogene*, **22**, 632–636

Burkhard C, Di Patre PL, Schüler D, Schüler G, Ysargil MG, Yonekawa Y, Lütolf UM, Kleihues P, Ohgaki H (2003) A population-based study on the incidence and survival rates of patients with pilocytic astrocytoma. *J. Neurosurg.*, **98**, 1170–1174

Edamoto Y, Hara A, Biernat W, Terracciano L, Cathomas G, Riehle HM, Matsuda M, Fujii H, Scoazec JY, Ohgaki H (2003) Alterations of RB1, p53, and Wnt pathways in hepatocellular carcinomas associated with hepatitis C, hepatitis B, and alcoholic liver cirrhosis. *Int. J. Cancer*, **106**, 334–341

T. Nishikawa, preparing tissue microarrays

S. Horstmann

Nutrition and Cancer

Chief of Unit
Dr E. Riboli

Scientists
Dr W. Al-Delaimy
Ms R. Arndt-Charrondiere
Dr G. Davey
Mr M. Fahey
Mr P. Ferrari
Dr M.D. Friesen
Dr N. Slimani

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Dr R. Saracci, Italy
Dr M. van Bakel, Netherlands

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Ms C. Ventura

Trainee
Ms G. Skeie

Technical assistance
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Mr S. Chanlon
Mr T. Cler
Ms S. David
Mr B. Hémon
Mr C. Lallemand
Mr J. Vignat
Ms S. Villar-Michel
Ms B. Vozar

Secretary
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, lifestyle 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.

Selected publications

Saadatian-Elahi M, Toniolo P, Ferrari P, Goudable J, Akhmedkhanov A, Zeleniuch-Jacquotte A, Riboli E (2002) Serum fatty acids and risk of breast cancer in a nested case-control study of the New York University Women's Health Study. *Cancer Epidemiol. Biomarkers Prev.*, **11**, 1353–1360

Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondière UR, Hémon B, Casagrande C, Vignat J, Overvad K, Tjønneland A, Clavel-Chapelon F, Thiébaut A, Wahrendorf J, Boeing H, Trichopoulos D, Trichopoulou A, Vineis P, Palli D, Bueno-de-Mesquita HB, Peeters PHM, Lund E, Engeset D, González CA, Barricarte A, Berglund G, Hallmans G, Day NE, Key TJ, Kaaks R, Saracci R (2002) EPIC: study populations and data collection. *Publ. Health Nutr.*, **5**, 1113–1124

Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G, Kroke A, Trichopoulos D, Trichopoulou A, Lauria C, Bellegotti M, Ocké MC, Peeters PHM, Engeset D, Lund E, Agudo A, Larrañaga N, Mattisson I, Andren CJ, Johansson I, Davey G, Welch AA, Overvad K, Tjønneland A, van Staveren WA, Saracci R, Riboli E (2002) EPIC calibration study: rationale, design and population characteristics. *Publ. Health Nutr.*, **5**, 1125–1145

Norat T, Riboli E (2003) Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur. J. Clin. Nutr.*, **57**, 1–17

Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T, Clavel-Chapelon F, Kesse E, Nieters A, Boeing H, Tjønneland A, Overvad K, Martínez C, Dorronsoro M, González CA, Key TJ, Trichopoulou A, Naska A, Vineis P, Tumino R, Krogh V, Bueno-de-Mesquita HB, Peeters PHM, Berglund G, Hallmans G, Lund E, Skeie G, Kaaks R, Riboli E (2003) Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet* , **361**, 1496–1501

S. Chanlon, C. Lallemand

Radiation and Cancer

Chief of Unit
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Dr I. Deltour
Dr V. Drozdovitch
Dr A. Kesminiene
Dr L. Richardson
Dr M. Vrijheid

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Dr D. McLean, New Zealand
Dr T. Zhunussova, Kazakhstan

Students
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Mr M. Rouch

Trainee
Ms M. Moissonnier

Technical assistance
Ms E. Combalot
Ms N. Encrenaz
Ms J. Hua
Ms H. Tardy
Ms V. Tenet

Secretary
Ms C. Chassin

Rationale

Ionizing radiation is a model carcinogen for risk assessment, and studies of its effects are important for elucidating mechanisms of carcinogenesis. Few data are available on the risk associated with low-dose exposures, 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.

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 basis of radiation protection (ionizing and non-ionizing), and to increase our understanding of biological mechanisms of carcinogenesis.

Selected publications

Kesminiene A, Cardis E, Tenet V, Ivanov VK, Kurtinaitis J, Malakhova I, Stengrevics A, Tekkel M (2002) Studies of cancer risk among Chernobyl liquidators: materials and methods. *J. Radiol. Prot.*, **22**, 137–141

Pearce MS, Cardis E (2001) Depleted uranium – cause for concern or just a good story? [Editorial] *Pediat. Hematol. Oncol.*, **18**, 367–370

Ahlbom A, Cardis E, Green A, Linet M, Savitz D, Swerdlow A (2001) Review of the epidemiological literature on EMF and health. *Environ. Health Perspect.*, **109**, 911–934

Cardis E, Richardson D, Kesminiene A (2001) Radiation risk estimates in the beginning of the 21st century. *Health Phys.*, **80**, 349–361

Cardis E, Amoros E, Kesminiene A, Malakhova IV, Poliakov SM, Piliptsevitch NN, Demidchik EP, Astakhova LN, Ivanov VK, Konogorov AP, Parshkov EP, Tsyb AF (1999) Observed and predicted thyroid cancer incidence following the Chernobyl accident. Evidence for factors influencing susceptibility to radiation induced thyroid cancer. In: Thomas G, Karaoglou A, Williams ED, eds, *Radiation and Thyroid Cancer*, World Scientific Publishing, pp. 395–405

Rear: H. Tardy, M. Vrijheid, T. Zhunussova, E. Combalot, V. Drozdovitch, M. Moissonnier, D. McLean, A. Kesminiene, E. Maceika, V. Tenet
Front: L. Richardson, E. Cardis, C, Chassin, I. Deltour

Computer Services Group

Head of Group
Mr M. Smans

Systems manager
Mr P. Damiecki

Technical assistance
Mr P. Boutarin
Mr C. Jack
Ms B. Kajo

Trainees
Mr M. Boniol
Mr F. Vuong

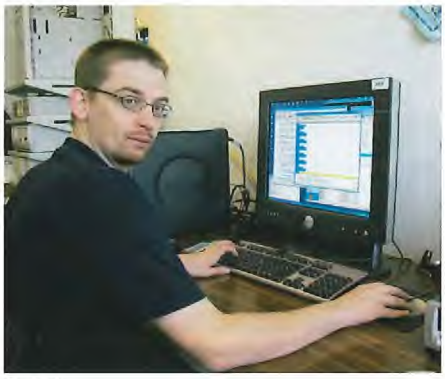
The Computer Services Group manages the framework of central computing at IARC. This includes provision of central services for statistical analysis, database storage and access, file management and communications services, as well as the management of the local area network (LAN) that allows both scientific and administrative users to connect to these services.

Thanks to major funding from the Governing Council Special Fund, a new "Storage Area Network" (SAN) was installed in late 2002 and is being used gradually to transfer data from a collection of servers that the team had been installing and managing over previous years. This important new resource will allow the Agency to cope with the ever-increasing demand for data storage and at the same time improve our ability to recover from potential disasters, since the hardware is now split between the main building and the Latarjet building.

During the biennium, several new applications have been implemented or developed for the Administration and this trend is likely to continue for some time since there is much pressure to harmonize systems in this area across all WHO offices.

The local area network (LAN) is more or less constantly being upgraded, with more segments running at 100 Mb/sec and the introduction of a 'gigabit backbone' at the same time that the SAN was installed. The Agency's link to the Internet via the University of Lyon (Institut National de Physique Nucléaire et de Physique des Particules; IN2P3) has been upgraded from 128 kb to 2 Mb (a 16-fold increase), which has provided much improved access to our web databases for users outside IARC.

M. Smans, P. Damiecki



C. Jack

Communications

Chief of Unit
Dr N. Gaudin

Senior editor
Dr J. Cheney

Visiting scientists
Dr F. Soylemezoglu, Turkey
Dr W. Biernat, Poland
Dr H. Mattock, UK
Dr R. Millis, UK
Dr N. Napalkov, Russian Federation
Dr L. Roth, USA

Assistants (IARCPress)
Ms S. Cotterell
Ms D. Flint (Washington office)
Ms A. Meneghel
Ms C. Mogenet
Ms S. Söring
Ms S. Thomas

Technical assistance
Ms A. Blum
Mr J. Croibier
Ms C. Goebels
Ms L. Goldman
Ms L. Hunter
Mr F. Kroenert
Mr G. Mollon
Ms P. Rousson-Dia

Trainees
Ms A. Asante
Ms C. Dezutter
Ms I. Forcier
Ms R. Greenfield
Ms V. Meyronein
Ms K. Müller
Mr T. Odin
Ms A. Ohara
Mr S. Sivadier

Secretaries
Ms B. Geoffre
Ms C. Zorian

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.

R. Greenfield, in the IARCPress bookstore


A. Blum, L. Goldman, during layout work for a WHO Classification of Tumours volume on urogenital tract tumours

Library

Librarian
Ms S. Grant
Ms H. Miido

Technical assistance
Ms M. Coudert
Ms L. Ossetian

Trainee
Ms L. Bouanzi

The library continues to provide information and education services to IARC staff, visiting researchers and non-affiliated users. However, the services and technology of the library have changed significantly in the last two years. In 2002, the library initiated the web- and email-based Order Reprints service from the British Library, allowing staff to order journal articles and books that are not in the IARC collection; users receive most articles electronically at their desktops within two or three days.

The coordination of electronic resources with WHO HQ and the UN Libraries Consortium has become an important priority. This coordination is necessary for collection building and development in an era of information proliferation, shrinking library budgets and escalating costs for accessing relevant research information. The availability of electronic information resources to IARC staff increased significantly through access provided by the WHO HQ initiative GIFT (Global Information Full Text) and the UN Libraries Consortium. While a number of print subscriptions have been cancelled in the IARC library, the GIFT initiative supplements the collection by providing access to over 1000 full-text journals, key databases such as Journal Citation Reports and authoritative reference resources such as Oxford Reference Online.

The availability and use of electronic resources increased dramatically and as a result the IARC Library web site has emerged as an important service—an efficient means of keeping users up to date about new information resources and a gateway for delivering library services. The web site has been re-designed. A significant amount of evaluated content has been added and access to the increasing amount of electronic resources available has been facilitated.

Other projects of the Library include: cataloguing of IARC Press publications and WHO documents; scanning reprints of articles written by IARC staff and making these available electronically; optimizing the functionality of the Sydney Plus Library catalogue; weeding the collection; developing seminars and instructional materials for teaching the efficient use of digital information resources; and developing more subject-specific web pages.

L. Bouanzi, S. Grant

Common Laboratory Services

Animal facility

Responsible scientist
Dr Z.-Q. Wang

Veterinary consultant
Dr L. Zenner

Technical assistance
Ms M. Becker
Mr J. Cardia-Lima
Ms M.-P. Cros
Mr R. Dray
Ms D. Galendo
Mr J. Garcia
Ms O. Gaultier-Sabard
Ms E. Moudilou
Mr F. Zeroual

Trainee
Mr L. Desmarthon

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 are a powerful tool for understanding mechanisms of cancer development. In addition, these mice are indispensable models for studying the functions of newly identified genes that confer cancer susceptibility in humans. Instrumentation and facilities in the animal house are in compliance with the European Union guidelines. Records are kept of all experimental studies performed, 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.

J. Garcia, M.-P Cros

Histopathology laboratory

Responsible scientist
Dr H. Ohgaki

Technical assistance
Ms N. Lyandrat

Trainees
Ms C. Carreira
Ms S. Tierrie

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 B. Sylla

Technical assistance
Ms F. Batomen
Ms M. Essertel
Ms N. Farina
Ms M. Maranhao
Ms C. Tchangwo
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.

Safety is an important concern on IARC premises, particularly in laboratories handling potentially hazardous chemical and biological agents. A special committee chaired by Dr. J. Hall regularly reviews all aspects of safety, and periodic exercises on the use of fire extinguishers are held.

Administration and Finance

Director
Ms V. Hay

Administrative assistant
Ms V. Vocanson

Budget and finance

Budget and finance officer
Mr R. Thomas

Finance officer
Ms D. Pantua

Administrative assistants
Mr C. Augros
Ms W. Fevre-Hlaholuk
Ms M. Ongaro

Clerks
Mr P. Binet
Ms F. Florentin
Mr D. Hornez
Ms N. Lamandé
Ms D. Lombardo
Ms F. Roche
Mr. F. Rousset
Ms A. Seguret

Trainees
Ms S. Armand
Mr A. de Campou
Ms C. Fontana

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.

To provide enhanced support to the scientific units, the Agency began several automation projects, including the introduction of a travel and meetings administration system, electronic payments system and computerized grants management system. A study was carried out on the feasibility of budgeting in euro. In September 2003, the Office of Internal Audit and Oversight conducted a Control Self-Assessment course to evaluate the effectiveness of the business processes while minimizing the associated risks.

Human resources

Personnel officer
Ms R. Alloin
Mr G. Mortier

Assistant
Ms E. El Akroud

Clerks
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Ms I. Poncet

Trainees
Ms A. Alenda
Ms H. Lau

Social adviser
Mr H. Paraton

The Personnel Office provides services in the field of human resources and staff development in order to meet the requirements of the Agency's programmes, to ensure efficient recruitment of staff, and administer benefits and entitlements and related services. Several important changes took place during 2002–2003:

A new performance management and development system (PMDS) was introduced for all staff.

In 2003, the Agency moved from a six-grade salary scale to a seven-grade scale for General Service staff. As a result about 30% of general service posts were graded at a higher level. This exercise was done in parallel with a survey of local employers in Lyon and the establishment of a new salary scale.

Staff training courses have been organized on an individual basis as required, and in groups on topics such as office information software packages, scientific writing and registration and certification in animal experimentation.


M. Ongaro, C. Augros


A. Alenda, E. El Akroud

Administrative services

Administrative services officer
Mr G. Guillerminet

Administrative assistant
Ms S. Servat

Support staff
Mr P. Barbieux
Mr M. Bazin
Mr J.-P. Bonnefond
Ms O. Drutel
Mr J.-F. Durand-Gratian
Mr W. Goudard
Ms M. Greenland
Mr M. Javin
Ms R. Kibrisliyan
Ms F. Lelong
Ms G. Lett
Ms M. Marsal
Ms L. Monnerat
Mr L. Ripert

Trainees
Mr D. Benkhaled
Ms M. Dusenberg
Mr E. Mitride
Mr M. Roche-Aborine
Ms F. Wanlin

P. Barbieux, W. Goudard

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.

In the present biennium, some important developments have been the replacement of the hazardous goods lift and the renovation of the heavy duty lift, the creation of laboratories with P2 and P3 safety levels and installation of a cold room on the ninth floor of the tower, and the equipping of third and fourth floors of the Latarjet building

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.

M. Bazin, M. Javin, R. Kibrisliyan

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 17 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 2002-2003, the IARC Governing Council voted a regular budget of US $35.8 million. Of this, 78% 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 2000-01 biennium, extra-budgetary funds constituted approximately 30% of the Agency's overall budget.

PARTICIPATING STATES AND REPRESENTATIVES AT THE FORTY-THIRD SESSION OF THE IARC GOVERNING COUNCIL

9–10 May 2002

United Kingdom of Great Britain and Northern Ireland
Dr D. Dunstan, *Chairperson*
Medical Research Council
London

Dr D. Smith
Medical Research Council
London

Australia
Dr R. Smallwood
Department of Health and Aged Care
Canberra

Mr R. Eckhardt
Department of Health and Aged Care
Canberra

Mr T. Kingdon
Department of Health and Aged Care
Canberra

Belgium
Ms A.-M. Sacré-Bastin
Ministère de la Santé publique
Brussels

Canada
Dr J. Larivière
Health Canada
Ottawa, Ontario

Dr P. Branton
McGill University
Montreal, Quebec

Denmark
Mr I. Knudsen
Danish Veterinary and Food Administration
Søborg

Finland
Professor E. Vartiainen
Finnish National Public Health Institute
Helsinki

France
Mrs C. Feuillet
Direction des Nations Unies et des Organisations Internationales
Paris

Dr A. Pinteaux
Ministère de l'Emploi et de la Solidarité
Paris

Germany
Mr H. Voigtländer
Federal Ministry of Health
Bonn

Italy
Dr F. Belardelli
Istituto Superiore di Sanità
Rome

Japan
Dr H. Imada
Ministry of Health, Labour and Welfare
Tokyo

Dr M. Sakoi, *Vice-Chairman*
Ministry of Health, Labour and Welfare
Tokyo

Dr H. Chimura
National Cancer Centre
Tokyo

Netherlands
Professor D. Kromhout
National Institute for Public Health and the Environment
Bilthoven

Dr J.-W Hartgerink, *Rapporteur*
Ministry of Health, Welfare and Sport
The Hague

Norway
Dr L.E. Hanssen
Norwegian Board of Health
Oslo

Dr B. Mørland
National Centre for Health Technology
Blindern
Oslo

Sweden
Dr C. Hall
Swedish Research Council – Medicine
Stockholm

Switzerland
Dr T. Zeltner
Office Fédéral de la Santé Publique
Bern/Liebefeld

United States of America
Dr J. Harford
National Cancer Institute
Bethesda, MD

Ms A. Blackwood
US Department of State
Washington, DC

World Health Organization
Dr R. Bengoa
Director – Management of Noncommunicable Diseases

Mr A. Ullrich
Programme on Cancer Control

Mr G.-L. Burci
Senior Legal Officer

Ms J. McKeough
Office of Legal Counsel

Observers
Dr L. Borysiewicz
Incoming Chairman, Scientific Council

Dr M. Aguet
Outgoing Chairman, Scientific Council

Dr M. del Carmen Rodriguez Blas
Ministerio de Sanidas y Consumo
Madrid, Spain

Dr L. Denis
UICC Representative

External Auditor
Mr S. Fakie
Auditor-General
Pretoria, South Africa

Mr G. Randall
Office of the Auditor-General
Pretoria, South Africa

Ms J. Englund
Office of the External Audit, WHO, Geneva

FORTY-FOURTH SESSION OF THE IARC GOVERNING COUNCIL

15–16 May 2003

Canada
Dr J. Larivière, *Chairperson*
Health Canada
Ottawa, Ontario

Dr P. Branton
Institut de Recherche sur le Cancer CIHR
Montréal, Québec

Australia
Mr T. Kingdon
Department of Health and Ageing
Canberra ACT

Ms J. Quigley
Department of Health and Ageing
Canberra ACT

Belgium
Ms A.-M. Sacré-Bastin
Ministère fédéral des Affaires sociales, de la Santé publique et de l'Environnement
Brussels

Denmark
Mr I. Knudsen
Danish Veterinary and Food Administration
Søborg

Finland
Dr J. Huttunen
Finnish National Public Health Institute
Helsinki

France
Dr G. Lenoir
Institut Gustave Roussy
Villejuif

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Dr M. Sakoi
Ministry of Health, Labour and Welfare
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Norwegian Board of Health
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Dr B. Mørland
National Centre for Health Technology
Blindern
Oslo

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Minister of Health and Consumer Affairs
Madrid

Sweden
Dr H. Wallberg-Henriksson
Swedish Research Council – Medicine
Stockholm

Switzerland
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Office Fédéral de la Santé publique
Bern/Liebefeld

United Kingdom of Great Britain and Northern Ireland
Dr D. Dunstan
Medical Research Council
London

Dr D. Smith
Medical Research Council
London

United States of America
Dr J. Harford
National Cancer Institute
Bethesda, MD

Ms A. Blackwood
US Department of State
Washington, DC

World Health Organization
Dr G. H. Brundtland
Director-General

Dr R. Bengoa
Director – Management of Noncommunicable Diseases

Dr A. Ullrich
Programme on Cancer Control

Mr G.-L. Burci
Senior Legal Officer

Ms F. Mourain-Schut
Office of the Legal Counsel

Observer
Dr L. Borysiewicz
Chairman, Scientific Council

External Auditor
Mr S. Fakie
Auditor-General
Pretoria, South Africa

Mr G. Randall
Executive Manager, Office of the Auditor-General
Pretoria, South Africa

MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS THIRTY-EIGHTH SESSION

4–6 February 2002

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Institut Suisse de Recherches Expérimentales sur le Cancer
Epalinges-sur-Lausanne
Switzerland

Dr J. Bénichou
CHU de Rouen
Rouen
France

Dr F. Berrino
Istituto Nazionale dei Tumori
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Italy

Dr D. Bootsma
Erasmus University Rotterdam
Rotterdam
The Netherlands

Dr Anne-Lise Børresen-Dale
Institute for Cancer Research
Norwegian Radium Hospital
Montebello
Oslo
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Professor L.K. Borysiewicz (*Vice-Chairman*)
Imperial College School of Medicine
London
United Kingdom

Professor G. G. Giles
Cancer Control Research Institute
Carlton South, Vic.
Australia

Dr K. Hemminki
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Karolinska Institute
Huddinge
Sweden

Dr S. Narod
Women's College Hospital
Toronto, Ontario
Canada

Dr J. Olsen
University of Aarhus
Aarhus
Denmark

Professor J.D. Potter
Fred Hutchinson Cancer Research Center
Seattle, WA
USA

Dr H. Rabes
Universität München
Munich
Germany

Professor H. Van Oyen
Institut d'Hygiène et d'Epidémiologie
Brussels
Belgium

Dr K. Yamaguchi
National Cancer Centre Research Institute
Tokyo
Japan

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Sutton
Surrey UK

Governing Council
Dr D. Dunstan (*Chairman*)
Medical Research Council
London
United Kingdom

Mr I. Knudsen (*Vice-Chairman*)
Danish Veterinary and Food Administration
Søborg

World Health Organization
Dr R. Bengoa
Management of Noncommunicable Diseases

Dr M.C. Sepulveda Bermedo
Programme on Cancer Control

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Dr L. Denis
Oncology Centre Antwerp
Antwerp
Belgium

Observer
Dr T. Philip
Centre Léon Bérard
Lyon

MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS THIRTY-NINTH SESSION

3–5 February 2003

Dr H. Autrup
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Aarhus
Denmark

Dr J. Bénichou
CHU de Rouen
Rouen Cedex
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Dr F. Berrino
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Helsinki
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Munich
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Dr F. van Leeuwen
Netherlands Cancer Institute
Amsterdam
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Professor H. van Oyen
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Shizuoka Cancer Centre
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Dr H. zur Hausen
DKFZ
Heidelberg
Germany

Observer
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Lyon

Meetings and workshops organized by IARC

Ambillikai, India
2–3 May 2002
Training course in cervical cancer screening methods using visual inspection with acetic acid and Lugol's iodine, and treatment of lesions with cryotherapy and LEEP

Athens
15–16 March 2002
EPIC working group on colorectal cancer

Bangalore, India
3–7 March 2003
Workshop on CanReg-4 and ICD-O-3

Bertinoro di Romagna, Italy
28 August–1 September 2002
7th course in cancer genetics

5–9 September 2003
8th course in cancer genetics

Bhaktapur, Nepal
12–14 March 2002
Training course in cervical cancer screening methods using visual inspection with acetic acid and Lugol's iodine, and treatment of lesions with cryotherapy and LEEP

Bridgetown, Barbados
10–14 February 2003
Workshop on CanReg-4 and ICD-O-3

Calcutta, India
11–12 February 2002
Meeting of investigators in IARC studies of lung, laryngeal, hypopharyngeal and breast cancer in South Asia

Chennai, India
3–4 March 2003
Meeting of investigators in IARC studies of lung, laryngeal, hypopharyngeal and breast cancer in South Asia

Cluj, Romania
25–29 August 2003
ENCR course on population-based cancer registration and CanReg-4

Conakry, Guinea
28 September–1 October 2002
Cours sur le dépistage du cancer du col utérin par inspection visuelle après application d'acide acétique et de soluté de Lugol, et sur les traitements par cryothérapie et résection à l'anse diathermique (RAD). Contrôle de qualité en histopathologie. Techniques de laboratoire

Dakar, Senegal
5–8 August 2003
Cours sur le dépistage du cancer du col utérin par inspection visuelle avec soluté de Lugol, acide acétique et colposcopie. Traitement des lésions par cryothérapie et résection à l'anse diathermique (RAD)

Dar es Salaam, Tanzania
20–24 November 2002
Training course in cervical cancer screening methods using visual inspection with acetic acid and Lugol's iodine, and treatment of lesions with cryotherapy and LEEP

Granada, Spain
2–3 July 2002
ICD-O-3 training course

Hat Yai, Thailand
3–5 April 2002
Workshop on CanReg-4 and ICD-O-3

Havana, Cuba
24 March 2003
GRELL steering committee meeting

Heidelberg, Germany
15–16 June 2003
Epilymph-Europe coders workshop

Honolulu, HI, USA
13–20 June 2003
IACR annual meeting

Hyderabad, India
2–5 April 2002
Training course in cervical cancer screening methods using visual inspection with acetic acid and Lugol's iodine

Kannur, India
26–28 May 2003
Course on loop electrosurgical excision treatment for cervical precancers

Lausanne, Switzerland
15 January 2003
Meeting on the Swiss HIV/cancer record linkage study

London, UK
5–6 February 2002
ICD-O-3 training course

Luanda, Angola
5–9 November 2002
Training course in cervical cancer screening methods using visual inspection with acetic acid and Lugol's iodine, and treatment of lesions with cryotherapy and LEEP

Lyon, France
11 January 2002
5ème Journée de Montchat

15–18 January 2002
ENCR course on geographical analyses

28–29 January 2002
Dosimetry subcommittee – nuclear workers

12–19 February 2002
Monographs working group. Volume 82: some traditional herbal medicines, some mycotoxins, naphthalene and styrene

4 March 2002
Cancer mortality atlas of Europe scientific steering committee meeting

5 March 2002
GEN-AIR project meeting

5–12 March 2002
IARC Handbooks of Cancer Prevention working group on breast cancer screening

16–20 March 2002
WHO Classification of Tumours – pathology and genetics of tumours of the female genital organs

18–19 March 2002
ACCIS scientific committee meeting

19 March 2002
Evaluation procedures in food composition

20–22 March 2002
European nutrient database workshop

22–23 March 2002
First meeting of study group on alcohol-related cancers and genetic susceptibility in Europe (Arcage)

8–12 April 2002
ENCR course on population-based cancer registration

18–19 April 2002
International BRCA1/2 carrier cohort study

24–28 April 2002
WHO Classification of Tumours – pathology and genetics of soft tissues and bone

25–26 April 2002
IARC Fellowships Selection Committee

6–24 May 2002
Course on cancer registration methods and applications in epidemiology

27–28 May 2002
Worksafe Meeting

3–4 June 2002
Meeting of the study group on environmental exposures and lymphoid neoplasms (Epilymph)

3–5 June 2002
EPIC steering committee

5–6 June 2002
EPIC working group on breast cancer

10 June 2002
Meeting of investigators in Epihealth-Russia study

11 June 2002
Working group meeting on occupational exposure in INTERPHONE project

11 June 2002–18 June 2002
Monographs working group, Volume 83: Tobacco smoke and involuntary smoking

12 June 2002
Exposure assessment subcommittee – INTERPHONE study

12 June 2002
Field Work Coordination – INTERPHONE Study

13–14 June 2002
Full Study Group meeting – INTERPHONE Study

17–21 June 2002
International course on radiation epidemiology

1–2 July 2002
Full study group – nuclear workers

3 July 2002
International BRCA1/2 carrier cohort study

23 August 2002
Meeting on the Swiss HIV/cancer record linkage study

17–27 September 2002
CanReg 4/ICD-O-3 workshop

18–20 September 2002
Workshop on CanReg-4 and ICD-O-3 for English-speaking African countries

19–20 September 2002
RNAi: principles and applications to functional genomics in cancer research

23–24 September 2002
Epilymph-Europe coders workshop

25–27 September 2002
Workshop on CanReg-4 and ICD-O-3 for French-speaking African countries

26–27 September 2002
EPIC working group on fish consumption

29 September 2002
Meeting of the study group on environmental exposures and lymphoid neoplasms (Epilymph)

30 September–2 October 2002
Workshop on perspectives of epidemiological research on non-Hodgkin's Lymphoma: the InterLymph collaborative project

15–16 October 2002
25th ENCR steering committee

15–22 October 2002
Monographs working group. Volume 84: Some drinking water disinfectants and contaminants, including arsenic

21 October 2002
Meeting on lung cancer among workers exposed to titanium dioxide

24 October 2002
Exposure gradient task force – INTERPHONE study

4 November 2002
Analyses task group – INTERPHONE study

18–19 November 2002
Time trends workshop

21–23 November 2002
Joint IARC, FAO and WHO planning meeting on management of mycotoxins in foods and feeds for improving public health

2 December 2002
Dosimetry meeting – case–control study on cancer risk among Chernobyl liquidators

3–4 December 2002
Full study group – case–control study on cancer risk among Chernobyl liquidators

5–6 December 2002
Epidemiology subcommittee – case–control study on cancer risk among Chernobyl liquidators

14–18 December 2002
WHO Classification of Tumours – pathology and genetics of tumours of the urinary system and male genital tract

6 January 2003
Working Group for the preparation of the application to the EU 6th Framework Programme (FP6)

6–7 January 2003
ENCR EUROCARE-EUROPREVAL workshop

10 January 2003
Meeting with ACIES (consulting company) for possible collaboration in the preparation of the FP6 application to EU

13–14 January 2003
Exposure assessment subcommittee – INTERPHONE study

14–15 January 2003
Epidemiology subcommittee – INTERPHONE study

14–17 January 2003
ENCR course on statistical analysis methods – time trends

27 January 2003
Meeting on DDRC-NCI-IARC studies of oesophageal cancer in north-eastern Iran

6–7 February 2003
International BRCA1/2 carrier cohort study

6–7 February 2003
Dosimetry subcommittee – Gene-Rad-Interact (breast cancer)

10 February 2003
Measurement issues for IGF-related analytes in epidemiology research

10–12 February 2003
ENCR steering committee meeting

17 February 2003
Exploratory meeting on a comparative breast cancer study in Lyon and Tunis

11 February 2003
Joint ENCR/EUROCARE-PREVAL working group

11–12 February 2003
ENCR automated cancer registration working group meeting

11–14 February 2003
IARC Monographs advisory group meeting

17 February 2003
Informal meeting on a comparative breast cancer study in Lyon and Tunis

18–19 February 2003
ENCR Meeting combined with working group for the preparation of the FP6 application to EU

24–25 February 2003
EPIC working group on breast cancer

25–27 February 2003
EPIC steering committee

27–28 February 2003
Epidemiology subcommittee – Gene-Rad-Interact (breast cancer)

4–12 March 2003
Handbooks of Cancer Prevention working group on fruit and vegetables

7 March 2003
Working group for the preparation of the FP6 application to EU

12–16 March 2003
WHO Classification of Tumours – pathology and genetics of tumours of the lung, thymus and heart

17–18 March 2003
Fourth Working Group for the preparation of the FP6 application to EU

18–19 March 2003
ACCIS scientific committee

4 April 2003
Ethical Review Committee meeting

4 April 2003
Meeting of the section on applied functional genomics of the European Federation of Biotechnology

7–11 April 2003
Course on pathology of the uterine cervix cytology, histopathology, quality control

22 April 2003
Meeting with industry representatives on proposed case-control study of lung cancer among European asphalt workers

22–23 April 2003
Cancer Incidence in Five Continents – Vols.1–8

23–26 April 2003
WHO Classification of Tumours - pathology and genetics of tumours of endocrine organs

5–6 May 2003
IARC fellowships selection committee

19 May 2003
Candidate genes in the NPC study

20–21 May 2003
Consultation on behavioural and social sciences relevant to cancer

26–27 May 2003
Exposure assessment subcommittee – INTERPHONE study

26 May–13 June 2003
Course on methods of cancer registration and their applications to epidemiology

27–28 May 2003
Analyses task group – INTERPHONE study

5–6 June 2003
Combined analyses meeting – Child-Thyr (thyroid cancer)

11–18 June 2003
Monographs working group on betel-quid and areca-nut chewing and some related nitrosamines

12–13 June 2003
Dosimetry subcommittee – Gene-Rad-Interact (breast cancer)

24 June 2003
ACCIS scientific committee

30 June–3 July 2003
Functional consequences of TP53 mutations: characterization of common and rare p53 mutants and relevance to human cancer

7–10 July 2003
ENCR Automated Cancer Registration Course

16–19 July 2003
WHO Classification of Tumours – pathology and genetics of head and neck tumours

18–19 August 2003
Analyses task group – INTERPHONE study

1–2 September 2003
Iodine deficiency subcommittee – environmental and host factors in the risk of thyroid cancer

1–2 September 2003
Thyr-Risk meeting

17–19 September 2003
Occupational exposure subcommittee – INTERPHONE Study

18–19 September 2003
Monitoring incidence and mortality of cervical cancer in Europe and the impact of cervical cancer screening policies

22–23 September 2003
Dosimetry subcommittee – Gene-Rad-Interact (breast cancer)

22–25 September 2003
WHO Classification of Tumours – pathology and genetics of tumours of the skin

29–30 September 2003
Planning meeting for network for epidemiology of human genome and cancer

7–14 October 2003
Monographs working group meeting, Volume 86, Some metals used in the hard metal and semiconductor industry

13 October 2003
EPIC working group on breast cancer

14–16 October 2003
EPIC steering committee

16 October 2003
EPIC working group on biomarkers

24 October 2003
Ethical Review Committee Meeting

27 October 2003
Région Rhône-Alpes - cervical cancer network meeting

30–31 October 2003
Full study group – nuclear workers

7–8 November 2003
Overview of hormonal and other factors in cervical cancer

13–15 November 2003
Editorial board meeting on management of mycotoxins in foods and feeds for improving public health

18–25 November 2003
Handbooks of Cancer Prevention working group on cruciferous vegetables, isothiocyanates, and indoles

28–29 November 2003
Meeting of the study group on environmental exposures and lymphoid neoplasms (Epilymph)

11–12 December 2003
Full study group – INTERPHONE study

Moscow, Russian Federation
13–14 May 2002
Seventh meeting of investigators in the study of occupation, environment and cancer in central and eastern Europe

19–20 December 2002
Meeting of investigators in Epihealth-Russia study

Moscow, Barnaul, Biysk and Novgorod, Russian Federation
1–6 October 2003
Meetings of investigators and/or interviewers in Epihealth-Russia study

Nouakchott, Mauritania
17–20 April 2002
Cours sur le dépistage du col utérin par inspection visuelle après application d'acide acétique et de soluté de Lugol et sur les traitements par cryothérapie et résection à l'anse diathermique (RAD)

Oslo, Norway
15–16 September 2003
ENCR course on ICD-O-3 coding for cancer registry staff

Paris, France
21–22 October 2002
EPIC working group on breast cancer

3–6 December 2003
North–south workshop on EBV-associated nasopharyngeal carcinomas

Prague, Czech Republic
17–18 March 2003
Sixth meeting of coders in the study of occupation, environment and lung cancer in central and eastern Europe

20–21 March 2003
Eighth meeting of investigators in the study of occupation, environment and cancer in central and eastern Europe

Quito, Ecuador
5–8 November 2002
Workshop on CanReg-4 and ICD-O-3

Riyadh, Saudi Arabia
9–13 October 2002
Workshop on CanReg-4 and ICD-O-3

São Paulo , Brazil
9–10 May 2003
Sixth meeting of investigators in the study of larynx and oral cavity cancer in South America

Seoul, Republic of Korea
3–6 December 2002
Workshop on CanReg-4 and ICD-O-3

Sfax, Tunisia
17–20 December 2002
Workshop on CanReg-4 and ICD-O-3

Talavera de la Reina, Spain
22–24 April 2002
ENCR course for EUROCIM users on advanced statistical analysis of cancer registry data

Tampere, Finland
24 June 2002
First meeting of study group on second primary neoplasms - a systematic analysis of cancer registries

25–27 June 2002
IACR annual meeting

Trieste, Italy
17–19 July 2002
ENCR course for EUROCIM users on advanced statistical analysis of cancer registry data

Trivandrum, India
1–12 September 2003
International course on cancer epidemiology – principles and methods

Venice, Italy
24–25 January 2003
Second meeting of study group on alcohol-related cancers and genetic susceptibility in Europe (Arcage)

Seminars presented at IARC

Dr A. Altieri, Italy
Epidemiology and etiology of gestational trophoblastic diseases

Dr K. Andersson, Norway
Structure and spectroscopical studies of the possible oncoprotein mammalian R2 proteins from ribonucleotide reductase

Dr B. Armstrong, Australia
Contribution of solar radiation to human lymphomas

Dr H. Autrup, Denmark
Mutagenesis in colon and liver of big blue rat: diet–environment interaction

Dr P. Bach, USA
A model for assessing changes in lung cancer mortality rates in screening and prevention studies

Dr J.A. Baron, USA
Colorectal cancer prevention: real possibilities by Ca^{+} and aspirin

Dr I. Bondarev, USA
Human LINE-1 retrotransposon mediated maintenance of telomeres in cancer. New potential for treatment and prevention

Dr A.C. Casson, Canada
Molecular alterations in oesophageal cancer

Dr S. Chanock, USA
SNPing away at innate immunity

Dr G. Chenevix-Trench, Australia
High-penetrance ATM mutations in familial breast cancer

Dr D. Conti, USA
Hierarchical models in genetic association studies

Dr S. Cuzzocrea, Italy
Role of free radican in inflammation, shock and ischemia and reperfusion

Dr W. Deppert, Germany
Selection of p53 responses to genotoxic stress

Dr S. Devesa, USA
Lymphoma incidence patterns in the United States by histologic type

Ms E. de Vries, Netherlands
Trends in melanoma incidence and mortality in Europe

Dr P. Dhillon,USA
Bias due to misclassification and rising screening trials: PSA screening and prostate cancer mortality

Mr V. Dubus, France
A new and innovative mouse transgenesis technology with SpeedyMouse Technology

Dr R. Elder, UK
Biological and biochemical consequences of murine *N*-glycosylase deletion

Dr B. Figueiredo, Brazil
Childhood adrenocortical tumour: survival rate, surveillance protocol and molecular findings

Dr M. Finkbeiner, Germany
Building new cells within old ones: the morphogenetic pathway at the end of meiosis in yeast

Dr G. Fronza, Italy
Multiple applications of a yeast assay for the functional characterization of p53 mutant proteins

Dr A. Giuliano, USA
HPV infection among US men

Dr M. Glatzel, Switzerland
Prions: host-pathogen interaction at the molecular level

Dr B. Griffin, UK
Burkitt's lymphoma in Africa yesterday and today

Dr M.P. Hande, USA
Telomere-chromosome integrity bu DNA repair factors: a molecular cytogenetic approach

Dr J. Hulin, Italy
Antibody engineering: characterisation of protein and DNA binding specificity of human VH homodimers(homo-VHDs)

Dr R. Iori, Italy
The chemistry of the myrosinase-glucosinolate system of Brassicaceae in cancer research

Dr V. Kipnis and Dr D. Midthune, USA
Effect of dietary measurement error on energy adjustment in nutritional epidemiology: results of the OPEN biomarker study

Dr R.W. Kriwacki, USA
p53 Mutation and adrenal cortical carcinoma; new insights from structural studies

Dr O. Laerum. Norway
Bio-banks and use of archival material for molecular pathology in Norway

Dr T. Lindahl, UK
Endogenous DNA damage: the enemy within

Ms J. Loizou, UK
Mammalian DNA single strand break repair

Dr I. Magrath, Belgium
Clues to lymphomagenesis from observations in various world regions

Dr G. Margison, UK
DNA alkylation: from carcinogenesis to cancer chemotherapy (a tale of three cities?)

Dr M. Masucci, Sweden
Modulation of proteolysis in virus-infected and malignant cells

Dr J. McKay, Australia
Genetics in Tasmania, focusing on large prostate cancer pedigrees

Dr M. Miwa, Japan
Role of poly(ADP-ribosyl)ation in centrosome duplication

Dr H. Møller, UK
Impact of organised mammographic screening on breast cancer incidence and mortality

Dr M. Mori, Japan
Nitric oxide- and endoplasmic reticulum stress-mediated apoptosis

Dr B. Moscicki, USA
The natural history of HPV and HIV among female adolescents

Dr A. Nagler, Israel
Lymphomagenesis, role of modest-to-moderate immune dysfunction in stem cell transplantation

Dr N. Olea, Spain
Biomarkers of exposure to environmental oestrogens: their utility in epidemiology

Dr C. Piyathilake, USA
Gene-nutrient interactions and risk of cervical cancer

Dr Q. Rahman, Germany
Risk assessment in asbestos exposed population

Dr I. Romieu, Mexico
Carbohydrates and the risk for breast cancer among Mexican women

Dr D. Roth, USA
Genetic and biochemical analysis of V(D)J recombination

Dr D. Saranath, India
Molecular pathogenesis of chewing-tobacco induced oral cancers in India

Dr M. Serafini, Italy
Total antioxidant capacity as a tool to investigate the association between diet and oxidative stress-related diseases: advantage, limits and novel applications

Dr K. Strong, WHO
SURF1 Report 1 – surveillance of risk factors related to NCDs: current status of global data

Dr H. Suzuki, Italy
Camomile, a new anti-tumour drug?

Dr J. Torres, Mexico
Differences in *H. pylori* infection between children and adults

Dr B. Tudek, Poland
Endogenous DNA damage induced by lipid peroxidation: mutagenesis, stability and repair

Dr V. Vasilyev, Russian Federation
A step towards modelling human mitochondrial disorders

Dr H. Vesper, USA
Assessment of human exposure to acrylamide – a new project within CDC's Biomonitoring Program

Dr H. zur Hausen, Germany
New perspectives for the role of viruses in human lymphomas

Publications by IARC staff

1. Agudo A, Slimani N, Ocké MC, Naska A, Miller AB, Kroke A, Bamia C, Karalis D, Vineis P, Palli D, Bueno-de-Mesquita HB, Peeters PHM, Engeset D, Hjartåker A, Navarro C, Martínez García C, Wallström P, Zhang JX, Welch AA, Spencer E, Stripp C, Overvad K, Clavel-Chapelon F, Casagrande C, Riboli E (2002) Consumption of vegetable, fruit and other plant foods in the EPIC cohorts from 10 European countries. *Public Health Nutr.*, **5**, 1179–1196

2. Akaike T, Okamoto S, Sawa T, Yoshitake J, Tamura F, Ichimori K, Miyazaki K, Sasamoto K, Maeda H (2003) 8-Nitroguanosine formation in viral pneumonia and its implication for pathogenesis. *Proc. Natl Acad. Sci. USA*, **100**, 685–690

3. Akhmedkhanov A, Zeleniuch-Jacquotte A, Lundin E, Micheli A, Lukanova A, Afanasyeva Y, Lenner P, Krogh V, Muti P, Rinaldi S, Kaaks R, Berrino F, Hallmans G, Toniolo P (2003) Serum follicle-stimulating hormone and risk of epithelial ovarian cancer in postmenopausal women. *Cancer Epidemiol. Biomark. Prev.* (in press)

4. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ (2002) The associations of diet with serum insulin-like growth factor-I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol. Biomark. Prev.*, **11**, 1441–1448

5. Allen NE, Appleby PN, Davey GK, Key TJ, Rinaldi S, Kaaks R (2002) The effect of diet on serum insulin-like growth-factor-I and its main binding proteins. In: Riboli E, Lambert R, eds, *Nutrition and Lifestyle: Opportunities for Cancer Prevention* (IARC Scientific Publications, Vol. 156), pp. 295–296, Lyon, IARCPress

6. Allen NE, Appleby PN, Kaaks R, Rinaldi S, Davey GK, Key TJ (2003) Lifestyle determinants of serum insulin-like growth factor-I (IGF-I), C-peptide and hormone binding protein levels in British women. *Cancer Causes Control*, **14**, 65–74

7. Altieri A, Bosetti C, Talamini R, Gallus S, Franceschi S, Levi F, Dal Maso L, Negri E, La Vecchia C (2002) Cessation of smoking and drinking and the risk of laryngeal cancer. *Br. J. Cancer*, **87**, 1227–1229

8. Altieri A, Franceschi S, Ferley J, Smith J, La Vecchia C (2003) Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol.*, **4**, 670–678

9. Angèle S, Falconer CS, Foster P, Tanière P, Eeles RA, Hall J (2003) ATM protein over-expression in prostate tumors: possible role in telomere maintenance. *Am. J. Clin. Pathol.* (in press)

10. Angèle S, Lauge A, Fernet M, Moullan N, Beauvais P, Couturier J, Stoppa-Lyonnet D, Hall J (2003) Phenotypic cellular characterization of an ataxia telangiectasia patient carrying a causal homozygous missense mutation. *Human Mutation*, **21**, 169–170

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