WORLD HEALTH ORGANIZATION

International Agency for Research on Cancer

Biennial Report 2004/2005

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WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

BIENNIAL REPORT

2004–2005

International Agency for Research on Cancer

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Participating States of the
International Agency for Research on Cancer

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Director
Dr Peter Boyle

Visiting scientists
Dr Graham Giles (from September 2005)
Dr Jose Maria Martin-Moreno (July–December 2004)
Dr Nikolai Napalkov
Dr Rodolfo Saracci
Dr Witold Zatonski (from October 2005)

Administrative officer
Ms Caroline Granger (from January 2005)

Administrative assistants
Ms Margot Geesink
Ms Elizabeth Rivière (until August 2004)

IARC's scientific programme emphasizes prevention and is based on high quality, uniqueness and added value over and above what can be achieved in a single national centre. The strategy is based on the development of an internal programme and also on using the IARC infrastructure to allow collaborations between leading cancer research groups to take place. The Agency's scientific activity has been organized into five research Clusters. One cluster (Epidemiology and Biology Cluster) investigates the major lifestyle causes of cancer. A second cluster (Genetics and Epidemiology Cluster) concentrates on the role of genetics in cancer and its interaction with environmental factors. A further cluster (Pathogenesis and Prevention Cluster) focuses on prevention research and molecular pathology. Underpinning these activities is a strong activity in biostatistics and bioinformatics. In addition to playing and developing a support role, the wide range of quantitative research activities continues to be strengthened (Biostatistics and Epidemiology Cluster). Further support comes from the presence of strong laboratory activity (Molecular Carcinogenesis Cluster), which provides the research necessary to use observations made on populations to obtain a better understanding of mechanisms. In addition to its role in easing scientific management, the development of the Clusters is designed to enable closer working of Groups in each Cluster and closer working together of Clusters.

Some unique scientific programmes which are of great value are in progress, and these will be nurtured and encouraged to develop further. These include programmes in descriptive epidemiology, human papillomavirus, nutrition and hormones, Screening, Biomarkers, genetic epidemiology and the IARC Monographs Programme for Carcinogen Identification and Evaluation.

This Report comprises two distinct parts. The first part describes the work and achievements of each Group at the Agency during the biennium 2004-2005. These are presented by Cluster. A second part contains highlights of some of the key findings and publications arising from the work of the IARC during the biennium and attempts to place this in its wider context wherever possible.

Scientific findings

Cancer is a rapidly increasing problem in low-resource and medium-resource countries at present and cancer control activities are in an early stage of development. Much important etiological research remains to be done in these areas, notably Central and Eastern Europe, in Western Asia, South-East Asia and Latin America and the Caribbean. During 2004-2005, several major publications from IARC reflect emphasis on research in low- and medium-resource countries. Notable among these are the reports on Oral Cancer Screening in southern India and the studies of cervix cancer screening and HPV detection around the world.

The final volume of the Blue Book series Pathological Classification of Tumours, was published in 2005 and the work for the fourth edition is currently underway. Work is on-going to produce Volume IX of Cancer Incidence in Five Continents and an update of Globocan is underway. The TPS53 database continues to be developed and grow further in utility and there have been important findings published on Thyroid Cancer Risk Following the Chernobyl Nuclear Accident and an International Collaborative Study of Cancer Risk in Radiation workers.

In the field of nutrition, further clarification of the role of vegetables and fruit intake on breast cancer risk has been published and the interaction between genetic factors and vegetable intake on lung cancer risk has helped move this field forward. The importance of alcohol

consumption on cancer risk is taking on increasing emphasis and will be the subject of an IARC Monograph evaluation during the forthcoming biennium. The results of each Monograph Meeting are now published in Lancet Oncology within 6-8 weeks of the meeting finishing thereby allowing a wide audience to have rapid access to the evaluations made by the Working Group.

Key elements

During the biennium, new developments at IARC included the creation of a Tobacco Group and a Screening Quality Control Group. Steps were also initiated to strengthen two major areas of IARC scientific activity which will become effective during 2006. The Biostatistics Groups will be significantly strengthened and the Descriptive Epidemiology Programme will be significantly strengthened by the creation of a new Group whose focus will be on the analysis and interpretation of the masses of cancer data available.

Research training is one of the key elements of the IARC mission and the Research Training Fellowship Programme has been a major success since its inception. With the passage of time, many of the opportunities offered by the IARC Fellowships Programme that used to be unique now find themselves duplicated. This programme focuses on training opportunities that do not exist elsewhere and on providing training for students from low- and medium-resource countries. The programme is being expanded to incorporate a scheme to allow students for these countries to study at IARC and to receive a Masters or PhD. IARC course activity has concentrated on activities in the IARC in Lyon, with the establishment of the IARC Summer School.

Arrivals and Departures

There have been departures among the Group Heads: Dr David Goldgar, Head of the Genetic Epidemiology Group; Dr Emmanuel Lazaridis, Head of the Biostatistics Group; Dr Max Parkin, Head of the Descriptive Epidemiology Group; and Dr Elio Riboli, Head of the Nutrition and Hormones Group. All at IARC thank them for their service to IARC and wish them the very best for the future. New Group Heads appointed were Dr Carolyn Dresler (Tobacco Group), Lawrence von Karsa (Screening Quality Control Group) and Dr Paul Brennan (Genetic Epidemiology Group).

Fortieth Anniversary of the IARC

The International Agency for Research on Cancer was established by resolution of the 18th World Health Assembly and came into existence in September 1965. Throughout its forty years of existence, the defined mission of the Agency has remained to conduct and promote international collaboration in cancer research with the objective of improving health through a reduction in the incidence of and mortality from cancer throughout the world.

The Official Ceremony recognising this Anniversary was celebrated on 12th May 2005, immediately prior to the 47th Meeting of the IARC Governing Council, in the presence of Mr Jean-Pierre Lacroix, the Préfet, Mr Jean-Jack Queyranne, the President of the Région Rhône-Alpes and Mr Gérard Collomb, the Mayor of Lyon. A message from the President of France, Mr Jacques Chirac was delivered by Professor David Khayat and Dr Klaus Theo Schröder, State Secretary, German Federal Ministry of Health and Social Security, one of the five founding nations, made a short presentation. A Scientific Symposium was held with five speakers making presentations on key areas of science where IARC had made a fundamental contribution.

IARC Medal of Honour

In 2004, the recipients of the IARC Medal of Honour were Professor Umberto Veronesi (Italy), Professor Witold Zatonski (Poland) and Dr Andrew von Eschenbach (United States). Recipients in 2005 were Dr Brian MacMahon (United States), Professor David Lane (UK) and Professor Tadao Kakizoe (Japan). Each one has made a significant contribution to cancer research and prevention and it has been a pleasure to acknowledge these contributions by this award.

Peter Boyle
Director

Publications

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Boyle P. Tobacco Smoking and British Doctors' Cohort (Editorial). *Brit J Cancer* 2005; 92: 419-420

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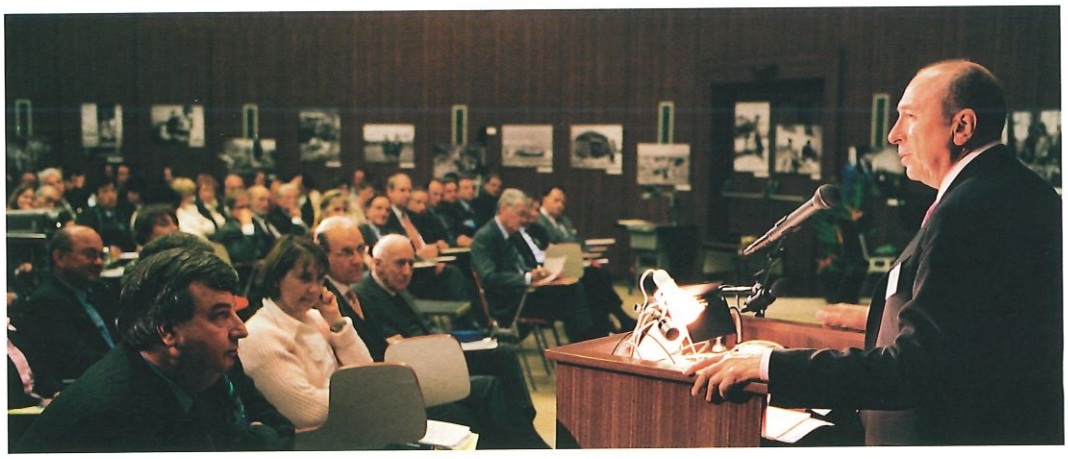
40th Anniversary Ceremonies



M. G. Collomb, Sénateur-Maire de Lyon

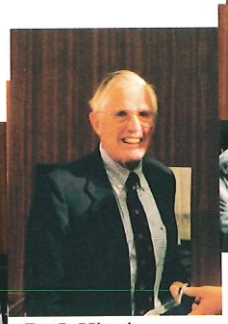
M. J.-P. Lacroix, Préfet du Rhône et de la Région Rhône-Alpes

Dr D. Khayat, President, Institut National du Cancer

M. J.-J. Queyranne, Président du Conseil Régional Rhône-Alpes

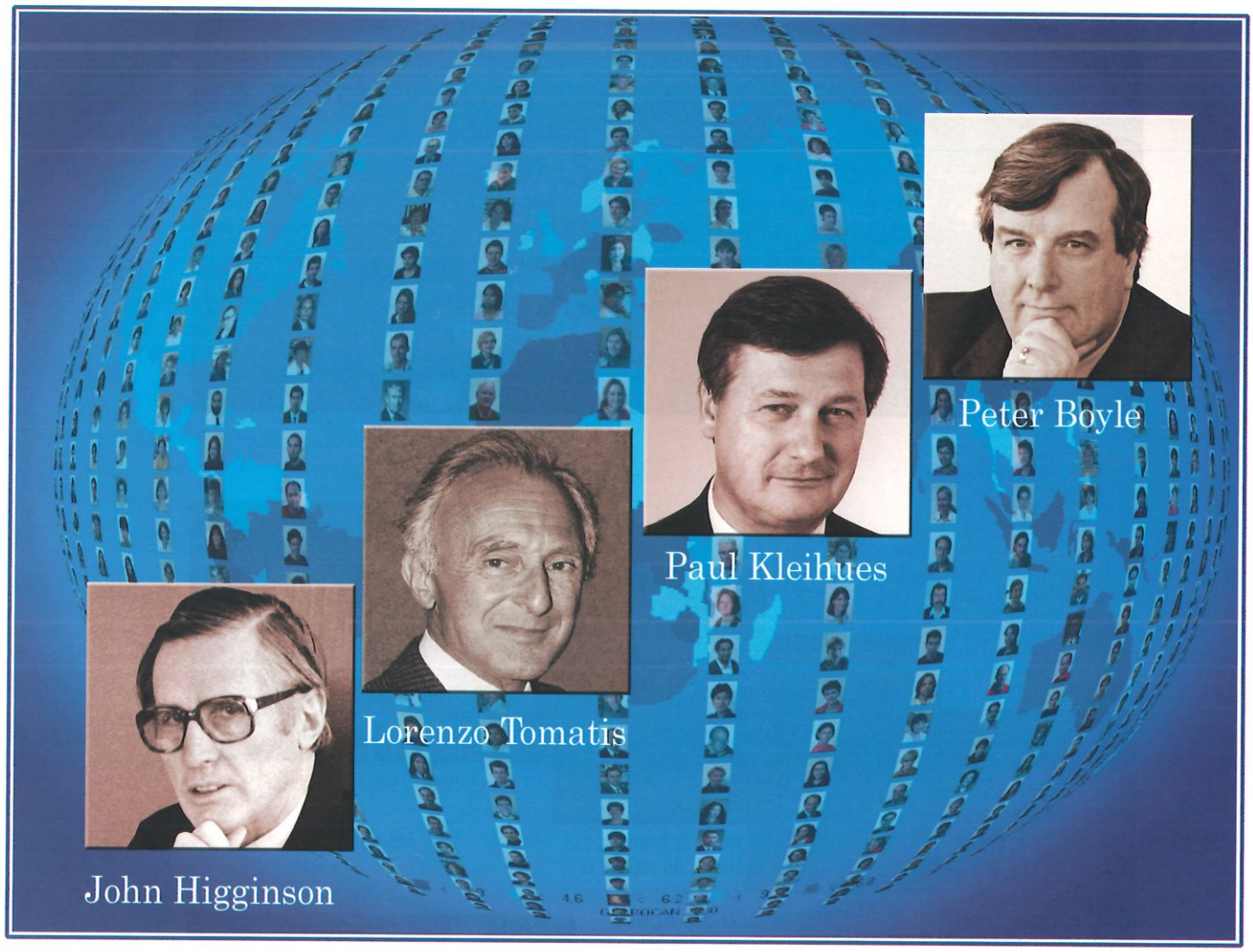
Dr K.T. Schröder, State Secretary, Federal Ministry of Health & Social Security, Germany

Dr J.-W. Hartgerink, Chairman, IARC Governing Council



Dr J. Higginson, IARC Director (1965–1982)

Dr B. MacMahon Harvard University, USA



IARC 1965-2005

Medals of Honour

Roger Sohier Lecture

1993 Gérard Orth (Institut Pasteur, Paris) – Papilloma virus and human cancer
1994 Guy Blaudin de Thé (Institut Pasteur, Paris) – Epidémiologie moléculaire des rétrovirus oncogènes
1995 Richard Peto (Oxford University, UK) – Avoidance of premature death
1996 Dirk Bootsma (Erasmus University, Rotterdam, The Netherlands) – DNA repair: maintaining nature's perfection
1997 Luca Cavalli-Sforza (Stanford University, USA) – Gènes, peuples, langues, cultures
1998 Charles Weissmann (University of Zurich, Switzerland) – Biology and transmission of prion diseases
1999 Jan Pontén (Uppsala University, Sweden) – Sunlight and skin cancer: new insights
2000 Richard Klausner (National Cancer Institute, Bethesda, USA) – The war on cancer: where we are and where research is taking us
2001 Oliver Brüstle (Institut für Neuropathologie, University of Bonn, Germany) – Embryonic stem cells: basic concepts and therapeutic applications
2002 Jeffrey Koplan (Centers for Disease Control, Atlanta, USA) – Bioterrorism and public health preparedness
2003 Paul Kleihues (Director, IARC) – Poverty, affluence and the global burden of cancer
2004 Umberto Veronesi (European Institute of Oncology, Milan, Italy) – Breast cancer management and care. Current results and future perspectives
2005 David Lane (University of Dundee, UK) – p53 and human cancer: the next 25 years

Richard Doll Lecture

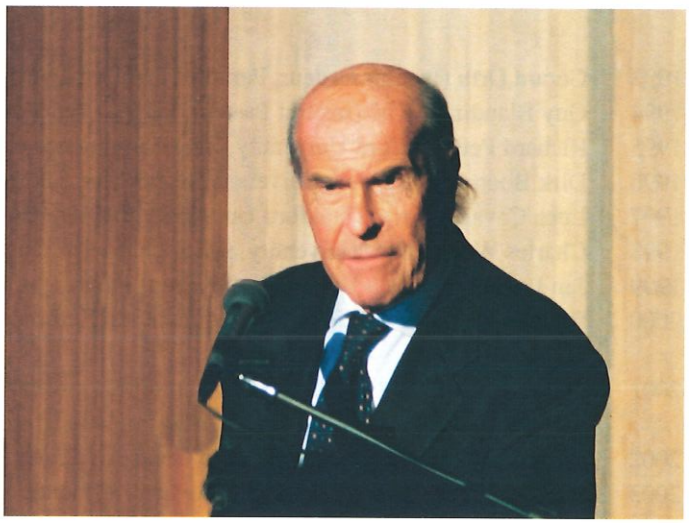
2004 Richard Doll (University of Oxford, UK) – Fifty years follow-up of British doctors
2005 Brian MacMahon (Harvard University, Boston, USA) – Epidemiology and the causes of breast cancer

IARC Lecture

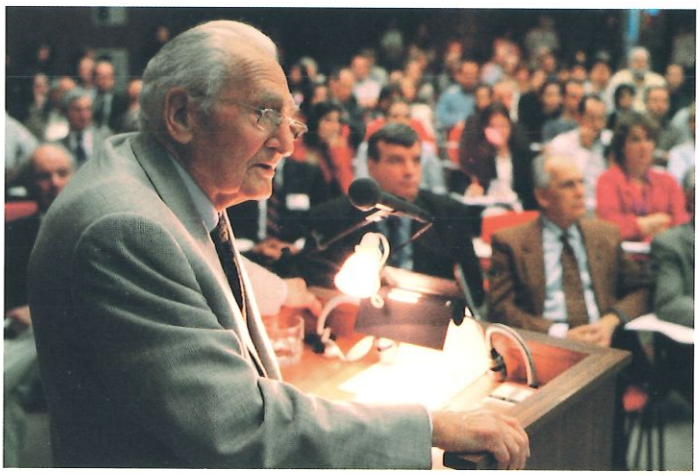
2005 Tadao Kakizoe: (National Cancer Centre, Tokyo, Japan) – Bladder cancer: a model of human cancer determined by environmental factors and genetics

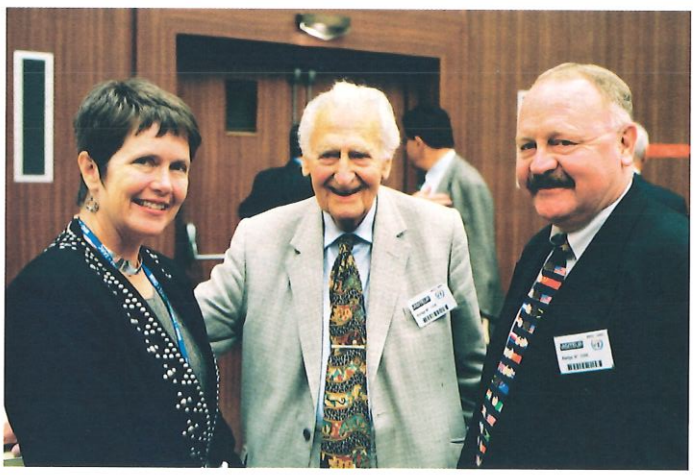
Medals of Honour 2004

IARC Day
Umberto Veronesi, Andrew von Eschenbach, Witold Zatonski



12th Roger Sohier Lecture
Umberto Veronesi: 'Breast cancer management and care. Current results and future perspectives'





1st Richard Doll Lecture
Sir Richard Doll: 'Fifty years follow-up of British doctors'

Medals of Honour 2005

Inaugural IARC Lecture 2005
Tadao Kakizoe: 'Bladder cancer: a model of human cancer determined by environmental factors and genetics'

2nd Richard Doll Lecture
Brian MacMahon: 'Epidemiology and the causes of breast cancer'

13th Roger Sohier Lecture
David Lane: 'p53 and human cancer: the next 25 years'

IARC Scientific Structure

Director

Dr Peter Boyle

Biostatistics and Epidemiology Cluster (BEC)

Mr Michel Smans (Acting)

Epidemiology and Biology Cluster (EBC)

Dr Silvia Franceschi

Molecular Carcinogenesis Cluster (MCC)

Dr Pierre Hainaut

Genetics and Epidemiology Cluster (GEC)

Dr Paolo Boffetta

Pathogenesis and Prevention Cluster (PPC)

Dr Hiroko Ohgaki

Biostatistics Group (BIO)

To be appointed

Infections and Cancer Biology Group (ICB)

Dr Massimo Tommasino

Carcinogen Identification and Evaluation Group (CIE)

Dr Vincent Cogliano
(Reports to Office of the Director)

Gene-Environment Biology Group (GEB)

Dr Zhao-Qi Wang

Pathology Group (PAT)

Dr Hiroko Ohgaki

Descriptive Epidemiology Group (DEP)

Dr Paola Pisani
(Acting)

Infections and Cancer Epidemiology Group (ICE)

Dr Silvia Franceschi

Endogenous Risk Factors Group (ERF)

Dr Hiroshi Ohshima

Gene-Environment Epidemiology Group (GEE)

Dr Paolo Boffetta

Screening Group (SCR)

Dr Rengaswamy Sankaranarayanan

Information Technology Services Group (ITS)

Mr Michel Smans

Nutrition and Hormones Group (NTH)

Dr Rudolf Kaaks
(Acting)

Molecular Carcinogenesis Group (MOC)

Dr Pierre Hainaut

Genetic Epidemiology Group (GEP)

Dr Paul Brennan

Screening Quality Control Group (ECN)

Dr Lawrence von Karsa
(Acting)

Radiation Group (RAD)

Dr Elisabeth Cardis
(Acting)

Tobacco and Cancer Group (TOB)

Dr Carolyn Dresler

Common Laboratory Services (CLS)

To be appointed

Genetic Susceptibility Group

Dr Sean Tavtigian

Gambia Hepatitis Intervention Study (GHIS)

To be appointed

Office of the Director

Communications Group (COM)

Dr Nicolas Gaudin

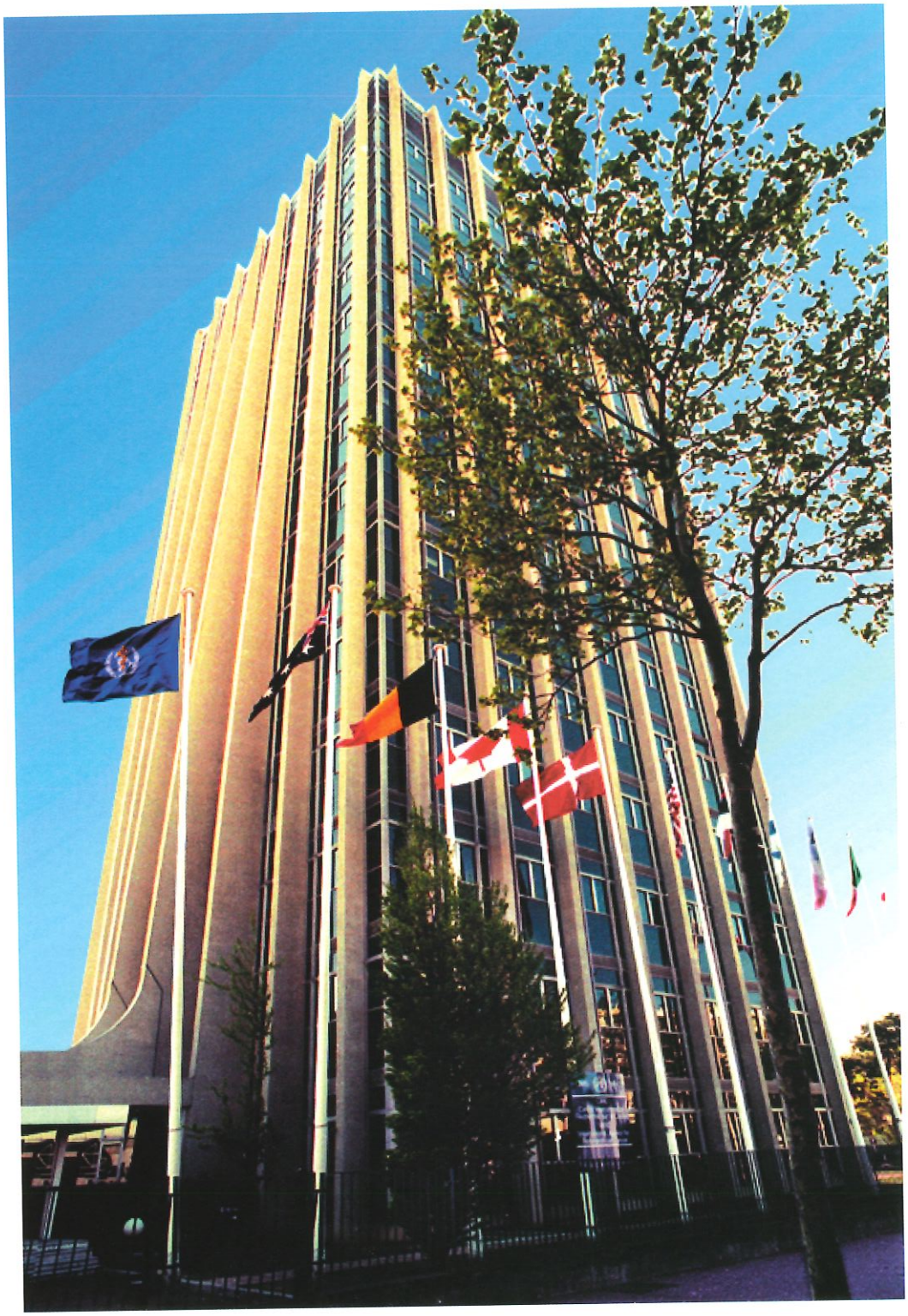
EUROCAN+PLUS Group (CAP)

Dr Philippe Autier
(Acting)

The Cabinet

Dr P. Boffetta, Cluster Coordinator
Dr S. Franceschi, Cluster Coordinator
Dr P. Hainaut, Cluster Coordinator
Dr H. Ohgaki, Cluster Coordinator
Mr M. Smans, Cluster Coordinator (Acting)
Mr M. Johnson, Director of Administration and Finance
Dr P. Boyle, Director
Dr S. Tavtigian, Member without porfolio*

(*replaced Dr E. Riboli)



IARC Group and Cluster Reports, 2004–2005

Biostatistics and Epidemiology Cluster

Cluster Coordinator: Mr Michel Smans (Acting)

The Biostatistics and Epidemiology Cluster (BEC) brings together groups involved in assembly and analysis of large data collections. A fundamental requirement of this type of activity nowadays is powerful computing facilities, and the Information Technology (ITS) Group is responsible for not only providing the data-storage and processing capabilities for the Cluster, but also managing all other computing requirements of IARC's scientists and administration. This includes the provision of powerful electronic communications and access to the internet.

The Descriptive Epidemiology (DEP) Group provides the starting point for much epidemiological research by bringing together and validating vast quantities of information on cancer occurrence from around the world, for dissemination in standardized formats, both printed and electronic, and for analyses within the Group itself, by other IARC Groups and by scientists elsewhere. Good relations with cancer registries worldwide are maintained in order to provide a unique resource for cancer researchers. The development of standardized methods, classifications and computer systems for use in the recording of cancer data is another crucial aspect of this work. Important work has also been carried out on analysing time trends in cancer occurrence and on examining the distribution and causes of childhood cancer.

The Biostatistics (BIO) Group has the task of developing and applying statistical and informatic methods to the processing of diverse types of data generated during the course of the research by the Agency's scientists. This activity has been at a relatively low level in recent years, but is now a priority area for development. Traditionally of importance for analysing data collected by epidemiological studies, biostatistical research is also now focusing on how to process the floods of data automatically generated by modern systems for analysis of individual genotypes.

The Radiation (RAD) Group carries out studies of the cancer-inducing effects of radiation that involve particularly complex issues of collection and processing of large data-sets. Major studies have been in progress for a number of years, all of which have required careful attention to the methodology of measurement of radiation exposures. The study on nuclear workers has generated unique results on the effects of low-dose long-term exposure to ionizing radiation, of critical importance for setting radiation protection standards. The largest study to date of the effects of exposure to non-ionizing radiation due to use of mobile phones (cell phones) is nearing completion, and will provide answers to questions of wide public concern about this technology.

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The Biostatistics Group's mission is to facilitate the IARC research programme by investigating, developing, and deploying statistical and informatics tools and solutions across the Agency. Following the departure of its previous head, the recruitment of a new leader is in progress and a new programme of activities is being developed.

Active support is provided to the existing Laboratory Information Management System (LIMS) for the Genetic Cancer Susceptibility Group, as well as to the definition and acquisition of an Agency-wide LIMS. Expertise on web technologies is made available to the Communications Group and various research Groups, while close collaboration is maintained with the ITS Group.

The Group has actively participated in several working groups of the International Association of Cancer Registries (Artificial Light and Skin Cancer, Avoidable Causes of Cancer, Chernobyl) and provided statistical advice to external collaborators (Cancéropole Clermont-Ferrand, Prostate working group Innsbruck), as well as IARC research groups.

Members of the Group attended Melanoma EORTC congresses in Brussels (spring 2005) and in Warsaw (autumn 2005) and the 6th World Melanoma Congress in Vancouver (September 2005).

Publications

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Descriptive Epidemiology Group

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Monitoring of cancer occurrence provides fundamental data on which to base research into the etiology of the disease, as well as to plan and evaluate public health interventions. Geographical comparisons, temporal trends and ecological studies provide clues regarding the etiology of cancer. At the same time, incidence and mortality data quantify the size of the problem in a population so that suitable cancer control measures can be adopted.

Cancer registry data

A core activity of the Descriptive Epidemiology (DEP) Group consists in coordinating, supporting and promoting cancer registration worldwide. Cancer registries provide information on cancer incidence and survival and are the only source of data on cancer occurrence in countries where mortality statistics are not available. A fundamental component of the programme is the systematic collection of existing data on cancer incidence, mortality and survival. These data are then evaluated and refined before dissemination to the scientific community in a standardized and comparable format. The *Cancer Incidence in Five Continents* series is the best known product of this activity, with its regular five-yearly publication of statistics on cancer incidence worldwide, of which volume VIII was published in 2002. The preparation of a new issue to appear in 2007 has been initiated, with an editorial board set up and the content and procedure defined. A new feature will be the inclusion of all available years of incidence from 1998 (the last year mentioned in volume VIII) to date, rather than the traditional group of five years only. A major innovation in 2005 was an electronic version of the eight volumes of *Cancer Incidence in Five Continents* which are now available on the internet (www-dep.iarc.fr). Incidence rates and numbers as originally published in the volumes can be accessed using a special software that allows the user to perform selections, tabulations and graphs. For registries that contributed to any of the volumes and are still active and able to provide historical data, a separate database permits simple analyses of time trends. The data to be included in volume IX of *Cancer Incidence in Five Continents* will be prepared in a format compatible with the eight-volume database, to allow its incorporation.

An interim update of the GLOBOCAN database that provides estimates of incidence, mortality and prevalence in all countries of the world around 2002 has been made available on internet. This has become a widely referenced basic resource in the absence of any direct source of information on cancer occurrence in many countries and regions.

The comparative value of the statistics that cancer registries produce depends upon the use of common methods and definitions, so that international collaboration in this area is essential. DEP coordinates expert working groups and proposes standards in collaboration with international associations of cancer registries. Agreed rules and methods are described in documents and manuals that DEP distributes and promotes. Much effort is put into advising on methodology and providing technical support and training to established and new cancer registries alike, in particular in regions where the lack of disease surveillance systems is most critical. During the biennium, new versions of the DEP CanReg4 software have been developed and installed in Africa (Algeria, Cameroon, Ghana, Mali, Morocco, Namibia, South Africa, Sudan), Latin America (Argentina, Chile, Colombia, Dominica, French Guiana, Jamaica, Martinique, Netherlands Antilles), Asia and the

Western Pacific (Cambodia, China, French Polynesia, India, Lebanon, Malaysia, Tonga, Turkey, Vanuatu, Yemen). Some new European registries in Belgium, Bosnia-Herzegovina, France and Italy have also adopted the IARC software. Registry staff were trained in three regional courses held in Cameroon, Turkey and Yemen, and in the IARC Summer School held each year in Lyon.

The DEP Group also provides administrative facilities and the secretariat to the International Association of Cancer Registries (IACR) and the European Network of Cancer Registries (ENCR). Collaborative activities include (a) site visits to assess the feasibility and to advise on the setting up of new registries; (b) follow-up including data analyses to monitor progress; (c) development, maintenance and support of *ad hoc* software for the routine management of the registry data; and (d) individual and group training on rules, coding systems and the use of the software. Two priorities are to assure an efficient technical support service in the face of increasing requests and to revitalize the working groups and collaborations of the ENCR.

The principles and rules of cancer registration were described in a manual published by IARC in collaboration with IACR in 1991 that has been the reference text for all registries. The manual has, however, fallen out-of-date and its revision is in progress. Some crucial topics that will be covered include the adoption of the third revision of the International Classification of Diseases for Oncology (ICD-O), published in 2000, recommendations to expand the minimum set of variables to include, in particular, stage at diagnosis, and the recording of *in situ* tumours occurring at some sites that are the object of screening programmes.

Time trends

A major focus of the Group's work in collaboration with the ENCR has been the comprehensive and systematic analysis of time trends in cancer incidence and mortality in Europe. Time trends studies, to quantify how the burden is changing over time, may be used to predict the future burden and risk of cancers, and may offer clues as to the underlying determinants of the disease under study. For studies of trends in uterine cancer, the methodological problem of correctly interpreting mortality trends when a high proportion of the data is classified as "uterus, unspecified site" has been considered and a pragmatic approach to adjust imprecisely coded data was developed and applied to European data. The analyses of trends of cervical and endometrial cancer have revealed a general decline in mortality from endometrial cancer throughout Europe, that is more marked in the Western and Southern countries, and period-specific declines in cervical squamous cell carcinoma in several countries, with the greatest decreases seen in Northern Europe. A pattern emerged across Europe of escalating risk in successive generations born after 1930. In Finland, despite a highly successful cervical cancer screening programme since the mid-1960s, cohort- and period-specific increases occurred in the 1990s and in cohorts born after 1945, respectively. In Western European countries, a decrease followed by a stabilization of risk by cohort was accompanied by period-specific declines. In Southern Europe, stable period but increasing cohort trends were observed.

General increases over time in skin melanoma were documented; in high-risk countries, the increase was accompanied by a clear trend to present at earlier stages, indicating improved awareness as well as clinical monitoring of the population. Mortality has generally slowed down or even decreased.

Analyses of time trends in ovary and testis cancers, overall and by histological group, have been completed. A project to analyse trends in thyroid cancer incidence in adults and children by histological type has been established.

Childhood cancer

The systematic analysis of a large database of childhood cancer incidence, assembled over several years, has been initiated. An updated classification of childhood cancer based on the third revision of the ICD-O has been developed and published, that forms the basis for new analyses of incidence and survival data. Between 1970 and 1999, there were generalized increases in Europe in both incidence and survival for virtually all types of tumour among both children and adolescents. The trends were more marked in Western European countries than in the less affluent Eastern ones; significant differences in survival between West and East were also reported. The extent to which increased ascertainment and improved registration over time are responsible for the increases observed remains a matter of debate.

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Book chapter

Parkin DM, Bray F. Descriptive studies. In: Ahrens W, Pigeot I (ed.) Handbook of Epidemiology. Berlin, Heidelberg: Springer-Verlag, 2005; 157-230

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The Information Technology Services (ITS) Group maintains and develops the Agency's central computing and electronic communications services. The Group has been re-organized into two teams: the Support team ensures the day-to-day operations and provides assistance to all users in the research Groups and the Administration. The Information Technology Development team develops the information technology infrastructure as well as specific tools and applications for the administration and for the research groups.

The old computer room was enlarged and renovated in 2004 and the local area network (LAN) backbone completely re-designed. Other developments are under way, in particular in the area of network security and management. The e-mail facility was also re-designed and a new mail server put in place in early 2005.

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The work of the Radiation Group (RAD) encompasses both ionising and non-ionising radiation research.

Ionising radiation is one of the most intensively studied and ubiquitous carcinogens in our environment. The main basis for radiation protection standards is the study of survivors of the Japanese atomic bombings, who were exposed primarily at high dose rates. The major public health concern, however, is to protect people from relatively low-dose, protracted or fractionated exposures such as those received by the public in the general environment, by patients through repeated diagnostic procedures, and by radiation workers. Studies by the RAD Group are addressing outstanding questions regarding the effects of ionising radiation exposure pattern, radiation type and factors which may modify radiation-induced risks (including host and environmental factors).

Recent years have seen a great increase in the number and diversity of sources of non-ionising electromagnetic fields (EMF), principally extremely low-frequency (ELF) and radio-frequency (RF) fields used for individual, industrial and commercial purposes. Although these have made our lives easier, they have brought with them concerns about possible associated health risks. At IARC, work on EMF is mainly focused on RF exposure, which can occur in a number of ways in occupational and environmental settings.

Ionising radiation

An International Collaborative Study of Cancer Risk among Radiation Workers, a retrospective cohort study of cancer mortality among nuclear industry workers in 15 countries, has been conducted in order to provide precise direct estimates of risk after protracted low-dose exposures and to strengthen the scientific basis of radiation protection. Analyses included 407,391 workers individually monitored for external radiation, with a total follow-up of 5.2 million person-years, making the study the largest of nuclear workers ever conducted. The excess relative risk for cancers other than leukaemia was 0.97 per sievert (95% CI 0.14–1.97). This estimate is higher than, but compatible with, risk estimates used for radiation protection. Analyses indicate that, although confounding by smoking may be present, it is unlikely to explain all of this increased risk. The results suggest that there is a small excess risk of cancer at the low doses and dose-rates typically received by nuclear workers. Extension of the mortality follow-up of the cohorts included in the study is being considered, as well as a cancer morbidity follow-up in countries having a comprehensive national cancer registry.

The estimation of risk associated with radiation exposure is most difficult for lung cancer, because of potential confounding by smoking and internal radionuclide contamination. A nested case–control study is therefore being set up, focusing on cohorts of workers employed in fuel fabrication and research facilities in Belgium, France, the UK and the USA where internal exposure to plutonium and uranium isotopes is most prevalent. In parallel, a similar nested case–control study of leukaemia is also being set up in these cohorts.

The effects of low-dose protracted exposures to ionising radiation are also the subject of case–control studies of leukaemia, non-Hodgkin lymphoma (NHL) and thyroid cancer among Chernobyl "liquidators" from Belarus, Estonia, Latvia, Lithuania and the Russian Federation. The fieldwork and dose reconstruction in these studies, which include 119 interviewed cases of leukaemia and NHL, and 127 cases of thyroid cancer have been completed and analyses are under way.

A population-based case–control study of thyroid cancer in young people, coordinated jointly with the Sasakawa Memorial Health Foundation of Japan, has been carried out in the regions of Belarus and the Russian Federation most contaminated by the Chernobyl accident. The aim was to evaluate the risk of thyroid cancer related to exposure to iodine-131 (^{131}I) in childhood and adolescence and the role of modifying factors such as age at exposure, stable iodine intake, genetic background and reproductive history. The 276 thyroid cancer cases were all under 15 years of age at the time of the accident. Individual doses were estimated for each subject. A strong dose–response relationship was observed ($P < 0.001$), with estimated odds ratios for a dose of 1 Gy varying from 5.5 to 8.4, depending on the model. The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas than elsewhere. Administration of potassium iodide as a dietary supplement after the accident reduced this risk by a factor of three. These results have important public health implications: stable iodine supplementation in iodine-deficient populations can greatly reduce the risk of thyroid cancer related to radioactive iodine after accidental releases and medical exposures in childhood.

The CHILD-THYR project has brought together data from studies of thyroid cancer in relation to ^{131}I exposure in childhood and adolescence (the IARC study described above and other studies in Belarus, the Russian Federation, French Polynesia, the USA and the Marshall Islands), to improve the precision of risk estimates, compare risk estimates across studies conducted in different settings and assess the role of environmental and host modifying factors. Data from all these studies have been received and analysis has started.

Studies of the joint roles of radiation exposure and genetic susceptibility in the etiology of breast cancer in young women are being set up, within the multinational GENE-RAD-RISK project, partially funded by the European Union. Nested case–control studies of breast cancer will be conducted in two complementary populations, chosen on the basis of high prevalence of radiation exposure (cohorts of cancer survivors) and/or high prevalence of known mutations in susceptibility genes (cohorts of mutation carriers), to maximize the power of the study. Genes of particular interest are those involved in the detection and repair of radiation-induced DNA damage. The project will also address the possible existence of a common genetic profile in radiation-induced breast tumours. Approximately 1000 cases of breast cancer and matched controls from eight European countries (Denmark, Finland, France, Italy, the Netherlands, Norway, Sweden, UK) and possibly Canada and Israel will be included.

An ecological epidemiological study was conducted to describe spatial and temporal trends in breast cancer incidence in the regions of Belarus and Ukraine most contaminated by the Chernobyl accident, and to evaluate whether reported increases correlate with radiation exposure. Increases in incidence were seen in all areas, reflecting improved cancer diagnosis and registration. In addition, a significant two-fold increase in risk during the period 1997–2001 in the most contaminated districts was observed (average cumulative dose 40.0 mSv or more) compared to the least contaminated districts. The increase (based on relatively small numbers of cases) appeared approximately 10 years after the accident, was highest among women who were younger at the time of exposure and was observed for both localized and metastatic diseases.

In parallel with this ecological study, the feasibility of conducting a population-based case–control study of breast cancer in young women in these regions was assessed. This indicated that such a study was feasible and detailed study documents have been prepared.

Wide concern has been expressed that depleted uranium is associated with increases in cancer incidence in Iraq, and among military personnel using depleted uranium munitions. Feasibility and pilot studies initiated in 2002 were suspended due to the war and the subsequent security situation in Iraq. Contacts have been made in 2005 and the possibility of restarting the work is being evaluated.

The issue of paediatric exposure to X-rays in computerized tomography (CT) and subsequent cancer risk is one of great concern among the general public, as well as in the health and radiation protection communities. In collaboration with the US National Cancer Institute and the University of Newcastle, UK, a group of investigators interested in studying this relationship has been assembled and information is being collected to evaluate the feasibility of setting up a multinational study.

Non-ionising radiation

The INTERPHONE Study is a series of multinational case–control studies set up to determine whether mobile telephone use increases the risk of cancer and, specifically, whether the radio-frequency radiation emitted by mobile telephones is carcinogenic. Separate studies have been carried out for acoustic neurinoma, gliomas and meningiomas and tumours of the parotid gland. This is by far the largest epidemiological study of these tumours to date. The studies used a common core protocol in Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK, to collect information on history of mobile telephone use, as well as on occupational exposure to EMF and ionising radiation, medical history of the subject and medical radiation exposures. Retrospective and prospective validation studies have been conducted to assess the accuracy of self-reported use of mobile phones. Prospective validation studies include the use of software-modified telephones to allow the collection of information on distribution of emitted power in different countries and regions and by pattern of use.

Because exposure to RF from mobile phones is very localized, it was judged essential to identify as precisely as possible the location of origin of each brain tumour and to evaluate the RF "exposure" at that location. A protocol developed for neuro-radiologists to identify the anatomical origin of the tumour from magnetic resonance imaging and CT scans is being used in all participating countries.

Data collection and validation are now complete, with a total of approximately

2600 gliomas, 2300 meningiomas, 1100 acoustic neurinomas, 400 parotid gland tumours and their respective controls. Analysis of mobile phone use history in the international database and analyses of the effects of estimated exposure to RF are in progress.

As a follow-up to INTERPHONE, a project to evaluate the feasibility of a study of cancer risk in relation to RF exposure from mobile telephone use in childhood and adolescence is being set up.

The Group also continues its involvement in a number of multinational projects aimed at pooling the resources of relevant international and national agencies and key scientific institutions in order to assess health and environmental effects of exposure to static and time-varying electric and magnetic fields (EMF). These include:

- The WHO International EMF Project, in which the RAD Group at IARC provides assistance in the evaluation of health risks from EMF, identification of gaps in scientific knowledge and recommendations about research protocols.
- The EU-funded EMF-Net consortium, aimed at collating and critically evaluating results of research activities on the biological effects of EMF, in order to provide policy-relevant interpretation and advice for the facilitation of policy development in non-ionising radiation protection. Within this consortium, the RAD Group is part of the Steering Committee and the Fast Response Team and is responsible for a work package on EMF epidemiology.

Methodological developments

Errors in the estimation of exposures or doses are a major source of uncertainty in epidemiological studies of cancer and other chronic diseases, particularly for ionising and non-ionising radiation. A method to take these errors into account in risk estimation has been developed and implemented, using Monte-Carlo simulations.

Dose reconstruction

Extensive efforts have been made to develop, test and implement dosimetric models for reconstruction of radiation doses following the Chernobyl accident as well as following atmospheric weapons tests in French Polynesia. A method (RADRUE; Realistic Analytical Dose Reconstruction with Uncertainty Estimation) was developed for calculating external doses to liquidators. For the thyroid cancer case–control study, individual doses to the thyroid have been estimated taking into account intake of ^{131}I and other short-lived radioiodine and radiotellurium isotopes via inhalation and ingestion; external irradiation from radionuclides deposited on the ground and other materials; and intake of long-lived radionuclides with locally produced foodstuffs. Work is also continuing on estimation of RF energy absorbed in different anatomical locations of the brain for the INTERPHONE Study. All dose-reconstruction efforts include assessment of sources of uncertainty.

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Epidemiology and Biology Cluster

Cluster Coordinator: Dr Silvia Franceschi

The Epidemiology and Biology Cluster (EBC) includes Groups that carry out international studies on the most important avoidable causes of cancer.

Two Groups, Infections and Cancer Epidemiology (ICE) and Infections and Cancer Biology (ICB), focus their efforts on chronic infections that, altogether, account for nearly 20% of cancer worldwide, with low- and intermediate-resource countries being hit hardest. Research on human papillomavirus, the cause of cervical cancer and of a sizeable proportion of other cancers of the anogenital tract and oropharynx, is the current priority in both the ICE and ICB Groups. In the last two years, the ICE Group has mainly carried out large-scale population-based studies of the distribution of different human papillomavirus types in women with and without cervical cancer. Conversely, the ICB Group has engaged mainly in smaller-scale biological studies, the aim of which is to characterise the oncogenic properties of specific human papillomavirus types. These biological studies complement, in terms of the mechanisms involved, the overwhelming epidemiological evidence on the role of certain human papillomavirus types in the aetiology of cervical cancer. They also allow the identification of other human papillomavirus types (notably cutaneous types) that represent good candidate causes for cancer at other sites for which a viral aetiology is plausible but not firmly established (e.g., non-melanomatous skin cancer).

Although the activities of the ICE and ICB Groups are largely independent, they have converged in some significant innovative studies carried out jointly on the role of cutaneous human papillomavirus types in some rare cancers, such as cancer of the conjunctiva. Another point of convergence is the re-examination of data from large IARC epidemiological studies to consider previously unexplored aspects, such as differences in oncogenic potential between variants in a single human papillomavirus type. In addition to its work on human papillomavirus, the ICE Group carries out studies on the excess of liver cancer and lymphomas due to hepatitis B and C viruses and the influence of concurrent human immunodeficiency virus (HIV) infection on the incidence of virus-associated cancers.

The two Teams of the Nutrition and Hormones (NTH) Group also represent an example of close collaboration on a broad series of research projects on the role of dietary habits, metabolism and genetic variants in the aetiology of cancer at specific sites, notably the breast, colon and prostate. The continuing follow-up of the EPIC cohort, with half a million volunteers from 10 European countries and already approximately 30,000 incident cancers recorded, provides by far the main source of information and of biological specimens for the activities of the NTH Group. However, for studies of hormones and growth factors, progress has been made in involving additional cohorts from North America.

Last but not least, the Tobacco and Cancer (TOB) Group was established in 2004, in view of the fact that tobacco is the greatest avoidable cause of cancer and deserves a specific focus within IARC. This Group is less strictly research-oriented than other Groups in the EBC Cluster, but has a broad remit, i.e., the evaluation of scientific evidence on all important aspects of tobacco use in society. The aim is to provide a basis for improved prevention of tobacco uptake and increased cessation of its use.

The EBC Cluster encourages exchanges and collaborations in every possible way, formal and informal. As well as the systematic collaborations that have already been mentioned, many others are in the pipeline. Extension of projects on viruses and cancer to the EPIC project is planned and will include nested case-control studies on human papillomavirus, hepatitis C virus and *Helicobacter pylori*. The ICB and TOB Groups are working together, with the help of the Genetics and Epidemiology Cluster, on the evaluation of a possible involvement of human papillomavirus in the aetiology of lung cancer. All Groups in the EBC Cluster regularly exchange their expertise with other Clusters in order to fully exploit biological samples from studies coordinated by the EBC Cluster in work on genetic and epigenetic cancer markers.

A few hundred publications in the biennium provide good evidence of the high productivity and range of topics and international collaborations entailed in projects coordinated by the EBC Cluster. Several successful grant applications in Europe and the USA also confirm the international recognition of the EBC Cluster's work on infections, diet, hormones and tobacco, the major causes of cancer.

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The main goal of the Infections and Cancer Biology (ICB) Group is to define the causal roles of specific infectious agents in human cancer. Two complementary approaches are being pursued:

(1) Biological studies to characterize the oncogenic properties of specific infectious agents to help in defining their role in human carcinogenesis.
(2) Epidemiological studies to determine the role of infectious agents in the etiology of human cancers.

The Group's current research is focused on the epitheliotropic human papillomaviruses (HPV), a large and ubiquitous family of viruses. Over 100 different HPV types have already been characterized and they can be divided into mucosal and cutaneous types according to their tissue tropism. A group of the mucosal HPV types, known as "high-risk" HPV types, is now well established as the cause of cervical carcinomas as well as of a subset of anogenital and head and neck carcinomas. Functional studies on the mucosal high-risk HPV types have demonstrated that the products of two early viral genes, E6 and E7, play a key role in the malignant transformation of infected cells. Both viral proteins induce deregulation of the cell cycle and apoptosis, telomerase dysfunction and chromosomal instability. However, not all HPV infections progress to invasive cancers, since the infection is usually cleared by the immune system in a relatively short time. Persistence of the viral infection is an essential requirement for the development of invasive cancer.

The group of cutaneous HPV types is very heterogeneous, comprising over twice as many types as the mucosal group, and new types are constantly being reported. Their biological properties and their role in human carcinogenesis are still poorly understood. Emerging evidence strongly suggests that a subgroup of cutaneous HPV types belonging to the beta genus of the HPV phylogenetic tree is linked to human carcinogenesis. These were first isolated in patients suffering from a rare autosomal recessive genetic disorder, *epidermodysplasia verruciformis* (EV), associated with cancer susceptibility, and are consistently detected in non-melanoma skin cancer (NMSC) of EV, immunocompromised and normal individuals. However, a direct role of the EV HPV types in cancer development remains to be proven.

The ICB Group is conducting studies on both mucosal and cutaneous HPV types. Regarding the mucosal HPV types, the main aim is to identify factors that influence the clinical outcome of mucosal high-risk HPV infections. Initial studies indicate that genetic factors and natural HPV variations play a role in determining the persistence or regression of a viral infection. Epidemiological studies are planned to confirm these findings. The ini-

tial goal of the programme on the cutaneous HPV types is to determine whether these types are causally involved in the development of human cancers. Several lines of biological and epidemiological evidence have been obtained that support a role of the beta group HPV types in carcinogenesis.

Polymorphisms of HPV16 and clinical outcome

A cross-sectional study has been performed in the population of several European countries to evaluate the spectrum of HPV16 E6 and E7 variants in cervical intraepithelial neoplasia (CIN) grades I–III and invasive cervical carcinomas. Initial findings indicate that E6 variants, but not E7 variants, play a role in the development of cervical lesions. It has been observed that the risk of specific E6 variants may depend on the human leukocyte antigen (HLA) class II haplotype of the infected woman. To confirm these findings, we conducted a prospective study in a homogeneous French population, in collaboration with the ICE Group and with Dr Christine Clavel (Pathology Department of the CHU of Reims) and Dr Ingeborg Zehbe (TBRHSC, Thunder Bay, Canada). HPV16 and HLA polymorphisms were analysed in three groups of HPV16-positive women: (a) women who had cleared their infection, (b) women with persistent infection and (c) women who had progressed to high-grade lesions. Both HPV16 and HLA polymorphisms seemed to be involved in the progression of HPV infection to high-grade lesions, thus confirming the results of previous cross-sectional studies.

These findings may provide a basis to improve gynaecological health programmes, by allowing identification of molecular diagnostic markers to predict whether an HPV16 infection will be cleared or will progress to a lesion.

Properties of uncharacterized cutaneous HPV types

In this programme, the biological properties of the E6 and E7 oncoproteins of several cutaneous HPV types have been characterized. We have shown for the first time that members of the beta HPV group display transforming activities that are similar to those of oncogenic mucosal HPV types. HPV38 E6 and E7 are able to immortalize primary human keratinocytes, the natural host of the virus. Similarly to E7 of high-risk mucosal HPV16, HPV38 E7 efficiently inactivates pRb and alters cell-cycle control. In addition, we have recently identified a novel HPV mechanism of inactivation of the tumour-suppressor p53 that differs substantially from that previously described for mucosal high-risk HPV types. Thus, while HPV16 E6 promotes p53 degradation via the ubiquitin pathway, HPV38 E6 and E7 induce accumulation of a specific form of p53 with altered transcriptional functions. To evaluate the oncogenic activities of HPV38 in an *in vivo* model, transgenic mice expressing HPV38 E6 and E7 were generated under the control of the bovine homologue of the human keratin 10 (K10) promoter. Initial data showed that these mice display skin hyperproliferation and susceptibility to chemical carcinogenesis.

Our data on the transforming ability of HPV38 *in vitro* and *in vivo* led to the hypothesis that HPV38 and other types of the beta group may represent risk factors for development of non-melanoma skin cancer. In a pilot case–control study to verify this hypothesis, healthy skin, actinic keratoses (that are considered a premalignant lesion) and NMSC were collected at the Dermatology Department of the University of Bari, Italy (Dr Raffaele Filotico). The presence of HPV38 DNA, determined in each specimen by PCR and Southern blotting, was found to be positively associated with NMSC.

In a further study in collaboration with Drs Anna Giuliano and Robin Harris (Arizona Cancer Research Center, Tucson, AZ, USA), we determined the prevalence of a large number of cutaneous HPV types in healthy skin from individuals with or without a history of NMSC. Cases were approximately six times more likely to have HPV DNA detected in forearm skin biopsies than controls.

Beta HPV types and conjunctival cancer

A pilot case–control study, in collaboration with the ICE Group and with the Karolinska Institute, Sweden, was conducted in Uganda on squamous cell carcinomas of the conjunctiva. The incidence of this rare tumour, associated with heavy sun exposure, has increased in some sub-Saharan African countries over recent decades in parallel with the spread of human immunodeficiency virus (HIV), strongly suggesting the involvement of an infectious agent. A broad spectrum of HPV types was tested using PCR-based assays. EV HPV types were found in 86% of conjunctival cancer cases and 36% of controls.

HPV38 and HPV38-related types were very frequently detected in conjunctival cancer cases. No mucosal high-risk HPV types were detected in either cases or controls. Serological analyses for HIV were not available for the study patients and medical records did not mention AIDS, but it is likely that a majority of the cancer cases were HIV-positive, as found in a previous study in Uganda. Thus, the higher prevalence of EV-associated HPV types in cancer cases could be explained by two alternative hypotheses: (a) they are causally associated with the development of conjunctival cancer or (b) they are associated with HIV-mediated immune impairment. To discriminate between these two possibilities, we collected post-mortem eye specimens from individuals with no conjunctival lesions and with known HIV status. Only 10% of these specimens were positive for EV HPV types and the prevalence did not differ between HIV-negative and HIV-positive individuals, providing support for the first hypothesis.

In conclusion, the pilot studies on human specimens provide additional lines of evidence for the role of HPV38 and members of the beta group in human carcinogenesis.

Dok1 signalling and its role in human malignancies

Proper regulation and coordination of biochemical signalling pathways are important for normal cellular proliferation and differentiation. Various diseases including cancer can occur due to altered regulation of the signalling network necessary for cellular homeostasis.

Dok1 (downstream of tyrosine kinases) is an adaptor protein that is involved in several cellular signalling pathways. It is heavily tyrosine phosphorylated in many transformed cells and this

tyrosine phosphorylation can be induced after exposure of cells to a number of growth factors. In addition to be a tyrosine kinase substrate, Dok1 can be phosphorylated by IκB kinase β (IKKβ), a master kinase involved in NF-kB activation. IKKβ-mediated phosphorylation regulates Dok1 functions.

Dok1 inhibits several signalling pathways that are important for cell proliferation and exhibits tumour suppressive activity. Subsequent to this observation, we have further reported a mutation and down-regulation of Dok1 expression in chronic lymphocytic leukemia (CLL). This Dok1 mutant had a nuclear localization in contrast to the cytoplasmic wild-type protein. We have recently shown that Dok1 expression was down-regulated in all Burkitt's lymphoma (BL) and X-linked lymphoproliferative syndrome (XLP) cell lines analyzed, in comparison to the control cells. No Dok1 mutation or polymorphism was found in the coding region of Dok1. However DNA sequence analysis revealed the presence of four nucleotide changes in Dok1 intronic gene. The $C^{89487}T$ and $A^{87714}G$ changes were detected in 9% and 6% of analyzed BL lines respectively, but never in the control and XLP-LCL cells, indicating that this nucleotide substitution occurred during tumour development. Interestingly, the $C^{89487}T$ variant is associated with a significantly lower level of Dok1 expression compared to the control samples. In addition we found a positive association between the presence of EBV in BL and the Dok1 genetic variation. Our data indicate that alterations of Dok1 expression and structure are involved in a subset of Burkitt's lymphomas.

Since Dok1 can be mislocalized in some tumour cells, we questioned whether Dok1 can be a shuttling protein. We discovered that Dok1 shuttles between the cytoplasm and the nucleus and contains a functional nuclear exclusion site (NES). We also demonstrated that Dok1 subcellular localisation can be modulated by Src tyrosine kinase and IKK, and this is important to regulate its functions.

In conclusion, our findings support the notion that Dok1 is a tumour suppressor and that alterations of its functions can occur in haematopoietic tumours by either mutation or low expression. Subcellular mislocalization could also be a mechanism to inactivate Dok1. Further investigation is required to evaluate on a large-scale the extent of involvement of Dok[1] in other lymphoid or solid tumours.

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Approximately one fifth of all human cancers worldwide are attributable to persistent infection with viruses, bacteria or parasites. The Infections and Cancer Epidemiology (ICE) Group aims to identify the epidemiological features of cancers associated with human papillomavirus (HPV), human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), hepatitis C virus (HCV), *Helicobacter pylori* and other infections.

HPV

The development of HPV testing and vaccines presupposes knowledge of the type-specific distribution of HPVs in different parts of the world. In order to address this issue, the ICE Group has carried out systematic reviews of all published studies with type-specific data on HPV prevalence in women with and without cervical cancer and has conducted 14 population-based HPV prevalence surveys among cancer-free women in four continents.

Overall HPV prevalence in cancer-free women varied from 1.3% in Spain to 24.7% in Nigeria. The most commonly identified HPV type, in either single or multiple infections, was HPV16. Prevalence of all HPV types was highest in Africa and lowest in Europe, but the variation in HPV16 prevalence across continents was smaller than in high-risk types other than HPV16 and in low-risk types.

Women's age was the variable by far most strongly associated with HPV positivity, but the relationship with age varied greatly by study area. Along with the most common age pattern (i.e. an early peak of HPV prevalence in young women), U-shaped (mainly in Latin America) and flat distributions (in Nigeria, China and India) were found. The extent to which the difference in the age pattern of HPV prevalence across populations depends on cohort effects or international differences in reinfection/clearance probability in various age groups remains unclear. Other associations were weak (e.g. number of sexual partners, husband's extramarital sexual relationships) or inconsistent (e.g. smoking, contraceptive methods) across countries.

To fill remaining gaps in knowledge about many parts of the world, the ICE Group has planned new surveys of HPV prevalence, with HPV DNA testing performed, as before, at the Vrije University, Amsterdam, The Netherlands, and serological tests at the Deutsches Krebsforschungszentrum, Heidelberg, Germany. Priority is given to areas of high risk for cervical cancer for which little information is available (e.g. eastern Europe and central Africa) and countries where major social changes and migration from rural to urban areas may lead to a substantial increase in HPV infection among young women (e.g. China and other Asian countries). Collaborative reanalyses of studies on HPV or cervical cancer by IARC or other groups are continuing.

Special efforts are being made to improve the participation of young women in HPV surveys. The sampling of a larger number of young women allows for a better projection of cervical cancer incidence 20 to 30 years from now, based on current HPV prevalence. It will also help in defining the age-window when a prophylactic vaccine may be most effective in developing countries. Some specific studies focus on HIV-positive women.

In collaboration with the Cancer Epidemiology Unit of Cancer Research UK, Oxford, published and unpublished data from aetiological studies on cervical cancer have been combined in a reanalysis of HPV and cervical cancer for a critical evaluation of co-factors such as hormonal contraceptives, smoking, sexual behaviour, reproductive factors and menopause.

The ICE Group is collaborating with the US National Cancer Institute in the analysis of the interaction between different HPV types in the Atypical Squamous Cells of Undetermined Significance and Low-Grade Squamous Intraepithelial Lesions Triage Study.

In collaboration with the ICB Group, the oncogenic potential of HPV16 variants will be examined among HPV16-positive women with and without cancer from studies in different populations by the ICE Group.

HIV/AIDS

Our studies of cancer excess in people with HIV/AIDS in Italy and Switzerland have confirmed highly elevated incidence (compared with the general population) for Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL). The ICE Group also contributed to defining the excess of Hodgkin lymphoma, liver cancer, skin cancer and cervical cancer. The introduction of highly active antiretroviral therapy in 1996 has greatly decreased the incidence of KS and NHL, but not that of HPV-associated cancer and Hodgkin lymphoma.

An interesting by-product of the study of AIDS-related KS has been the possibility to re-evaluate the epidemiology of classic KS in the same countries. Incidence rates found for classic KS in Italy were relatively high, whereas in the Vaud Canton of Switzerland, classic KS was seen only among migrants from Mediterranean areas.

The ICE Group is updating record linkage between the Italian AIDS Registry and 19 cancer registries which cover 23% of the Italian population, with an initial goal of linking approximately 15,000 people with AIDS.

The enrolment of some 12,000 HIV-positive people in the Swiss HIV Cohort Study (SHCS) since 1988 also allows for record-linkage studies like the one described for Italy. The major strength of the SHCS, however, is the availability of detailed clinical follow-up information and biological samples. This provides, for instance, an ideal opportunity to study HCV-related lymphomagenesis, because approximately 30% of cohort participants are co-infected with HCV and HIV. A nested case-control study is being set up to evaluate the contribution of HCV and hepatitis B virus (HBV) in the aetiology of NHL and Hodgkin lymphoma in HIV-positive people.

HCV/HBV

The involvement of HCV and perhaps HBV infection in the development of lymphoma in the general population has been well documented in recent years; several of the most important studies were carried out in collaboration with IARC. Nested case-control studies in collaboration with the European Prospective Investigation into Cancer and Nutrition (EPIC) (see NTH Group) have been designed to assess the proportions of NHL and hepatocellular carcinoma attributable to hepatitis viruses in Europe. These will constitute the largest prospective study on the role of HCV/HBV in lymphomagenesis, which has so far been evaluated mainly in case-series and case-control studies.

Helicobacter pylori

The ICE Group has conducted studies on *Helicobacter pylori* and gastric cancer in Tachira State, Venezuela. A chemoprevention trial of precancerous lesions of the stomach, started in 1991, is now complete. The environmental risk factors for which associations were found in a previous case-control study were re-examined in the chemoprevention trial with these precancerous lesions as outcomes. The analysis confirmed associations with length of refrigerator use, smoking and a diet rich in starchy foods. Antioxidant vitamins (β-carotene, vitamin C and E) taken over a three-year period did not change significantly the probability of progression or regression of gastric lesions in this trial. The baseline data and biological samples from the Venezuelan chemoprevention trial are being used in a genetic association study to determine the combined effect on numerous polymorphisms and *Helicobacter pylori* in gastric carcinogenesis, in collaboration with Wayne University, Detroit, Michigan, USA, and Delft Diagnostic Laboratory, Voorburg, The Netherlands.

Other cancer sites

A network of multicentre case-control studies has been active in Italy for the last 25 years and has adapted to the development of new hypotheses on links between lifestyle and cancer. Recent studies, in collaboration with the Aviano Cancer Centre (Aviano, Italy), the Mario Negri Institute for Pharmacological Research (Milan, Italy) and the "Pascale" Tumour Institute (Naples, Italy) have focused on cancer of the prostate, kidney, ovary and haemolymphopoietic neoplasias. Studies on hepatocellular carcinoma and nasopharynx are providing new insight into the interaction between viral infection, alcohol drinking and tobacco smoking.

Statistical methods

Floating absolute risk (FAR), as proposed by Easton, Peto and Babiker, avoids the problems caused by the possibly arbitrary choice of reference categories when a risk factor has multiple levels by associating a 'floating' standard error with each level. FAR has now been put on a rigorous theoretical basis in the ICE Group, resulting in improved estimates of the floating standard errors, and a validity test to identify situations where the method cannot be applied. The improved algorithm has been implemented in the software packages Stata and R.

A common feature of infection-related cancers is the existence of precancerous states that require a clinical examination for diagnosis. Natural history studies generate data consisting of a sequence of precancerous disease states from clinical visits that may be unequally spaced in time. The transition times between disease states are not known exactly, but are interval-censored. The appropriate theoretical framework for such data is the multi-state Markov model. Studies often have further sources of complexity such as measurement error, missing data and multiple diagnoses or outcomes per subject. The analysis of such data is facilitated by use of Bayesian hierarchical models, which can subsume these additional sources of complexity. The ICE Group is developing a general-purpose program for the analysis of Bayesian hierarchical models that will be applied to these problems.

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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.

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. 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)

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.
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).
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 bio-repository 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.

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.

The variability of macronutrient intake distribution before and after calibration for measurement error has been evaluated 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.

Hormones and cancer

The Hormones and Cancer Team is examining whether relationships of nutritional lifestyle factors – particularly excess weight, lack of physical activity and macronutrient composition of diet – with cancer risk are mediated, at least in part, through changes in endogenous hormone and growth factor metabolism. The two main approaches are (a) prospective cohort studies of cancer risk in relation to prediagnostic blood or urine concentrations of endogenous hormones and growth factors (particularly, sex steroids, insulin, and IGF-I), and (b) genetic association studies. The focus over the current biennium has been on cancers of the breast, endometrium, ovary, prostate and colorectum.

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, breast, pancreas and endometrium. Such effects may be mediated either directly by insulin receptors in (pre)neoplastic cells or indirectly by changes in the bioactivity of insulin-like growth factor-I (IGF-I) or in sex steroid synthesis and bioavailability. In addition to changes in insulin and IGF-I metabolism, excess body weight is associated with increased levels of oestrogens in postmenopausal women and in men, and it can lead, in genetically susceptible subgroups of women, to increased ovarian and/or adrenal androgen synthesis. The types and amounts of fat, carbohydrates and protein in the diet can affect levels of endogenous sex steroids, insulin and/or IGF-I.

Two large prospective cohort studies on endogenous hormones and cancer risk were completed, one within the New York (NYUWHS) cohort (385 incident cases of breast cancer, 770 control subjects; in collaboration with Drs Zeleniuch-Jacquotte and Toniolo, New York University) and one within the EPIC cohort (677 cases plus 1309 controls), that both showed an increased risk of developing breast cancer among postmenopausal women who had elevated prediagnostic serum levels of androgens (dehydroepiandrosterone (DHEAS), androstenedione, testosterone) or oestrogens (estrone, total estradiol). Strongest relationships (approximately two-fold relative risks between the extreme quintiles of hormone concentrations) were found in relation to levels of bioavailable testosterone and estradiol unbound to sex hormone-binding globulin (SHBG). In the EPIC cohort study, breast cancer risk was also increased among premenopausal women who had elevated prediagnostic serum levels of DHEAS, androstenedione and testosterone, and low levels of progesterone. The latter results provide evidence against an old hypothesis about the role of endogenous sex hormones and breast cancer development – the oestrogen-plus-progesterone hypothesis – and in favour of an alternative hypothesis, which postulates that moderate ovarian androgen excess and luteal inadequacy may enhance breast tumour development.

Among both pre- and postmenopausal women, a direct association of breast cancer risk with circulating IGF-I levels (serum samples taken two or more years before tumour diagnosis) was seen in the study within the EPIC cohort (1195 cases). However, serum levels of C-peptide (a marker for pancreatic insulin secretion) showed a direct relationship with breast cancer risk only among postmenopausal women.

A parallel study within the EPIC cohort showed an increase in the risk of ovarian cancer among premenopausal women who had elevated serum concentrations of IGF-I, confirming findings from a previous combined study of three prospective cohorts in New York, Umeå (Northern Sweden) and Milan (Italy).

With regard to endometrial cancer, a study within the EPIC cohort showed an approximately three-fold increase in risk among both pre- and postmenopausal women who had elevated prediagnostic serum concentrations of C-peptide. These data support our hypothesis that chronic hyperinsulinaemia is an important risk factor for this cancer. Risk was also increased among postmenopausal women who had elevated serum concentrations of androstenedione, testosterone, estrone or estradiol, with highest (approximately four-fold) relative risks for women with high levels of estradiol unbound to SHBG. These results were very similar to our previous findings in a study combining prospective cohorts in New York, Umeå and Milan.

In a prospective study on prostate cancer within the Northern Sweden Health and Disease cohort in Umeå (in collaboration with Dr Pär Stattin), elevated plasma concentrations of IGF-I were also found to be associated with increased risk of prostate cancer, and especially of those diagnosed at a relatively advanced stage.

Finally, a large study on colorectal cancer, again within the EPIC cohort, showed a modest increase in the risk of developing colon cancer, but not rectal cancer, among men and women who had elevated serum concentrations of C-peptide. The association remained significant after adjustment for anthropometric indices of adiposity, and was fully in line with observations in previous prospective studies. Taken together, these and previous findings provide strong support to the hypothesis that chronic hyperinsulinaemia may be a cause of colon cancer. Serum concentrations of IGF-I and IGFBP-3, however, showed no relationship with colorectal cancer risk, in contrast to some previous prospective studies.

In well-nourished populations, about 50% of the variation in IGF-I is (co-)determined by genetic factors. Genes covering the regulation of IGF-I synthesis include those coding 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, but probably without altering plasma and prostatic tissue levels of IGF-I and/or IGFBP-3, include those encoding the IGF-I receptor and the IGF-binding proteins 1, 2, 4, 5 and 6. Similarly, a long list of candidate genes may affect the synthesis of androgens and estrogens, their transportation in blood, or their physiological effects through cellular receptors.

Several large genetic association studies are being conducted to identify specific genetic polymorphisms that determine endogenous hormone and growth factor synthesis, as well as risk of developing breast and prostate cancers. One is a collaboration involving the EPIC cohort and a consortium of prospective cohort studies in the USA and includes a total of 6000 cases of breast cancer and 9000 of prostate cancer. Pooled statistical analyses provide increased statistical power and allow examination of gene–gene and gene–environment interactions. Data for a first set of six genes have been analysed, and a total of some 50 candidate genes will be examined over the next 2–3 years. In parallel, relationships of prostate cancer risk with polymorphic variants of genes involved in IGF metabolism are being examined in collaboration with a Swedish case–control study of over 2000 cases ("CAPS": Cancer of the Prostate Sweden; Dr Grønberg and Dr Stattin, Umeå University).

The global strategy in each of these studies is to: (a) identify all single nucleotide polymorphisms (SNPs) (coding and non-coding regions) in candidate genes; (b) determine haplotypes, and haplotype-tagging SNPs; (c) assess the association of gene variants (haplotype-tagging SNPs) with levels of plasma steroid hormones and IGF-I, and with cancer risk; (d) assess interactions between genetic polymorphisms and endogenous hormone levels in determining breast and prostate cancer risk; and (e) assess interactions between polymorphisms and lifestyle and anthropometric factors, as determinants of endogenous hormone levels.

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Tobacco and Cancer Group

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Dr Nigel Gray (March-September 2005)
Dr Matti Hakama (January–June 2004)
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Mr Xavier Castille (March–July 2004)
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Mr Nicolas Voirin
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Tobacco is one of the best described human carcinogens and is carcinogenic in all forms of use. The Agency prepared a Monograph on Tobacco Smoking initially in 1986 which was revised in 2004 when the Working Party concluded that there was enough new information available to increase the numbers of cancer types deemed to be causally related to tobacco smoking. The risk associated with smoking and individual cancer sites was investigated in the British Doctors study (Doll *et al,* 2005). In eleven of thirteen cancer types considered by IARC to be causally related to tobacco smoking, and which could be identified on death certificates, Doll and colleagues found them to be significantly related to smoking. For the two remaining sites (nasopharynx, nose and nasal cavity) deaths in the Doctor's cohort were sparse although there was a suggestion that there could well be an association. These findings highlight the importance of tobacco smoking as a human carcinogen as well as being an excellent example of the robustness of the procedure which the IARC Monographs programme employs to evaluate carcinogenicity of a chemical, biological, physical or lifestyle exposure (Boyle, 2005).

The Tobacco and Cancer Group was initiated towards the end of 2004. An initial strategy meeting was held to determine potential subjects for Handbooks, which would analyze the scientific evidence available on specific areas within tobacco control. These Handbooks would then be available for the international community to help guide timely decisions as the Framework Convention on Tobacco Control is being implemented. The first Handbook will be on the Reversal of Risk/Benefits of Quitting Smoking and the Working Party will convene on 13-20 March 2006.

The group at IARC has been welcomed into the global tobacco control community with attendance or presentations at multiple meetings internationally such as the Society for Research on Nicotine and Tobacco (Prague), the European Medical Association's Capacity Building for Tobacco Control (Edin-burgh), or WHO's National Counterparts European Strategy for Tobacco Control (Paris).

A Global Strategy Planning meeting was convened in July 2005 with experts from around the world to help formulate a research plan for the Tobacco and Cancer Group. This comprehensive planning document will be thoroughly reviewed to ascertain its feasibility and which programs will be able to be implemented.

Visiting Scientist Dr Nigel Gray, continued his work on issues of concern in International Tobacco Policy drawing on his long experience in this area. The major focus was on regulation of the major constituents of tobacco smoke, including both tobacco toxicants and nicotine. His interest in global nicotine policy was reflected in a multi-author paper on this topic as well as discussion on alternative sources of nicotine to that provided by the cigarette. Due to Dr Gray's long term involvement in tobacco control and extensive knowledge, he is an active member on many international tobacco control committees providing expert advice on wide-ranging topics.

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Molecular Carcinogenesis Cluster

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The Molecular Carcinogenesis Cluster (MCC) bridges laboratory-based molecular research with various important aspects of epidemiological and public health research conducted at IARC. It includes the Group of Carcinogen Identification and Evaluation (CIE), the Group of Molecular Carcinogenesis (MOC), the Group of Endogenous Risk Factors (ERF) and will incorporate, from 2006, a new group dedicated to the application of biomarkers into epidemiological studies.

The main objective of the Cluster is to constitute a strong pool of expertise in carcinogenesis within IARC, involved in studies on biomarker discovery, assessment of function, validation and application to human subjects, including carcinogen identification and evaluation procedures. This approach explains the inclusion in the Cluster of the CIE Group, which develops the IARC Monographs series on the evaluation of carcinogenic risks to humans. At the same time, the Cluster has a clear focus on communication and cooperation with other Clusters and Groups. In this respect, the development of common technical platforms providing high-level service is an important strategic development at IARC, that requires a novel approach to the management of technical as well as human resources.

During 2005, the CIE Group set up an open and transparent process to revise the Preamble to the IARC Monographs, which describes the principles and procedures used in preparing the Monographs. This revision is aimed at incorporating scientific developments and procedural changes that have occurred since the Preamble was last amended in 1991, with new procedures for avoiding conflict of interests, additional guidance on the use of mechanistic data that takes into account new developments in the field of biomarkers, and a better explanation of the reasoning that working groups use in their evaluations. During the 2004–05 biennium, six new volumes of the IARC Monographs were developed, evaluating Inorganic and organic lead compounds (Volume 87), formaldehyde, 2-butoxyethanol and 1-*tert*-butoxy-2-propanol (Volume 88), smokeless tobacco and some related nitrosamines (Volume 89), human papillomaviruses (Volume 90), combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy (Volume 91) and polycyclic aromatic hydrocarbons (Volume 92). As the conclusions of IARC Monographs are of great interest to scientists and public health agencies worldwide, IARC and *The Lancet Oncology* have established a procedure for rapid publication of summaries of new evaluations within 4–8 weeks after each monograph meeting.

The ERF group has further developed its research activities investigating the role of chronic inflammation in carcinogenesis. Highlights of these activities include the demonstration of the association of chronic inflammatory stress caused by *Helicobacter pylori* infection with increased risk of stomach cancer, as well as progress in elucidating the molecular mechanisms by which infection with *Opisthorchis viverrini* causes an inflammatory condition that contributes to an increased risk of cholangiocarcinoma (CCA) in North-Eastern Thailand. Novel analytical methods have been developed to quantify 8-nitroguanine, an important molecular marker of DNA damage by reactive nitrogen species, in biological fluids such as urine or blood. Studies on etheno adducts, a DNA lesion formed by some environmental carcinogens and by lipid peroxidation products, in an animal model of liver cancers induced by urethane, have brought new insight on the dosimetry of adduct formation and on their effects on the cell cycle (apoptosis, proliferation), that may help in better assessing the risk of exposure to urethane.

The MOC Group focuses on mechanisms by which human cells respond to DNA damage, develop repair strategies, and acquire mutations that will lead to the development of cancer. A highlight of its activity is the development of the IARC *TP53* mutation database, which has broken a new ceiling with the inclusion of over 20,000 human mutations and extensive annotations on their effects on gene function. The development of new methods has facilitated the application of mutation and polymorphism detection methods to large-scale studies on human subjects. This has resulted in increased collaboration with epidemiology Groups, on mutation profiles and genetic susceptibility in lung cancers (GEE and GEP Groups), on mutations associated with human papillomavirus infection in oral cancer (ICE Group) and on plasma DNA as an indicator of cancer risk in subjects of the EPIC cohort (GENAIR study). On the mechanistic side, the Group has developed new approaches to better understanding critical aspects of the functions of the p53 protein, as well as for elucidating how mutant p53 participates in carcinogenesis. Finally, a new protein that emerged from fundamental studies has received much attention: RDM1, first identified as a potential DNA repair factor, appears to be involved in chromatin remodelling during several critical processes such as meiosis and responses to viral infections. Further studies will determine how this protein contributes to human cancer.

Carcinogen Identification and Evaluation Group

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The first step in cancer prevention is to identify the causes of human cancer. These include chemicals, complex mixtures, occupational exposures, physical and biological agents, and lifestyle factors. The Carcinogen Identification and Evaluation (CIE) Group produces the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, whose long-term objective is to review and evaluate the published scientific evidence on carcinogenic hazards to which humans are exposed. The *IARC Monographs* have since 1971 evaluated 900 agents and identified 416 of these as carcinogenic or potentially carcinogenic to humans.

Each monograph includes a critical review of the pertinent scientific literature and a consensus evaluation of an agent's potential to cause cancer in humans. It is written by an international, interdisciplinary working group of experts who have performed research on the topic. More than 1000 scientists from 50 countries have contributed to the *IARC Monographs*.

National and international health agencies use the *IARC Monographs* as a source of consensus scientific information to support their actions to prevent cancer. Individuals, too, can use this information to make better choices that reduce their exposure to carcinogens and their risk of developing cancer. In this way, the *IARC Monographs* contribute to cancer prevention and the improvement of public health.

During the 2004–05 biennium, six new volumes (87–92) of *IARC Monographs* were developed. Other significant activities have led to improvements in transparency and communications. These include an open process to update the principles and procedures used in developing monographs (the Preamble) and a new agreement with The *Lancet Oncology* for rapid publication of new monograph results. In addition, a special Advisory Group was convened to plan a series of future *IARC Monographs* on air pollution and an IARC Scientific Publication on the topic.

IARC Monographs prepared during the biennium

Volume 87: Inorganic and organic lead compounds.
All humans carry a body burden of lead. The predominant uses of lead are now in batteries and, to a lesser extent, in construction materials and lead-based chemicals. A working group of 20 scientists from 11 countries met in February 2004 and reached the following evaluations.

Inorganic lead compounds
Group 2A
Probably carcinogenic to humans

Organic lead compounds
Group 3
Not classifiable

Volume 88: Formaldehyde, 2-butoxyethanol and 1-*tert*-butoxy-2-propanol.
Common sources of formaldehyde exposure include vehicle emissions, particle board and similar materials found in buildings and furniture, and carpets. 2-Butoxyethanol and 1-*tert*-butoxy-2-propanol are solvents that are widely used in paints, cleaning agents, and other consumer products. A working group of 26 scientists from 10 countries met in June 2004 and reached the following evaluations.

Formaldehyde
Group 1
Carcinogenic to humans

2-Butoxyethanol
Group 3
Not classifiable

1-*tert*-Butoxy-2-propanol
Group 3
Not classifiable

Volume 89: Smokeless tobacco and some related nitrosamines.
Hundreds of millions of people are addicted to smokeless tobacco, and use by young people is increasing in many regions of the world. Many types of smokeless tobacco are marketed for oral or nasal use. All contain nicotine and nitrosamines, such as NNN, NNK, NAB, and NAT, at differing levels. A working group of 19 scientists from seven

countries met in October 2004 and reached the following evaluations.

Smokeless tobacco
Group 1
Carcinogenic to humans

NNN and NNK
Group 1
Carcinogenic to humans

NAB
Group 2B
Possibly carcinogenic to humans

NAT
Group 3
Not classifiable

NNN, N-nitrosonornicotine; NNK, 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone; NAB, N-nitrosoanabasine; NAT, N-nitrosoanatabine

Volume 90: Human papillomaviruses.
HPVs infect human mucosal and cutaneous tissue. Persistent infection with a carcinogenic HPV type is found in virtually all cases of cervical cancer, the second-leading cancer in women worldwide. Nearly 80% of cancer cases occur in developing countries without effective screening programmes. A working group of 25 scientists from 13 countries met in February 2005 and reached the following evaluations.

HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66
Group 1
Carcinogenic to humans

HPV types 6, 11 and some types of genus beta (including types 5, 8)
Group 2B
Possibly carcinogenic to humans

Volume 91: Combined estrogen–progestogen contraceptives and combined estrogen–progestogen menopausal therapy.

Worldwide, over 100 million women – about 10% of all women of reproductive age – now use combined hormonal contraceptives. The proportions who have ever used them are much higher, exceeding 80% in some developed countries. At its peak around the year 2000, approximately 20 million women in developed countries were using combined menopausal therapy. A working group of 21 scientists from eight countries met in June 2005 and reached the following evaluations.

Combined estrogen–progestogen oral contraceptives
Group 1
Carcinogenic to humans

Combined estrogen–progestogen menopausal therapy
Group 1
Carcinogenic to humans

Volume 92: Polycyclic aromatic hydrocarbons (PAHs).
There has long been concern that air pollution contributes to the global burden of cancer, particularly lung cancer. Combustion of organic materials generates PAHs and contributes prominently to indoor and outdoor air pollution. A working group met in October 2005 to develop evaluations of approximately 60 PAH compounds and 10 PAH mixtures found in various occupational settings. (See Table 1)

Improvements in transparency and communications

Amendment of the Preamble to the IARC Monographs
The Preamble describes the principles and procedures used in developing monographs, including the scientific criteria that guide the evaluations. During 2005, IARC updated the Preamble to reflect scientific developments and procedural changes that have occurred since the Preamble was last amended in 1991. These include new procedures for avoiding conflict of interests, additional guidance on the use of mechanistic data in identifying carcinogens, and better explanation of the reasoning that working groups use in reaching their evaluations. The amendment process included gathering suggestions from monograph meeting chairpersons, convening two advisory groups, and asking for public comments on a draft amended Preamble.

Agreement with The Lancet Oncology to publish monograph summaries
The results of *IARC Monograph* evaluations are of great interest to scientists and national health agencies worldwide, and there are frequent requests for rapid information about the scientific basis of the evaluations in a citable form. IARC and The Lancet Oncology have agreed to publish summaries of new evaluations within 4–8 weeks after each monograph meeting. During the biennium, five summaries were published, of volumes 88–92, plus an additional article on transparency in the *IARC Monographs*.

Future series of IARC Monographs *on air pollution*
A previous advisory group recommended that IARC develop a series of monographs on the broad topic of air pollution. In December 2004, IARC convened a scientific workshop to plan this series, to identify some agents and exposures to include, and to identify some key issues

Table 1. Overall evaluation of carcinogenicity of PAH

***Carcinogenic to humans* (Group 1)**
Benzo[a]pyrene*◆

Probably carcinogenic to humans (Group 2A)
Cyclopenta[cd]pyrene*◆
Dibenz[a,h]anthracene
Dibenzo[a,l]pyrene*◆

***Possibly carcinogenic to humans* (Group 2B)**
Benz[j]aceanthrylene*✳
Benz[a]anthracene
Benzo[b]fluoranthene
Benzo[j]fluoranthene
Benzo[k]fluoranthene
Benzo[c]phenanthrene*◆
Chrysene◆
Dibenzo[a,h]pyrene
Dibenzo[a,i]pyrene
Indeno[1,2,3-cd]pyrene
5-Methylchrysene

*Upgrade on basis of strong mechanistic data
✳First time evaluated
◆Higher group than previous evaluation

to consider in the evaluations. Workshop participants also drafted papers that will be compiled as individually authored chapters of an IARC Scientific Publication on air pollution and cancer. The first working group meeting for the series of monographs on air pollution, covering PAH compounds and mixtures, was held in October 2005 (see above).

The CIE Group is grateful to all participants in its Working Groups and Advisory Groups, who are listed in the respective volumes

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The Group of Endogenous Risk Factors studies the role of chronic inflammation in carcinogenesis at the molecular and cellular levels and in human subjects as well as in experimental animals. It also characterizes structural and functional modifications of nucleic acids and proteins induced 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.

Inflammation and cancer

Chronic inflammation caused by *Helicobacter pylori* infection has been associated with increased risk of stomach cancer. In collaboration with B. Bancel, B. Pignatelli, J. Estève and J.-C Souquet (Lyon, France) and S. Toyokuni (Kyoto, Japan) we have investigated levels of oxidative stress in preneoplastic and neoplastic gastric mucosa in relation to their pathological and histological subtypes. Over 100 human gastric adenocarcinoma samples were assessed immunohistochemically for expression of inducible nitric oxide synthase (iNOS) and occurrence of nitrotyrosine (NTYR)-containing proteins and 8-hydroxy-2'-deoxyguanosine (8-OH-dG)-containing DNA, as markers of nitric oxide production and damage to proteins and DNA. We found that iNOS-mediated oxidative stress was more frequent in intestinal-type carcinoma than in polymorphous carcinoma and diffuse carcinoma. In collaboration with T. Katoh (Miyazaki, Japan) and M. Tatemichi (Tokyo, Japan), we have also studied a possible association between stomach cancer and polymorphisms of some key enzymes and cytokines that play important roles in inflammation. We analysed polymorphisms in the promoter regions of the iNOS and interleukin-1 beta (*IL-1B*) genes in DNA samples from 158 Japanese gastric cancer patients (96 intestinal type and 62 diffuse type) and control subjects. We found an association between the intestinal type of gastric adenocarcinoma and higher promoter activity of the *iNOS* gene in women, especially those having higher promoter activity of the *IL-1B* gene and without a history of smoking. We also analysed a polymorphism in the promoter region of the haem oxygenase-1 *(HO-1)* gene in the same DNA samples. *HO-1* acts in cytoprotection against oxidants. Higher promoter activity of *HO-1* was associated with significantly increased risk of gastric cancer (intestinal and diffuse combined) in Japanese women. The effect of *HO-1* polymorphism was more significant when analysis was combined with *iNOS* polymorphism: gastric cancer risk was as much as 6.8 times higher in women having higher promoter activity of both *HO-1* and *iNOS* than in women with lower promoter activity of both enzymes. Similarly, in men, approximately three times higher gastric cancer risk was associated with higher promoter activity of both *HO-1* and *iNOS* compared with men having lower promoter activity of both. These results suggest that chronic inflammation, caused by nitric oxide generated by iNOS, and inhibition of cell death by HO-1 may contribute to *H. pylori*-induced gastric cancer.

Infection with *Opisthorchis viverrini* has been associated with increased risk of cholangiocarcinoma (CCA) in North-Eastern Thailand. In collaboration with P. Srivatanakul (Bangkok, Thailand), M. Miwa (Tsukuba, Japan) and S. Honjo, (Utsunomiya, Japan), we have investigated the role of chronic inflammation in development of CCA. Levels of nitrated and oxidized proteins as well as of 4-hydroxy-2-nonenal adducts were significantly elevated in plasma samples from CCA patients compared with those from healthy subjects. Modified proteins and those that are expressed specifically

in CCA patients but not in normal subjects are being isolated and characterized. Polymorphisms of a range of genes encoding oxidant-generating enzymes, enzymes that defend against oxidative stress and some cytokines have been analysed in DNA samples from normal subjects and CCA patients in Northern Thailand. We found an association between higher activity of the myeloperoxidase (MPO) gene promoter and CCA risk. In addition, we found a new polymorphism of the eosinophil peroxidase gene (EPO) that appears to be associated with increased risk of CCA. As parasite infection activates both MPO and EPO that generate oxidants such as hypochlorous acid and hypobromous acid, these polymorphisms may contribute to individual susceptibility to *O. viverrini*-associated CCA.

The roles in carcinogenesis of chronic inflammation and reactive nitrogen and oxygen species produced as part of an inflammatory response are being explored in an experiment with heterozygous Trp53-deficient (+/–) mice, which spontaneously develop sarcomas and thymic lymphomas, in collaboration with H. Tazawa (Tokyo, Japan), H. Ohgaki (IARC) and S. Kawanishi (Tsu, Japan). Chronic inflammation induced by subcutaneous implantation of a foreign body (a plastic plate) significantly increased the incidence and shortened the latency of sarcoma development in these mice, compared with mice without a foreign body. Strong accumulation of oxidatively and nitratively damaged proteins and nucleic acids (NTYR, 8-nitroguanine and 8-OH-dG) was detected immunohistologically. Loss of heterozygosity at the Trp53 locus was frequent and may be caused by increased production of reactive nitrogen and oxygen species. Efficacy of chemoprevention with various anti-inflammatory agents and anti-oxidants could be explored using this animal model.

Biomarkers

In collaboration with T. Akaike (Kumamoto, Japan) and M. Tatemichi (Tokyo, Japan), we have developed an analytical method to quantitate urinary 8-nitroguanine, which was first identified by our group as a major product of the reaction between guanine and peroxynitrite, a potent oxidizing and nitrating agent formed from nitric oxide and superoxide in inflamed tissues. Formation of 8-nitroguanine *in vivo* has recently been demonstrated immunohistochemically in samples from humans and animals with chronic inflammatory conditions associated with cancer susceptibility, such as gastric mucosa of patients with *H. pylori*-induced gastritis. 8-Nitroguanine formed in DNA may be mutagenic, inducing G to T transversions, possibly through depurination-dependent formation of mutagenic abasic sites and/or direct mispairing with adenine during replication. In order to study its role in carcinogenesis, we have developed a method to quantify 8-nitroguanine in biological fluids such as urine, using immunoaffinity purification with an anti-8-nitroguanine antibody, followed by quantitation with high-performance liquid chromatography with electrochemical detection. Using this method, we found that 8-nitroguanine is excreted in human urine and its urinary levels were higher in smokers (median, 6.1 fmol/mg creatinine) than in non-smokers (median, 0) ($P = 0.018$). The methodology developed can be used in molecular epidemiology studies to investigate the role of nitrative stress in human cancer associated with cigarette smoking and inflammation. In collaboration with T. Suzuki (Okayama, Japan), H.F. Mower (Hawaii, USA) and M.D. Friesen (IARC) we have also studied the reaction of tryptophan with several reactive nitrogen species and found that 6-nitrotryptophan may be useful as a biomarker of protein damage caused by reactive nitrogen species.

Etheno DNA adducts

Etheno DNA adducts are promutagenic lesions formed by some environmental carcinogens and by lipid peroxidation products. The role of etheno adducts in urethane-induced carcinogenesis has been further investigated, in collaboration with R. Wang (Corvallis, USA), using mice proficient or deficient in various DNA repair pathways. The results show that: (a) DNA ethenobases are repaired through the base excision repair pathway; (b) in addition, in replicating hepatocytes, they are repaired through the mismatch repair pathway; (c) 3,N^4-ethenocytosine is very efficiently repaired in mouse liver; (d) 1,N^6-ethenoadenine is a major initiating lesion in hepatocarcinogenesis induced by urethane or its proximate metabolite, vinyl carbamate; and (e) early stimulation of hepatocyte proliferation is another critical determinant of the hepatocarcinogenicity of urethane or vinyl carbamate. The dosimetry data obtained, in these studies, on DNA adduct formation and on effects on the cell cycle (apoptosis, proliferation) should be helpful in improving risk assessment related to urethane exposure.

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Publications

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The Molecular Carcinogenesis (MOC) Group conducts integrated studies on the mechanism of action of several genes involved in basic processes of tumorigenesis such as DNA repair, chromatin remodelling, cell-cycle control and apoptosis. Studies involve experimental approaches using cultured cells to investigate the effect of sequence variants and translational studies on biomarkers in a molecular epidemiological setting, as well as molecular pathological studies on well-defined series of tumour specimens.

DNA repair

Our work addresses the molecular mechanisms underlying DNA repair, as well as the contribution of chromatin dynamics to cellular responses to DNA damage and infection by tumour viruses. The *RDM1* gene (for *RAD52 M*otif 1) was identified as a result of a collaboration with Dr Buerstedde (Munich, Germany), by virtue of a small aminoacid motif shared with RAD52, a protein that plays a crucial role in DNA recombination and in repair of DNA double-strand breaks. We previously showed that RDM1 acts as a novel RNA recognition motif (RRM)-containing protein involved in the cellular response to the anti-cancer drug cisplatin and in the repair of cisplatin–DNA adducts. We have also recently discovered that RDM1 interacts with chromatin and plays a role in the epigenetic control of gene expression, a process that has a profound impact on the development and progression of tumours. RDM1 was also found to be specifically expressed during the response of a hepatoma-derived cell line *in vitro* to infection by the hepatitis B virus, one of the etiological factors of hepatocellular

carcinoma. These various facets of RDM1 are now being further explored.

The ATM (ataxia-telangiectasia (AT) mutated) protein plays a key role in the detection of DNA double-strand breaks and the cellular response. Epidemiological studies indicate that AT heterozygotes in AT families have an increased cancer risk, particularly of breast cancer. Data from extended AT families have been examined to investigate whether mutation type and position influence risk. Whilst no significant difference was found in the relative risk of cancer (breast or other) based on mutation type, the occurrence of breast cancer may be associated with truncating mutations in certain binding domains of the ATM protein.

The functional consequences of heterozygous *ATM* sequence variants on the cellular phenotype induced by ionizing radiation have been examined. Cell lines carrying heterozygous mutations and the linked sequence variants 2572T>C and 3161C>G had higher levels of radiation-induced micronuclei, suggesting that ATM alterations are associated with an altered cellular response to ionizing radiation. Presence of the 3161G variant allele was significantly associated with an increased risk of prostate cancer.

Proteins involved in detection and repair of DNA double-strand breaks are being studied in ten new patients with AT-like disorder (ATLD), all homozygous for an *MRE11* missense mutation. After exposure to ionizing radiation, fibroblast cultures carrying this mutation showed a dose-dependent defect in ATM signalling pathways, failure to form Mre11 foci and enhanced radiation sensitivity. These results show the importance of functional interactions between the three proteins of the Mre11-Rad50-Nbs1 (MRN) complex and lend support to its role as a sensor of DNA double-strand breaks, acting upstream of ATM.

In collaboration with I. Treilleux and J.-Y. Blay (Lyon), we found an association between reduced ATM or MRE11 expression in breast tumours and certain molecular characteristics of the tumour such as estrogen receptor expression.

To assess the relationship between the presence of variants in DNA damage detection and repair genes and risk of developing cancer, we are participating in large-scale studies in collaboration with several groups at IARC, with emphasis on analysis of DNA samples from cohorts of lung, head and neck and breast cancer patients and controls. The genotyping is being complemented with functional assays, making use of our large bank of lymphoblastoid cell lines.

The presence of certain polymorphisms in the human *XRCC1* gene has been associated with altered cancer risk, but the role of XRCC1 in single-strand break (SSB) repair in human cells remains unclear. To elucidate its role, RNA interference was used to modulate XRCC1 expression. Reduced protein levels led to decreased SSB repair capacity, hypersensitivity to the cell killing effects of DNA-damaging agents generating SSBs and enhanced formation of micronuclei and a significant delay in S phase progression after exposure to methyl methane sulfonate. These data clearly demonstrate that XRCC1 is required for efficient SSB repair and genomic stability in human cells.

Role of p53 and homologues in carcinogenesis

The *TP53* gene (encoding the p53 protein) plays a central role in carcinogenesis and is altered by mutation in many forms of cancer. Studies at IARC focus on the regulation and role of this gene in normal and diseased tissues. Novel mechanisms of p53 regulation at the mRNA level have been identified. The new p53 mRNAs differ in their coding capacity for an important functional domain of p53, resulting in the production of proteins that are unable to exert one of their key biological functions, gene transactivation. We are now studying how these mRNAs are produced, as well as the biological consequences of expression of these new, ubiquitous forms of the p53 protein.

Another important line of work is to elucidate the relationships between p53 and the mechanisms of the cell's response to stress, including in particular stress by oxidation/reduction. In collaboration with M.P. Merville (Liège, Belgium), we have shown that p53 can specifically up-regulate the pro-inflammatory enzyme Cox-2 (cyclooxygenase 2) by interacting with NF-κB, the main factor controlling the expression of Cox-2. We have also identified a role for thioredoxin and thioredoxin reductase, two cellular factors involved in the regulation of oxidized proteins, in the control of p53 protein activity.

The *TP53* gene belongs to a family that includes two other members, *TP63* and *TP73*. Studies have addressed whether and how these genes are altered in (squamous and adeno-) carcinomas of the oesophagus. Mounting evidence suggests that regulation of *TP63* is of central importance in determining the fate and pattern of differentiation of oesophageal mucosal cells. We are developing three-dimensional models for culturing normal oesophageal cells *in vitro* as tools to examine the role of *TP63* in the very early steps of oesophageal cell proliferation and differentiation.

We have developed new protocols to allow more rapid and accurate screening of *TP53, RAS* and *EGFR* mutations in cancers and have applied these approaches to lung cancers. Overall, at least one of these genes is mutated in the vast majority of lung cancers, but the nature, type and frequency of mutations show striking variations according to tumour histology and smoking history. Using a well-defined series of tumours from smokers, ex-smokers and never-smokers, we have demonstrated statistical differences in the patterns of mutations between the three groups. Whereas *TP53* mutations show special patterns in smokers in relation to exposure to tobacco carcinogens, *KRAS* mutations are more common in ex-smokers, whereas *EGFR* mutations are found almost exclusively in never-smokers. Thus, the genetic mechanisms of lung cancer development clearly differ according to the level, duration and continuation of smoking.

Over two thirds of all hepatocellular carcinomas (HCC) occur in low-resource countries, and are mainly attributable to interactions between chronic hepatitis B virus (HBV) infection and dietary exposure to aflatoxin. The latter is a potent mutagen that induces a specific mutation at codon 249 (ser249) commonly seen in HCC in low-resource countries. This mutation is being studied as an early marker for HCC risk in aflatoxin-exposed subjects. In a case–control study conducted in The Gambia, ser249-mutated *TP53*

was detected in plasma DNA of cancer and pre-cancer (cirrhotic) subjects, with a good overall concordance between its presence in the plasma and in the liver tissue. Studies are in progress on a large cohort of chronic HBV carriers and non-carriers to determine the timing of occurrence of the mutation in the plasma with respect to exposure to aflatoxin and development of precursor liver diseases.

In parallel, laboratory studies are being conducted to assess the functional impact of the ser249 mutant on liver cells. HCC cell lines expressing ser249 or other *TP53* mutants have been established and their properties have been compared. In collaboration with Dr K. Wiman and G. Selivanova (Stockholm, Sweden), these cell lines are being used to evaluate the cytotoxic effects of a prototypic anti-cancer drug, PRIMA-1, capable of specifically killing cancer cells that express defined forms of mutant *TP53*. The aim of these studies is to evaluate therapeutic approaches to the treatment of liver cancer in low-resource countries.

The IARC *TP53* mutation database is a web resource (http://www-p53.iarc.fr/) designed for the recording and analysis of *TP53* mutations associated with human cancers reported in the peer-reviewed literature. The latest updated database (July 2005) includes over 21,000 somatic and 280 germline mutations with related demographic, clinical and experimental information. The data can be freely analysed and downloaded through a dedicated web interface. Projects are in progress to analyse mutation patterns for identification of carcinogen fingerprints, and to characterize the biological impact of mutations. Within a collaborative European project on mutant p53 (http://www.mutp53.com/), we have assessed the prognostic value of *TP53* somatic mutations in a series of 1794 breast cancer patients. We found *TP53* mutation to be an independent factor of poor prognosis, with strong significance in tumours that retain hormone receptors. Moreover, different types of mutation may have different prognostic value. We are currently using bioinformatic approaches to predict the impact of mutations on protein structure and function.

Analysis of mutations in plasma DNA

In cancer patients, plasma often contains elevated amounts of altered free DNA released by cancer cells that may represent a marker for early cancer. GENAIR (GENetic susceptibility and AIR pollution) is a case–control study nested into EPIC (see Nutrition and Hormones Group), set up to clarify the association between air pollution or environmental tobacco smoking and cancers of the lung, upper aerodigestive tract and bladder as well as leukaemias in never-smokers and ex-smokers. Plasma DNA concentrations, measured in several hundred healthy subjects who later developed the cancers of interest and matched controls, revealed a significant association with the risk of developing leukaemia but not other cancers. A strong association was also found between subsequent bladder cancer development and detection of a mutation in *KRAS2*. Thus, mutations are detectable in the plasma of healthy subjects and may have value for early detection of cancer.

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Publications

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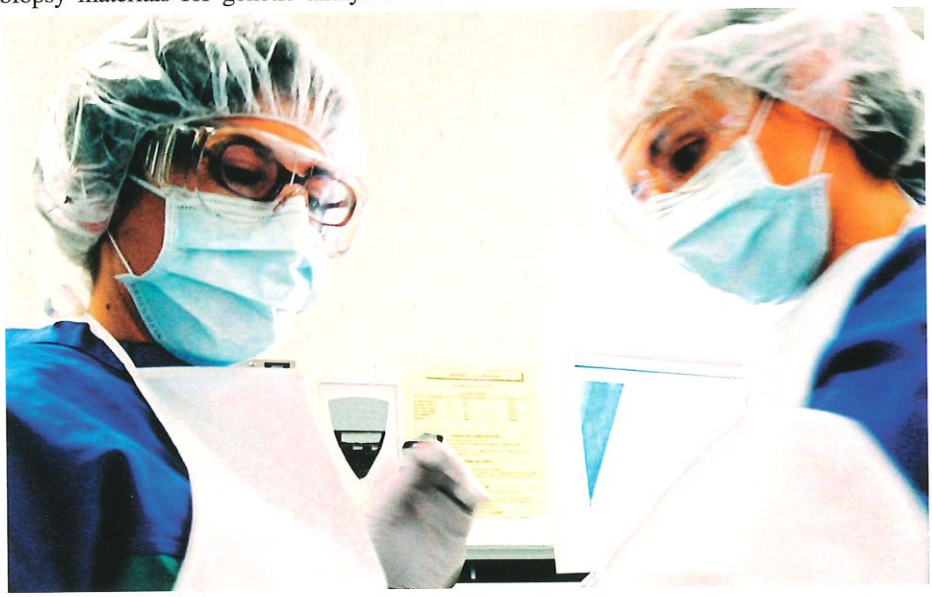
The IARC animal facility provides technical support for a range of studies of tumorigenesis. The technical staff perform and assist in a variety of procedures for research projects, such as chemical carcinogenesis, tumour implantation, hepatectomy, vasectomy and administration of chemical substances 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 Groups and programmes of IARC.

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.

Washing of glass laboratory equipment is centralized in order to ensure a reliable standard of cleanliness and to avoid duplication of effort.



Genetics and Epidemiology Cluster

Cluster Coordinator: Dr Paolo Boffetta

The overall goal of the Genetics and Epidemiology Cluster is to elucidate the contribution of genetic factors to the human cancer burden, as a component of the Agency's strategy of cancer control on a global scale.

The work of the four Research Groups comprising the Cluster extends from research on the structure and function of hereditary and acquired genetic alterations to the interactions between genetic and environmental factors in humans. Research in the Cluster encompasses several disciplines, including molecular biology, molecular genetics, population genetics, genetic epidemiology, molecular epidemiology and classical epidemiology.

The two main criteria used to prioritize research within the Cluster are: (a) the relevance of the subject of the research to the global burden of cancer, with particular emphasis on populations in low-resource countries, and (b) the opportunity for methodological developments, with emphasis on interdisciplinary approaches. As a consequence, many of the projects are based on collaborations within the Cluster and with other Groups in the Agency, and essentially all projects involve international collaboration.

The Gene–Environment Biology (GEB) Group conducts research aimed at identifying genes relevant to major human cancers, with emphasis on genes involved in DNA damage response and genomic stability. One important approach followed by the Group is the generation and characterization of animal models in which poly(ADP-ribose) polymerase (PARP-1), poly(ADP-ribose) glycohydrolase (PARG), Fanconi anaemia genes and NBS1 are mutated; these genes function in various cellular processes, including DNA repair, genomic stability, transcription and cell death. An additional important area of research of the Group is the functional and genetic study of chromatin modification and remodelling in gene transcription, cell-cycle control and DNA repair, encompassing both basic research on mechanisms of epigenetic alterations and applied studies on their role in human cancer.

The Genetic Cancer Susceptibility (GCS) Group is composed of two teams: the Genetic Services Platform Team is responsible for the laboratory component of medium- to large-scale genotyping studies conducted within the Cluster and by other IARC Groups, including standard sequencing and large-scale resequencing projects, while the High-Risk Genes Team conducts research on known and strong candidate high-risk cancer susceptibility genes as well as studies directed towards discovery of new moderate-risk and high-risk susceptibility genes.

The Genetic Epidemiology (GEP) Group conducts studies aimed at identifying specific genes predisposing to breast and nasopharyngeal carcinoma through linkage analysis of high-risk families, through association or case–control studies with known polymorphisms, and in the future, through whole genome scans. A further goal is to estimate the age- and site-specific risks of cancer conferred by mutations and polymorphic variations in these genes, and examine how these risks are modified by known environmental factors. In addition, together with the Gene–Environment Epidemiology Group, it coordinates and conducts multicentre case–control studies on genetic and environmental factors in the etiology and pathogenesis of cancers of the lung, the upper aerodigestive tract and the kidney, and of lymphoma.

In addition to working on the multicentre studies mentioned above, the Gene–Environment Epidemiology (GEE) Group coordinates international networks of investigators with the aim of exploiting existing research resources (e.g., pooled analysis of gene–environment interactions). It also conducts prospective cohort studies in low- and medium-income countries, to investigate the role of lifestyle and genetic factors in populations with specific cancer patterns.

During 2004–05, research within the Cluster has resulted in over 150 scientific papers and grants have been obtained from the European Commission, from several national programmes, including notably the US National Cancer Institute, and from charities and foundations. The Cluster has hosted a large number of doctoral and postdoctoral students and visiting scientists.

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Cancers are a combined consequence of genetic mutations and environmental factors that lead to inappropriate activation or inactivation of specific genes, thereby leading to neoplastic transformation. Many molecules involved in DNA repair and DNA damage signalling are thought to play an important role in maintaining genomic integrity in response to endogenous and exogenous DNA damage. Epigenetic modifications, including DNA methylation, histone acetylation, methylation and poly(ADP-ribosyl)ation, link chromatin remodelling and gene expression, which affect virtually every step in tumour progression. Studying the functions of relevant genes in chromosomal stability, DNA repair, cell-cycle control, cell death pathways, chromatin remodelling, and the role of environmental factors in causing specific genetic and epigenetic changes is therefore fundamental to improving our ability to prevent, diagnose and treat cancer successfully.

The Gene–Environment Biology (GEB) Group is using genetically modified cellular and animal models to study the molecular mechanisms of genes responsible for DNA damage response and cell-cycle control in regulating genomic stability and neoplastic transformation, and to establish relationships between cancer susceptibility and environmental exposures.

DNA damage response

Poly(ADP-ribosyl)ation is an immediate cellular response to DNA damage generated either exogenously or endogenously. This post-translational modification is an extensive but transient modification mediated by poly(ADP-ribose) polymerase (PARP-1) and broken down by poly(ADP-ribose) glycohydrolase (PARG). PARP-1 is known to be involved in various cellular processes such as DNA repair, genomic stability, transcription and cell death.

We found that mice containing a cleavage-resistant PARP-1 were protected from endotoxic shock and intestinal ischaemia/reperfusion, associated with a reduced inflammatory response, due to compromised production of specific inflammatory mediators. This has provided valuable insight into the function of PARP-1 in inflammation.

To investigate the function of PARG and degradation of polymers *in vivo*, we have generated mice lacking the principal form of the *PARG* gene, which were hypersensitive to alkylating agents and ionizing radiation and susceptible to streptozotocin-induced diabetes and endotoxic shock. In cell lines derived from these mice, DNA repair was delayed following genotoxic treatments, and sister-chromatid exchange, micronuclei,

chromosomal aberrations and amplification of centrosomes were increased.

Poly(ADP-ribosyl)ation is rapidly stimulated after DNA damage caused by the generation of reactive oxygen and nitrogen species during renal ischaemia/reperfusion. The degree of renal injury and dysfunction was significantly reduced in our mice lacking PARG, which were also protected from intestinal reperfusion-induced damage due to reduced expression of P-selectin and ICAM-1, and TNF-α-production. These results suggest that PARG activity modulates the inflammatory response in organ damage. Taken together, our data demonstrate that poly(ADP-ribose) homeostasis plays an important role in DNA damage response, genomic stability and in pathological processes.

In p53-mutant mice, PARP-1 deficiency leads to a higher frequency of mammary gland carcinomas and brain tumours. Analysing the molecular pathways by which PARP-1 and p53 cooperate in mammary carcinoma formation, we found that *PARP-1*-deficient mice developed mammary lesions with a long latency, and that introduction of *Trp53* mutations accelerated mammary tumorigenesis in *PARP-1*-deficient females. These mammary carcinomas displayed a multi-stage progression with local metastasis reminiscent of human breast cancers. Epithelial cells from these mammary tumours exhibited chromosomal aneuploidy and centrosome amplification. In addition, PARP-1 deficiency compromised recruitment of Brca1 to DNA damage sites. These results demonstrate a critical role for poly(ADP-ribosyl)ation in regulating Brca1 and p53 in mammary tumorigenesis. Moreover, we have identified heterozygous rare genetic variants in *PARP-1* exons in human sporadic breast cancers. Thus, PARP-1 may participate in the etiology of human breast cancer.

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disease characterized by microcephaly, growth retardation, chromosomal instability, immunodeficiency, radiosensitivity and predisposition to cancer. We have generated mutant mice in which the relevant gene, Nbs1, can be eliminated in specific tissues and cell types. When *Nbs1* was deleted in neural tissues, mice showed a combination of the neurological anomalies of NBS, ataxia telangiectasia (AT) and AT-like disorder, including microcephaly, growth retardation, cerebellar defects and ataxia, due to proliferation and apoptosis defects. Nbs1-deficient neuroprogenitor cells contained more chromosomal breaks, accompanied by ATM-mediated p53 overactivation. Depletion of p53 significantly rescued the neurological defects of these mice. This study demonstrates an essential role for *NBS1* and DNA damage response in the neurological anomalies of NBS. Moreover, inactivation of the *Nbs1* gene in the lens caused cataract due to disruption of normal lens epithelial and fibre cell architecture and incomplete denucleation of fibre cells, revealing a novel function of Nbs1 and the MRN complex in cataractogenesis. Finally, specific inactivation of *Nbs1* in lymphoid cells led to severely impaired immunoglobulin class switch recombination in B-lymphocytes suggesting an essential function of Nbs1 in this physiological process.

NBS1 functionally interacts with numerous DNA repair proteins, linking early DNA damage detection with DNA double-strand break (DSB) repair. We constructed mouse *Nbs1-null* embryonic stem (ES) cells and embryonic fibroblast cells (MEFs), and used them to show the indispensable role of Nbs1 protein in activation of both Atm- and Atr-mediated pathways in response to DNA damage. We also showed that Nbs1 modulates DSB repair pathways by promoting homologous repair while repressing non-homologous end-joining. These findings confirm the important role of Nbs1 in DNA damage response and DSB repair.

Fanconi anaemia (FA) is a rare autosomal recessive disease characterized by bone marrow failure, congenital abnormalities and predisposition to cancer. FA cells exhibit hypersensitivity to DNA interstrand cross-links and high levels of chromosome aberrations. The products of a number of genes associated with FA interact with BRCA1, RAD51 and the MRN complex, suggesting involvement in DSB repair. We investigated the pathway by which the FA complex functions in DSB repair using mouse and cellular models. Our observations have identified classical FA proteins as an integrated component in the early step of homologous repair of DSBs and suggest an early role for the FANC proteins in choice between homologous DSB repair pathways.

Epigenetic modifications, including chromatin modification/remodelling, play an important role in many important cellular processes, such as DNA replication, cell-cycle control, DNA repair and genomic stability. Recent genetic and molecular studies have provided a direct link between dysfunctional chromatin modification and human cancer. Many molecules and complexes involved in chromatin modification/remodelling have been identified, but their functional significance remains elusive. We have investigated the function of histone acetylation and chromatin remodelling in cellular processes, including cell proliferation, gene transcription, cell-cycle control as well as DNA repair. In mammalian cells, loss of the histone acetyltransferase (HAT) cofactor Trrap led to chromosome missegregation, mitotic exit failure and compromised mitotic checkpoint due to defective Trrap-mediated transcription of the mitotic checkpoint proteins Mad1 and Mad2. These results demonstrate that Trrap controls mitotic checkpoint integrity by specifically regulating the *Mad1* and *Mad2* genes.

We have also engineered a mammalian cellular system to examine chromatin modification/remodelling and the loading of DNA repair proteins specifically associated with DSBs. We showed that Trrap and Tip60 HAT bind to sites of DSBs *in vivo*, resulting in both DNA damage-induced histone H4 hyper-acetylation and accumulation of repair molecules at sites of DSBs. Depletion of Trrap resulted in defective homologous recombination repair. The impaired loading of repair proteins at sites of DNA breaks and the defect in DNA repair in Trrap-deficient cells could be counteracted by chromatin relaxation, indicating that the DNA repair defect observed in the absence of Trrap is due to impeded chromatin accessibility at sites of DNA breaks. Thus, cells may use the same basic mechanism involving Trrap-associated HAT

complexes to regulate distinct cellular processes, such as transcription and DNA repair. Taken together, these findings demonstrate the instrumental role of HAT components and histone acetylation in coordination of cell-cycle control and DNA repair.

Cell–cell interaction

The role of gap junction intercellular communication disorders in carcinogenesis is well established. Due to their ability to reverse cancerous phenotypes, certain connexin proteins (Cx) are considered to act as tumour suppressors. However, mutational alterations of connexin genes are rarely detected in human tumours. Since polymorphic variants of some connexin genes are detected in certain pathological conditions associated with perturbed cell growth and differentiation, we verified whether rare variants of the Cx26 (GJB2) gene could genetically predispose to certain types of human cancer. Genetic analysis of groups of patients with colon or stomach cancer from North-Western regions of the Russian Federation revealed a substantially higher frequency of heterozygous carriers of certain rare variants of this gene compared with healthy subjects, indicating that certain variants of Cx26 could be considered as new factors of genetic predisposition to digestive tract cancers.

The GEB Group is grateful to the following for their collaboration in its projects:

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Publications

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Research in the Gene–Environment Epidemiology (GEE) Group is aimed at identifying environmental causes of human cancer and their interactions with genetic factors. The work also contributes to methodological development in the field of molecular and genetic epidemiology. The focus has been on cancers of the lung, the upper aerodigestive tract and the kidney, and on lymphoma, and studies of pancreatic and childhood cancer are now being planned. The programme consists of multicentric international studies carried out in collaborating centres, coordination of networks of investigators and the use of existing resources such as cancer registry data. Various types of study design are used (case–control, cohort, record linkage) and all field studies include a biological component.

Multicentric case–control studies

During 2004–05, the GEE Group completed a series of multicentric case–control studies of lung cancer, upper aerodigestive tract cancer (cancers of the oral cavity, pharynx, larynx and oesophagus) and kidney cancer in Central and Eastern Europe and in South America, regions characterized by high incidence and mortality from these forms of cancer. Each study included a series of cases of cancer selected in major clinical centres of participating countries and a series of controls recruited either from the general population or among hospital patients with non-neoplastic diseases. For each participant, detailed information was collected via a questionnaire on environmental risk factors, including in particular tobacco smoking, alcohol drinking, dietary habits and history of employment. Exposure to a large series of known and suspected occupational carcinogens was assessed by teams of local experts. Blood samples were collected from all study subjects, to be used mainly as a source of DNA, and tumour tissue samples were collected from cases whenever possible. The large numbers of subjects in these studies allow the possibility to assess effects of weak risk factors and to investigate gene–environment interactions.

The full exploitation of this material will take several years; genotyping work is still in progress, in collaboration with the GEP and GCS Groups. Results already available on lung cancer include an increased risk among people in Central Europe who underwent a large number of occupational X-ray examinations, an apparent protective effect of eczema, an increased risk from indoor air pollution (mainly from cooking) in Central Europe and an increased risk from occupational exposure to vinyl chloride. Results of the analyses on effects of genetic variants on risk of lung and head and neck cancers are reported in the GEP and GCS sections. Further analyses of environmental factors and their interactions with genetic variants are continuing.

A similar approach has been used for a multicentric study of lymphomas, conducted in six European countries. Recruitment of cases and controls has been completed and statistical analyses

have revealed a decreased risk of lymphoma among users of statin drugs, while individuals with a family history of lymphatic neoplasms experienced a 70% increased risk. Tobacco smoking and alcohol drinking had no effect on the risk of this group of neoplasms.

The work of the Group in the epidemiological studies described above has been extended to the coordination of international consortia, which have the following goals: (a) fast and coordinated replication of new findings, (b) pooling of data for analyses for which large populations are needed, typically for gene–environment interactions, and (c) setting standards for future epidemiological research. In particular, the Group has played a key role in the establishment of consortia of studies of lymphoma (InterLymph [http://epi.grants.cancer.gov/InterLymph/index.html]), head and neck cancer (INHANCE [http://inhance.iarc.fr/]) and lung cancer (ILCCO). An initial pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer risk revealed no increased risk of head and neck cancer for the *ADH1C* Ile350Val polymorphism that encodes for an enzyme resulting in 'fast' metabolism of ethanol. Several additional pooled analyses have been started. The coordination of international consortia is likely to become a major component of the work of the Group in the next few years.

Cancer in populations in transition

The Group is supporting prospective studies of cancer in populations in transition. A first study was established in four cities of the Russian Federation (Barnaul, Bysk, Tomsk and Novgorod). Relatives and neighbours of individuals who died in the last 15 years are identified and invited to provide key information on the decedents: this part of the study, with a target of 80,000 deceased individuals, aims to assess the role of tobacco, alcohol and occupation in the recent dramatic mortality trends experienced by the Russian population. In addition, the same set of respondents is being invited to participate in a prospective study, by answering a questionnaire focused on the same risk factors and by providing a small blood sample. The goal for the prospective study is to recruit 160,000 individuals by 2006, who will be followed up via linkage with local mortality registries. A similar prospective study is being carried out in the Golestan province of North-Eastern Iran, an area of very high oesophageal cancer incidence. Following a successful pilot study, recruitment of inhabitants of the city of Gonbad and of rural areas of the province started in 2004 and is expected to reach the goal of 50,000 individuals, mainly of Turkmen ethnicity, in 2007. Each cohort member undergoes a detailed interview on dietary and lifestyle factors and provides samples of blood, urine, hair and nails. The follow-up was tested in 2005 and has proven effective in identifying deaths and occurrence of cancer. Finally, initial work has been carried out in two centres in Southern India (Chennai and Trivandrum) to set up a pilot study for a prospective cohort of diet and cancer, to be completed in 2007.

Methodology

Important achievements in the area of development of methods for molecular and genetic cancer epidemiology include the application of a novel statistical technique (hierarchical modelling) to combine the results of multiple genetic markers to a study of genetic polymorphisms and bladder cancer risk; and the use of serum cotinine as a marker of tobacco smoke exposure in a prospective study of lung cancer, which yielded a stronger dose–response relationship than that obtained using questionnaire data.

Tobacco carcinogenicity

The Group has also aimed to clarify important aspects of tobacco carcinogenicity. Relevant studies have shown (a) a link between smokeless tobacco products and pancreatic cancer risk, (b) a dose–response relationship between involuntary smoking and lung cancer risk, (c) a sharp decline in the cumulative risk of lung cancer after cessation of tobacco smoking, even among smokers who quit after the age of 50 years, (d) the tobacco-related risk of specific histological types of lung cancer and of cancer in specific locations of the larynx, and (e) the role of tobacco in determining second primary neoplasms among laryngeal cancer survivors.

Risk of second primaries in cancer patients

Using a pooled data-set of over 4 million cancer patients registered in 15 registries, analyses have been conducted on risk of second primaries. After male breast cancer, risk of haematopoietic neoplasms was increased; after non-Hodgkin lymphoma, a complex pattern of associations could be explained by both treatment and shared risk factors; and after small intestine cancer, an increased risk of digestive and other neoplasms was explained by common risk factors and possibly overdiagnosis. Work to explore the risk of second primaries after other neoplasms is continuing.

Occupational cancer

A case–control study of lung cancer has been started among European asphalt workers, with the aim of clarifying whether the increased risk detected in the historical cohort phase of the study is due to exposure to bitumen fume, exposure to other agents in the asphalt industry, or to confounders such as tobacco smoking and exposures in other industries.

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It has long been recognized that family members of an individual with cancer are themselves at increased risk of cancer. This 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 genetic variants that increase the risk of common cancers, and how these genetic effects interact with known environmental risk factors, it will be possible to elucidate the reasons why cancers develop and to potentially identify individuals who are at particularly high risk.

The goals of the Genetic Epidemiology (GEP) Group are to:

1. Conduct large case–control studies of specific cancers, and participate in international consortia, in order to ensure that studies have adequate sample size.
2. Identify cancer-predisposition genes through linkage analysis of high-risk families, through association or case–control studies with known polymorphisms and, in the future, through whole genome scans.
3. Estimate the age- and site-specific risks of cancer conferred by mutations and/or polymorphic variations in these genes, and examine how these risks are modified by known environmental factors.
4. Contribute to the development of statistical tools for analysing genetic data.

Alcohol- and tobacco-related cancers

While it is clear that lung and upper aerodigestive tract cancers are caused predominantly by exposure to tobacco and alcohol products, only a minority of heavy smokers and heavy drinkers develop such a cancer. Furthermore, second primary cancers in this group are common, suggesting a high initial genetic susceptibility among these individuals.

A series of large multicentre case–control studies of lung and head and neck cancers have been completed in Europe and Latin America, comprising over 15,000 subjects. Genetic analysis of 60 potential susceptibility genes has been completed among 2000 lung cancer cases, 1000 head and neck cancer cases and 2000 controls in the European component of these studies. Three notable initial findings include (a) the modification of the protective effect of cruciferous vegetable consumption by GST genes, providing strong evidence for a substantial protective effect of cruciferous vegetable consumption on lung cancer, which is unconfounded by other dietary and lifestyle factors, (b) an important role of cell-cycle control genes in lung cancer etiology, and in particular variants of the *TP53* gene, and (c) identification of variants in the *ADH1B* and *ALDH2* genes that explain a substantial proportion of head and neck cancers.

Work is now being planned to replicate positive findings in independent studies. For this purpose, the studies on head and neck cancer will be replicated in an independent series of studies in Latin America and Western Europe. Similarly, a series of over 1000 lung cancer cases, based on the EPIC cohort, will provide a suitable resource for replicating potentially important findings for this cancer. More extensive genotyping using comprehensive panels of haplotype tagging SNPs is also planned, and the feasibility of whole genome scans will be assessed. The Group is also coordinating the International Lung Cancer Consortium (ILLCO), with the aim of pooling information and results from all large studies of lung cancer.

Breast cancer

Women who carry germline mutations in the *BRCA1* and *BRCA2* genes are at greatly increased risk of breast cancer. Multiparity, early age at first childbirth and breastfeeding are known protective factors for breast cancer in the general population, although their effect in carriers of *BRCA1* or *BRCA2* mutations may be different. Further, the marked reduction in breast cancer risk following a prophylactic oophorectomy illustrates that endogenous hormones play an important role in the etiology of breast cancer among *BRCA1/2* mutation carriers, as they do in the general population. So far, little is known about the safety of oral contraceptives among *BRCA1/2* mutation carriers, who have much higher premenopausal background rates of breast cancer. Furthermore, numerous studies have shown that exposure to ionizing radiation is a risk factor for breast cancer. Because of the role of the BRCA proteins in DNA repair, we hypothesized that women who carry mutations in these genes might be more sensitive to ionizing radiation than women in the general population.

The current enrolment of the International *BRCA1* and *2* Gene Carrier Cohort Study (IBCCS) study includes 3460 subjects, mostly women. 74% of the participants are from three national-level studies in the UK, France, and the Netherlands, with further subjects from Austria, Canada, Denmark, Germany, Hungary, Italy, Poland, Spain and Sweden. Included in the cohort are 1885 subjects who were affected at the time of entry to the study (1647 total breast cancer diagnoses and 357 ovarian cancers) and 1283 women were unaffected at enrolment. Two-thirds of the unaffected women were aged 30–49 years at enrolment, thus in the period of highest breast cancer risk for *BRCA* mutation carriers. At least one follow-up questionnaire is already available on 966 of the enrolled subjects.

Special emphasis is now being placed on collection of detailed pathology, treatment and clinical data on all incident cases. Integration with existing studies in Australia, and expansion to include additional centres in Canada and the Czech Republic is planned to increase the total recruitment to 5000 mutation carriers by the end of 2006.

A retrospective cohort study of 1601 female BRCA1/2 mutation carriers, of whom 853 already had breast cancer at the time of interview, has also been performed. Breast cancer risk in mutation carriers was reduced by 11% with each birth. The protective effect was restricted to women aged over 40 years, and was consistent for carriers of mutations in either gene. Neither interrupted pregnancies nor breastfeeding had a significant effect on risk. Risk of breast cancer was slightly increased among *BRCA1/2* mutation carriers who had ever used oral contraceptives, with no difference according to features of oral contraceptive use such as time since stopping, duration of use, age at start and calendar year at start. In the entire cohort, any reported exposure to chest X-rays (compared with never-exposed) was associated with a significantly increased risk of breast cancer. This risk was increased in mutation carriers aged 40 and younger, and in women born after 1949, particularly those exposed before the age of 20 years. The risk increase in BRCA mutation carriers due to exposure to ionizing radiation was considerably higher than in other exposed populations. Although part of this increase may be attributable to recall bias, the observed patterns of risk in terms of age at exposure and attained age are consistent with those found in previous studies.

Combined effects of variants in low-penetrance genes seem to explain best the non-*BRCA1/2* familial susceptibility to breast cancer. We are examining the contribution of genetic variants in around 500 case–control pairs from Thailand, as an activity within the international Breast Cancer Association Consortium (BCAC). We predict our BC cases to be enriched in genetic susceptibility variants, as around 60% of them were diagnosed before age 50 years. We also expect a reduced number of phenocopies from environmental influences in this low-incidence Asian population, especially among women from rural areas. Our initial association studies are focusing on variants in DNA-repair and cell-cycle regulatory genes.

We are also assessing the influence of common variants in genes such as *RAD51* and *AIB1* which may modify the effect of *BRCA1* and *BRCA2* mutations in our sample set of around 1200 *BRCA1/2* mutation carriers. So far, no major breast cancer-modifying effect of any of these these genetic variants has been detected.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a malignancy with a wide range of incidence rates across the world. In most areas, it is rare (e.g., 0.5 cases per 100,000 per year in the UK), but in certain regions it occurs in an endemic form with an incidence 10 to 40 times higher. Endemic regions include the southern parts of China, other parts of South-East Asia and the Maghreb (Morocco, Algeria and Tunisia); NPC is also prevalent among inuit populations. We are conducting studies on the role of genes and environmental factors in the etiology of NPC in Sarawak (Malaysia) and North Africa.

The highest rates of NPC worldwide have been reported to occur among the Bidayuh population of Sarawak State, Malaysia, where age-standardized rates exceed 30 per 100,000 among men. In view of the relative homogeneity of this population, we are conducting studies to investigate both high-risk and moderate-risk susceptibility genes for NPC. For this purpose, we are recruiting a series of multi-case families with NPC in order to conduct a whole-genome linkage analysis. Detailed typing of HLA class I and other candidate genes in the HLA region will also be conducted on a group of 250 NPC cases, controls and unaffected parents or siblings. Further data on environmental exposure and infection with Epstein–Barr virus (EBV) will allow assessment of gene–environment interactions.

In the Maghreb, NPC is the most frequent ear, nose and throat cancer, accounting for 7–12% of all cancers and may appear as early as ages 8–10 years. In contrast with other high-risk populations, NPC in the Maghrebian population has a bimodal age distribution, one peak occurring in the teens and the other at 45–50 years. A multicentre case–control study of NPC has been performed in Morocco, Algeria and Tunisia including 664 cases. Initial genotyping and analyses are

focusing on 17 candidate genes involved in immune response (HLA A, B, E, G, DQ, DR, DO, Il 1, Il 4, Il 6, Il 10), detoxification (GSTM1, GSTT1), cell-cycle regulation (TP53), DNA repair (XRCC1, hOGG1) and immune regulation.

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During 2004–05, the Genetic Cancer Susceptibility Group (GCS) underwent a substantial reorganization. It is now composed of two teams, the Genetic Services Platform Team (GSP) and the High-Risk Genes Team (HRG). In general, GSP is responsible for the laboratory component of medium- to large-scale genotyping studies conducted within IARC, for standard sequencing, and for large-scale resequencing projects. On the other hand, HRG is responsible for ongoing analyses of known and/or strong candidate high-risk cancer susceptibility genes as well as studies directed towards discovery of new moderate- and high-risk susceptibility genes.

Establishing a laboratory platform

Over the last few years, the main effort of the GCS Group has been towards building a platform for relatively high-throughput genotyping, sequencing and mutation screening. Two key characteristics of this platform are: (a) the integration of several multipurpose laboratory robots into the process, dramatically increasing the number of samples that technicians can process, while decreasing the likelihood of pipetting errors; and (b) use of a laboratory information management system (LIMS) to track the progress of samples as they flow through the laboratory, while also reducing potential for sample tracking errors.

The principal genotyping technique used is TAQMAN. The laboratory automation allows SNP genotyping throughput to be regularly maintained at 40,000 genotypes per week and occasionally to exceed twice that level. The platform also supports fluorescent microsatellite genotyping, which is now being used to complete a genome scan for new breast cancer susceptibility loci. For the resequencing component of mutation screening projects, we rely mostly on dye primer chemistry, which is much less expensive than the more common dye terminator chemistry. The resulting sequence chromatograms are analysed with a program, written in Java at IARC, called *Java Mutscreen*. However, even with efficient laboratory automation and analysis software, large-scale mutation screening by resequencing is labour-intensive, and therefore a high-throughput mutation scanning process is now being developed.

Large-scale genotyping projects

During 2004–05, several large projects have used the high-throughput genotyping capacity of the GCS Group. These include: (a) genotyping for the EPIC project's investigation into the contribution of variation in genes of the steroid hormone pathway and the insulin-like growth factor (IGF-I) pathway, and their associated receptor proteins, to risk of breast and prostate cancer (approximately 460 000 genotypes analysed by August 2005); (b) the CAPS project, an investigation of variation in the genes of the IGF-I pathway in relation to prostate cancer risk in the Swedish population (25,000 genotypes analysed by August 2005); (c) EPIC's investigation of the contribution of genetic variation in the fatty acid synthesis pathway and the IGF-I pathways to risk of breast cancer (84,000 genotypes analysed by August 2005) and (d) the GEP Group's project on genetic susceptibility to tobacco- and alcohol-related cancers in central Europe (approximately 350,000 genotypes completed by August 2005).

Analysis of missense substitutions

Data from screening for mutations in high-risk susceptibility genes such as *BRCA1, BRCA2, MLH1* and *MSH2* are used in clinical practice to advise patients on their risks of breast, ovarian, colon, endometrial and other cancers, and on possible risk-reduction strategies. The latest clinical testing methods have very high sensitivity for clearly deleterious sequence variants such as frameshifts and other protein-truncating mutations, but also find many unclassified sequence variants (UCVs). Both types of mutation are reported to physicians, who in turn inform the patients, but test reports that include a UCV are ambiguous and create difficulties for both physician and patient. In recent years, considerable effort has been directed to analysis of UCVs, in particular unclassified missense substitutions, with the goal of developing efficient methods to classify many of them as either neutral or deleterious. An analytical framework has been developed that integrates four different methods of UCV analysis. Each of the four component methods is an independent estimator of risk. Accordingly, each risk estimate is formulated as an independent likelihood expression, and these are multiplied together in order to obtain the overall likelihood that a particular UCV is deleterious or not. This framework is already being applied in other laboratories, and should contribute to classification of a considerable number of UCVs over the next few years. One of the methods integrated within the framework identifies groups of unclassified substitutions that are highly enriched for deleterious mutations and other groups that are highly enriched for neutral substitutions. Such methods depend heavily on cross-species sequence comparisons of the genes of interest. Along these lines, we have developed new software (A-GVGD) for measuring the fit between missense substitutions and the evolutionary range of variation observed at their position in the protein of interest, and have also determined *BRCA1* and *BRCA2* gene sequences from a number of other species. The A-GVGD substitution analysis software is to be made available over the internet for interested external research groups. We are preparing to extend our systematic cross-species sequence analyses to cover other susceptibility genes such as *MLH1, MSH2, TP53,* and *CHEK2.*

Biological assays of gene function also contribute towards classifying UCVs. Thus assays that can discriminate between functional and non-functional alleles of *BRCA1* and *BRCA2* have been developed, and the output from these assays is being calibrated against human genetic data so that the results can be incorporated into Goldgar's integrated framework. Combined with better tools for measuring risk associated with these groups of missense substitutions, we expect the integrated framework and improved versions of the methods that it combines to provide an efficient, robust, and clinically useful approach to the analysis of UCVs in *BRCA1* and *BRCA2*. In addition, we are collaborating in plans to extend Goldgar's integrated framework to MLH1, MSH2 and other susceptibility genes.

Genes conferring susceptibility to common cancers

Germline mutations in the *BRCA1* and *BRCA2* genes explain only a minority of the excess familial aggregation observed for premenopausal breast cancer. The aims of this project are to identify the chromosomal location of one or more additional breast cancer susceptibility loci and to estimate the frequency of alterations in such genes and the associated risk. IARC has contributed linkage data from 275 individuals from 63 families to this international effort and a similar-sized contribution of more data to a second-round analysis.

Many of the early analyses suggest that there may be several breast cancer susceptibility genes yet to be identified (rather than a 'BRCA3' alone explaining all of the residual familial breast cancer aggregations). Future work will involve devising and testing strategies to identify groups of families whose cancers are more likely to be due to a similar genetic dysfunction (e.g., breast cancer morphology, age of onset, ethnicity).

IARC has brought together a consortium of geneticists and clinicians with interest in identifying the remaining predisposition genes for colorectal cancer. The aim is to document large numbers of multiple-case colorectal cancer families and related clinicopathological data centrally in a custom-designed database at IARC. Preliminary work to exclude known syndromes such as familial adenomatous polyposis (FAP) and mismatch repair-deficient hereditary non-polyposis colorectal cancer (HNPCC) has started. This will generate a valuable resource for future collaborative genome-wide scans for linkage and association studies.

Several concurrent projects are applying different strategies for the identification of prostate cancer susceptibility genes. One strategy has adopted an innovative study design utilizing resequencing and mutation scanning of germline DNA from highly selected, internationally collected, prostate cancer cases and controls in a candidate gene approach. A second approach is to collaborate with large international linkage studies searching for prostate cancer susceptibility loci, particularly linkage analysis of large extended pedigrees using high-density SNP-based genome-wide scans, in collaboration with the Menzies Research Institute, Hobart, Tasmania, Australia.

Identifying young women with breast cancer who carry BRCA1 mutations

Tumours arising in carriers of *BRCA1* germline mutations have a distinctive morphological appearance. In collaboration with the NCI-sponsored breast cancer family resource (BreastCFR), we have identified 700 cases of early-onset breast cancer that have this distinctive BRCA1-associated morphology and/or a very strong family history of breast cancer. We are assessing what proportion of these cases carry BRCA1 mutations that can be identified using routine approaches and applying additional screening methods to detect other types of BRCA1 mutations. The data from this study will allow treating physicians to estimate the likelihood of any woman diagnosed with early-onset breast cancer being a carrier of a *BRCA1* mutation. This could lead to referral of those identified as being at high risk of carrying a *BRCA1* mutation to genetic clinics and counselling. We hope to apply this very successful approach to other genes that are known to predispose to breast and colorectal cancer.

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Publications

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Pathogenesis and Prevention Cluster

Cluster Coordinator: Dr Hiroko Ohgaki

The Pathogenesis and Prevention Cluster (PPC) includes the Pathology Group, the Screening Group, the Gambia Hepatitis Intervention Study Group and Screening Quality Control Group. The Pathology Group studies the molecular pathology of human neoplasms, in particular brain and prostate tumours, using biopsy materials from patients with clinical data and follow-up. The objectives are to correlate histologically recognized phenotypes with genotypes, to elucidate the molecular basis and genetic pathways of human cancer, to identify genetic and expression profiles predictive of tumour progression and outcome of patients, and to identify etiological factors in the pathogenesis of human tumours. The Pathology Group also supervises the histology laboratory, that provides a high-quality routine histology service to all IARC Groups.

The Screening Group aims to facilitate the development of feasible, accurate and cost-effective screening and early detection interventions for breast, cervical, oral and other cancers and the development of quality assurance standards for screening in different settings by conducting field studies and model-based studies in collaboration with national institutions and by international consultation. In the domain of breast cancer control, a community-based cluster-randomized controlled trial has been planned to evaluate the effectiveness of a package of interventions consisting of health education, opportunities for clinical early diagnosis and the provision of readily accessible diagnosis and treatment services. Screening approaches such as low-intensity cytology, HPV testing and visual screening with acetic acid (VIA) and Lugol's iodine (VILI) are being evaluated for their efficacy in detecting cervical precancerous lesions and preventing cervical cancer in several cross-sectional and randomized controlled trials. The efficacy of screening in reducing oral cancer mortality among users of tobacco and alcohol has been established in a recently completed randomized controlled trial. Costing and modelling studies in the study contexts are being carried out to evaluate the cost–benefit relationship of each intervention. Efforts are made to develop quality assurance standards in different settings. A variety of training materials for screening diagnosis and treatment of precursor lesions have been produced in the context of these projects.

The Gambia Hepatitis Intervention Study, which was launched in 1986, has now reached its mid-point. This study aimed at assessing whether the vaccination of infants against Hepatitis B Virus may induce a long-lasting protection against liver cancer in adulthood. Ongoing GHIS activities include nationwide cancer registration in The Gambia, support to clinical and laboratory infrastructures for cancer detection and diagnosis, and research on the molecular epidemiology and natural history of hepatocellular carcinoma in the Gambian population. According to the original study, it is estimated that GHIS will deliver its final message in about 15–20 years.

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The Molecular Pathology Team has focused on the molecular pathology of brain tumours and is now planning similar studies on prostate cancer. In 2004–05, we completed the first population-based study combining incidence and survival rates with data on key genetic alterations in astrocytomas and oligodendrogliomas. A total of 987 cases were diagnosed in the Canton of Zurich, Switzerland, between 1980 and 1994 and patients were followed up at least until 1999. While the survival rate for pilocytic astrocytomas (WHO grade I) was excellent (96% at 10 years), the prognosis of diffusely infiltrating gliomas was poorer, with median survival times of 5.6 years for low-grade astrocytoma WHO grade II, 1.6 years for anaplastic astrocytoma (WHO grade III) and 0.4 years for glioblastoma (WHO grade IV). TP53 mutations were most frequent in gemistocytic astrocytomas, present in about half of fibrillary astrocytomas, but infrequent in oligodendrogliomas. Loss of heterozygosity (LOH) at 1p/19q typically occurred in tumours without TP53 mutations, and was most frequent in oligodendrogliomas (69%), but rare in low-grade astrocytomas. Glioblastomas amounted to two thirds of the total incident cases. The observed survival rate was 17.7% at one year. For all age groups, survival was inversely correlated with age. Primary (de novo) glioblastomas prevailed (95%), while secondary glioblastomas that progressed from low-grade or anaplastic gliomas were rare (5%). In primary glioblastomas, LOH 10q was the most frequent genetic alteration (69%). LOH 10q occurred in association with any of the other genetic alterations, and was the only alteration associated with shorter survival of glioblastoma patients. Secondary glio-blastomas were characterized by frequent LOH 10q and TP53 mutations. Over half of the TP53 mutations in secondary glioblastomas were in hot-spot codons 248 and 273, while in primary glioblastomas, mutations were more evenly distributed. G:C → A:T mutations at CpG sites were more frequent in secondary than primary glioblastomas, suggesting that the acquisition of TP53 mutations occurs through different mechanisms in these glioblastoma subtypes.

Low-grade astrocytomas are genetically characterized by frequent TP53 mutations and show a consistent tendency to progress to glioblastomas, while oligodendrogliomas show frequent and concurrent LOH 1p and 19q, and may progress to anaplastic oligodendrogliomas. The histological diagnosis of these gliomas may be very difficult, with marked inter-observer variation, particularly in cases that lack the typical patterns of astrocytic and oligodendroglial differentiation. This is at least partly due to the lack of specific and reliable markers for neoplastic oligodendrocytes. We carried out gene expression profiling on histologically and genetically typical oligodendrogliomas and low-grade astrocytomas, using a cDNA array containing 1176 cancer-related genes. Cluster analysis and partial least squares analysis of 79 genes that had at least a two-fold difference in expression between oligodendrogliomas and low-grade astrocytomas revealed clear distinctions between oligodendrogliomas, low-grade astrocytomas and normal cerebral white matter. Cluster analysis based on the entire gene set also divided the 17 subjects with oligodendrogliomas into two subgroups with significantly different survival. These results demonstrate that oligodendrogliomas and low-grade astrocytomas differ in their gene expression profiles, and that there are subgroups of oligodendrogliomas with distinct expression profiles related to clinical outcome.

Pilocytic astrocytoma (WHO grade I) is a circumscribed, slowly growing, benign astrocytoma that most frequently develops in the cerebellar hemispheres and in midline structures, and occurs predominantly in childhood and adolescence. In contrast to diffusely infiltrating gliomas in adults, survival of patients with pilocytic astrocytoma is excellent

after surgical intervention. To search for potential molecular mechanisms underlying its benign biological behaviour, we compared gene expression profiles of pilocytic astrocytomas with those of normal cerebellum, low-grade astrocytomas and oligodendrogliomas by cDNA array analysis. A number of immune system-related genes were up-regulated in pilocytic astrocytomas, and clustering analysis using selected subgroups of genes based on their molecular functions revealed that immune system-related genes (75 genes) showed similar power to the entire gene set for separation of pilocytic astrocytomas from diffusely infiltrating low-grade gliomas. Immunohistochemical analysis revealed diffuse expression of HLA-DRα in neoplastic cells of pilocytic astrocytomas. These results suggest that the benign biological behaviour of pilocytic astrocytomas may be at least in part related to up-regulation of immune defence-associated genes.

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The core function of the screening group involves evaluation of the accuracy, reproducibility, efficacy, benefits, harmful effects and cost-effectiveness of screening interventions for breast, cervical, oral and other cancers and the development of quality assurance standards for screening in different settings, in collaboration with national institutions. The objective is to guide the development of public health policies in implementing, monitoring and evaluating screening in a range of health-care settings, particularly in low- and medium-resource countries, leading to rational utilization of health-care resources and to improving quality of life, based on evidence from field- and model-based studies.

Breast cancer

Breast cancer incidence rates are increasing in many countries. Early detection linked to optimal treatment is currently the most effective strategy to reduce breast cancer mortality. Mammographic screening is an expensive intervention requiring substantial financial and manpower resources and thus is not feasible in developing countries. The efficacy of organized programmes using breast self-examination (BSE) and/or clinical breast examination (CBE) remains uncertain. Improved survival and outcome could be achieved by a package of interventions aiming at improving the awareness of the population on symptoms, signs and the good prognosis associated with treatment of early-stage disease, and at improved access to effective diagnostic and treatment services. A cluster-randomized controlled trial involving 120,000 women in Kerala, India has been initiated in collaboration with the Regional Cancer Centre, Trivandrum, India, to evaluate the effectiveness of a comprehensive intervention consisting of health education, opportunities for clinical early diagnosis and the provision of readily accessible diagnosis and treatment services, in terms of clinical early detection and improved outcome of breast cancer.

Oral cancer

Oral cancer is an important cancer globally, with two thirds occurring in less developed countries. Although it is largely preventable by avoidance of tobacco and alcohol use, a high incidence is observed in the Indian sub-continent, central and Eastern Europe, parts of Southern Europe, South America and Oceania. Oral cancer is a suitable disease for screening, in view of the detectable precancerous lesions and preclinical early invasive cancers and the improved survival following treatment of early cancers. A randomized controlled screening trial involving 178,000 subjects in Trivandrum district, Kerala, India, in collaboration with the Regional Cancer Centre, to address the efficacy of visual screening in reducing oral cancer mortality, was completed in 2004. The study was supported by the Association for International Cancer Research (AICR). More than 90% of the 96,500 eligible subjects in the intervention group were screened at least once and two thirds of the 5200 screen-positive subjects complied with referral investigations. A 34% reduction in oral cancer mortality was observed among tobacco/alcohol users in the screened group who completed three rounds of screening at three-year intervals, compared with the control group. This is the first time a reduction in oral cancer deaths following screening has been demonstrated in a randomized trial. The results imply that oral visual screen-

ing can reduce mortality among high-risk individuals and could prevent at least 37,000 oral cancer deaths annually worldwide.

The natural history of oral precancerous lesions such as leukoplakia and submucous fibrosis in terms of probabilities of regression, persistence and progression to invasive cancer, as well as factors influencing participation in screening, are also being addressed in the oral cancer screening trial. The overall and cause-specific mortality among participants in this study is being analysed to establish the risk and patterns of death associated with various types of tobacco and alcohol-drinking habits prevailing in the region.

Cervical cancer

Cervical cancer continues to be the major cancer among women in many regions of the world, with more than 80% of the world burden experienced in low- and medium-resource countries of Asia, Africa and Central and South America. Effective cytological screening has been responsible for impressive declines in cervical cancer incidence and mortality in the developed countries of Europe, North America, Japan and Australia, but in many low- and middle-income countries, screening has not been effectively implemented or has failed to reduce the cervical cancer burden. The difficulties and inadequate resources for implementing high-quality cytology screening programmes in such settings have prompted evaluation of the feasibility, accuracy, efficacy and cost-effectiveness of other screening methods such as visual inspection with 3–5% dilute acetic acid (VIA), magnified VIA (VIAM), visual inspection with Lugol's iodine (VILI) and HPV testing in preventing the occurrence of and deaths from cervical cancer. A major component of the work of the Screening Group involves evaluation of the comparative performance of these screening methods in cross-sectional and cluster-randomized controlled trials, in collaboration with national institutions and/or ministries of health in countries such as Angola, Burkina Faso, Republic of Congo, Guinea, India, Laos, Mali, Mauritania, Nepal, Niger, Nigeria and Tanzania. These studies are supported by the Bill & Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention (ACCP).

The results from pooled cross-sectional studies involving more than 52,000 women indicate that VIA and VILI are accurate and promising screening tests for detection of high-grade cervical cancer precursor lesions. These studies have helped to standardize the reporting of the visual test results, the training of test providers and quality assurance procedures. They have also served as a platform of service for the detection and treatment of cervical precancerous lesions and training of personnel in cervical cancer prevention in the health services of the participating countries.

The efficacy of a once-in-a-lifetime VIA screening in preventing cervical cancer is being assessed in two cluster-randomized controlled trials in India. In one of the studies, in Dindigul District, southern India, 78,000 women have been randomized to VIA screening by nurses or to a control group. The screening round has been completed and more than 70% of the women participated in the programme. In 1% of the screened women, a high-grade cervical precancerous lesion or invasive cervical cancer was detected. The study groups are being followed up to determine the reduction in mortality from cervical cancer in the screening group as compared to the control group.

The efficacy and cost-effectiveness of a single round of screening by VIA, cytology or HPV testing on cervical cancer incidence and mortality is being investigated in a cluster-randomized controlled trial in Osmanabad district, India. 143,000 women have been randomized into four arms for screening by trained midwives with either VIA, cytology or HPV testing or to a control group. More than 70% of the women in the different groups were screened. The detection rates of high-grade lesions were around 1% in all intervention arms. More than half of the invasive cancer cases in the screened groups had stage I (early) disease, compared with a fifth of those in the unscreened group. The results show that a high level of participation can be achieved in low-resource settings and that VIA is a useful alternative, but requires careful monitoring. The detection rates with HPV testing were similar to those with cytology and VIA, despite higher investment. The ultimate effectiveness of the three approaches will become clear with follow-up for cancer incidence and mortality.

The cure rates associated with cryotherapy, loop electrosurgical excision procedure (LEEP) and cold knife conization for cervical precancerous lesions are being studied in the above field studies. Formal costing of the various interventions is being carried out to facilitate studies of cost-effectiveness. A variety of training materials for screening, diagnosis and treatment of precancerous lesions have been produced in several languages based on the experience in field projects. New locations to evaluate existing and emerging screening technologies for different cancers are being explored.

Survival

Monitoring the survival of cancer patients in populations can contribute to improving the efficiency of health services and patient care. Survival outcome of 575,000 cancer patients registered during 1990–2001 in 29 population-based cancer registries in 16 countries (Brazil, China, Colombia, Costa Rica, Cuba, Gambia, India, Republic of Korea, Pakistan, Peru, Philippines, Singapore, Thailand, Turkey, Uganda, Zimbabwe) has been analysed and shows wide variations. Survival was better in locations with more developed health services, giving improved access and more opportunities for early detection and treatment (e.g. Singapore, Hong Kong, Republic of Korea) than in those with less developed health services (e.g. sub-Saharan Africa). For instance, the five-year age-standardized relative survival from breast cancer exceeded 70% in Singapore, Hong Kong, Republic of Korea (Incheon, Seoul, Busan), but was under 50% in India, Philippines, and only 10% in The Gambia. The results provide valuable insight on potential for improving cancer health services in low- and medium-resource settings.

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Book

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Screening Quality Control Group

Head
Dr Lawrence von Karsa

Secretary
To be appointed

The Screening Quality Control Group was established in September 2005, has a primary aim to develop and expand the scientific basis for the application and improvement of quality control in the process of cancer screening which extends from information of the target population, to performance of a given screening test, to subsequent diagnosis and therapy of screen-detected lesions. This activity should not only generate essential data and experience for countries seeking to establish and maintain effective cancer screening programmes fulfilling high ethical standards. Implementation of organized, quality assured activities at every step in the screening process generally also has a profound spin-off effect on the quality of cancer care delivered outside of screening programmes, due to the requisite development of infrastructure for screening. As a result, persons also benefit from such quality improvements when they undergo diagnosis and therapy outside of a screening programme. The overall reduction in mortality and improvement in quality of life resulting from such improvements in cancer services can therefore significantly exceed the benefit resulting solely from earlier detection of cancer in screening.

Initial activities of the Screening Quality Control Group are co-financed by the European Commission in the framework of the current EU Public Health Programme. They comprise coordination of the European Cancer Network (ECN) which serves as an umbrella organisation for the Cancer Screening Networks established under the Europe Against Cancer Programme (European Breast Cancer Network, European Cervical Cancer Network, European Network of Cancer Registries). The ECN umbrella will also be extended to the new EU Networks for Information on Cancer (EUNICE) and Colorectal Cancer Screening. Through the ECN the new Member States which entered the European Union in 2004 and applicant countries will be integrated into the mainstream of European projects to improve the quality of secondary prevention of cancer.

The Colorectal Cancer Screening Network is currently being established in a second project managed by the Screening Quality Control Group which has been earmarked for funding under the 2005 EU public health programme. The primary project aim will be to develop evidence-based guidelines for quality assurance of colorectal cancer screening.

Collaborators:

Dr Marc Arbyn, Brussels, Belgium; Dr M. Broeders, Nijmegen, The Netherlands;
Dr R. Holland, Nijmegen, The Netherlands; Susan Knox, Milan, Italy; Szilvia Madai, Public Association for Healthy People, Budapest, Hungary
Julietta Patnick, Oxford, United Kingdom; N. Perry, London, United Kingdom;
Dr Nereo Segnan, Turin, Italy; S. Törnberg, Stockholm, Sweden; C. de Wolf, Fribourg, Switzerland

External funding
European Commission

The Gambia Hepatitis Intervention Study

Project leader
Dr Pierre Hainaut

Registrar
Mr Ebrima Bah

Hepatocellular carcinoma (HCC) is the most frequent form of primary liver cancer and is a major cause of death in sub-Saharan Africa and eastern Asia. The main etiological factor in these regions is chronic infection with hepatitis B virus (HBV), namely the chronic carrier status. Other factors that contribute to the etiology of primary liver cancer in these regions include other hepatitis viruses (HCV) and dietary exposure to aflatoxins, a group of mycotoxins that are natural contaminants of the staple diet. The latter have a multiplicative effect on the virus-associated risk of developing HCC.

The Gambia Hepatitis Intervention Study (GHIS) is a collaborative undertaking by IARC, The Government of the Republic of The Gambia and the Medical Research Council of the United Kingdom. This programme was launched in 1986 with the objective of evaluating the efficacy of hepatitis B (HB) vaccination in childhood for the prevention of HBV infection, chronic liver disease and HCC in a population at high risk. The implementation of this study involves three overlapping phases. During phase I, the vaccine, approved by the World Health Organization, was phased into the Gambian Expanded Programme on Immunization (EPI) over a four-year period from July 1986 to February 1990. Two groups of children were recruited, one of about 60,000 children who received all EPI vaccines (BCG, DPT, polio, measles, yellow fever), and the other of a similar number of children who received all vaccines plus HB. Since February 1990, HB vaccination has been offered to all newborns as part of the EPI in The Gambia. During phase ll (1991–97), the efficacy of HB vaccine against infection and chronic carriage was estimated through longitudinal and cross-sectional surveys in selected groups of HB-vaccinated and unvaccinated children. Phase lll (initiated in 1998) consists of the long-term follow-up through cancer registration, using HCC as the primary end-point.

The cross-sectional phase II studies have demonstrated that by 10 years of age, the vaccine efficacy is of 83% against HBV infection and of 94% against chronic carriage. Despite waning antibody titres, the protection against carriage remains high into adolescence. A National Cancer Registry was set up early in the project to identify and record data on cancers of all types occurring in The Gambia. The cases are ascertained in public or private health departments with the support of the National Health Laboratory and Histopathology Services. For HCC diagnosis, clinical criteria, ultrasonography and alpha-fetoprotein measurement are used in combination according to a protocol validated against histology in Senegal. The final outcome of GHIS will be evaluated through record linkage between HCC cases in the registry and the GHIS database of vaccinated and unvaccinated children.

The proportion of HCC attributable to HBV and HCV infections was assessed in a recent case–control study on 197 incident cases of HCC and 405 matched, hospital-based controls. HBV carriage was present in 63% of HCC cases and 16% of controls, while 19% of HCC cases were HCV seropositive compared to 3% of controls. Increased HCC risk was strongly associated with chronic HBV, HCV and dual infection. Overall, the results suggest that between 60 and 80% of HCC under age 50 is attributable to HBV. In parallel, molecular analysis demonstrated an increased risk of HCC associated with several polymorphisms in genes involved in the metabolism and detoxification of aflatoxin, as well as in the repair of aflatoxin–DNA adducts.

In 2004, experts of the IARC Scientific Council carried out a comprehensive review of GHIS achievements, as well as a re-assessment of predicted outcomes. Twenty years after it was conceived, the design of the GHIS appears to have well resisted the trials of time and field experience. The evidence available indicates that the major endpoint of the study, the evaluation of the protective efficacy of childhood HB vaccine against HCC, will be attainable between 2017 and 2020, slightly earlier than under the initial assumption of an overall follow-up of 35–40 years. The final success of this unique, long-term endeavour will depend upon the continuing development of sustainable infrastructure for cancer detection, diagnosis and registration, for monitoring viral infections, and for performing record linkage. Such infrastructure will not only contribute to the final research outcome of GHIS, but may also provide a backbone for the development of other interventions aimed at preventing cancer and better managing patients in the setting of a low-resource African country. Finally, the strategy adopted for the development of GHIS provides a model for the introduction of new vaccines in the EPI of African countries.

The Gambia Hepatitis Intervention Study is grateful to the following for their collaboration:

Patrizia Carrieri, Marseille, France; Andrew Hall, London, UK; Funmi Lesi, Lagos, Nigeria;
Maimuna Mendy, Banjul, Republic of The Gambia; Ruggero Montesano, Lyon, France,
Sarah Rowland-Jones, Omar Sam, Banjul, Republic of The Gambia;
Simonetta Viviani, Ferney-Voltaire, France; Hilton Whittle, Banjul, Republic of The Gambia

Publications

Kirk GD, Lesi OA, Mendy M, Akano AO, Sam O, Goedert JJ, Hainaut P, Hall AJ, Whittle H, Montesano R. The Gambia Liver Cancer Study: Infection with hepatitis B and C and the risk of hepatocellular carcinoma in West Africa. *Hepatology* 2004; 39(1): 211-219

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EUROCAN+PLUS Group

Acting Head
Dr Philippe Autier

Secretary
Ms Asiedua Asante

The EUROCAN+PLUS project is funded by the European Commission and was launched in October 2005. The main objective of the project is to improve the coordination of cancer research efforts in Europe, including basic science, clinical science, epidemiology and public health aspects. The EUROCAN+PLUS Project is directly supported by the European Parliament and is funded by the European Commission. Both of these bodies are awaiting the conclusions of the Project in order to shape the future of cancer research within the European Union. Coordination of EURO-CAN+PLUS will be ensured by the EUROCAN+PLUS (CAP) Group of the Agency, under the aegis of the Director, IARC. This new project will collaborate with the European Institutions who are the most active in cancer research, and approximately 200 scientists are expected to participate in EUROCAN+PLUS.

The initial meeting of EURO-CAN+PLUS was held at the IARC in October 2005. The Project will progress through the activities of eleven 'working groups' who have specific objectives. The synthesis of the work done by the working groups will serve as the basis for future recommendations to the European institutions.

Communications Group

Head
Dr Nicolas Gaudin

Editor
Dr John Cheney (until September 2005)

Librarian
Ms Sharon Grant

Assistants (IARC*Press*)
Ms Susan Cotterell
Ms Donna Flint (until December 2004)
Ms Christine Mogenet
Ms Sibylle Soering (until April 2005)

Technical assistants
Mr Georges Mollon
Ms Maria de la Trinidad Valdivieso Gonzalez
Mr Jérome Croibier (until February 2004)
Ms Latifa Bouanzi

Secretary
Ms Bernadette Geoffre

Trainees
Ms Delphine Alloatti (April–July 2005)
Ms Rebecca Greenfield (January–April 2004)

The Communications (COM) Group 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 research Groups in all matters related to information.

Publications/editing service
The COM Group continues to assist all scientific Groups in disseminating their research results by providing editorial advice and help for publication of articles in international scientific journals, as well as graphic services. Under the IARC*Press* imprint, the Agency completed publication of the ten volumes in the third edition of the WHO Classification of Tumours. It also made available free access to the updated Globocan 2002 through the Descriptive Epidemiology server on the IARC web site, and is preparing to set up similarly easy access to the larger database of Cancer Incidence in Five Continents, Volumes I–VIII.

Web services
The COM Group maintains the Agency's internet site, which has been developed in the period under review into a bilingual presentation enabling users to switch language, at document level, between English and French, the Agency's two official and working languages. The Group also manages the intranet service, which provides staff with many administrative resources, and maintains several central databases for the Personnel and Finance offices.

IARC*Press*
The Washington, DC office of IARC*Press* was closed at the end of 2004, and arrangements are now being made to transfer the entire responsibility for marketing and distribution of new and older books to the corresponding service at WHO Headquarters in Geneva, which already markets IARC publications.

Pubic relations

Press relations
The Public Relations Service ensures relations between the Agency and the media, writing and distributing press releases, and organizing press conferences. By means of a database of media contacts around the world, the service dispatches press releases to about 2300 e-mail addresses, press agencies, individual journalists and decision-makers.

The impact of this effort is evident from the news coverage raised by several releases over the biennium, that made headlines around the world. This service coordinates the issue of press releases on new evaluations within the Monographs programme with publication of a summary in the Lancet Oncology Policy Watch section, which offers the Agency a regular tribune for independent and transparent results.

External relations
The COM Group also plays a role in promoting the external relations of the Agency, and arranged the IARC 40th anniversary celebrations in 2005, that brought together in Lyon the past and present Directors of the Agency, several world-class keynote speakers, representatives of the local medical and scientific community and local officials.

Translation
The Translation Service provides translations from English to French of all official documents of the Governing Council and Scientific Council of IARC, as well as articles, technical documents,

correspondence, memoranda and other texts for all the scientific and administrative Groups. It also organizes successful language courses in both working languages for the Agency's staff, as well as administering the United Nations language proficiency examinations.

Library

The Library supports the information and research needs of IARC scientists through a wide range of electronic resources, a traditional print library collection, and by providing responsive, user-centred reference and instructional services. Desktop access to electronic information is facilitated by participation in resource-sharing and collaborative programmes with the WHO Library and Information Networks for Knowledge.

The Library's Intranet web site is the gateway for the delivery of information services and resources to the IARC community. This provides access to the library catalogue, electronic journals, databases, electronic reference resources and document delivery services.

The IARC Library also responds to external needs by providing reciprocal services to specialized libraries in Lyon and by welcoming reference enquiries from the public.

IARC Education and Training

One of the statutory functions of the Agency in its mission to promote international collaboration and support of all phases of cancer research is the training and education of personnel. The Agency seeks to achieve this aim through its fellowship programme and its courses programme which are designed to assist the development of cancer research and prevention in all countries, with special emphasis on low- and medium-resource countries, as well as those in which such work is not well established, and to train future collaborators in the scientific programme of the Agency.

Cancer research fellowships

IARC Research Training Fellowships

The aim of this programme has been to provide young postdoctoral scientists from any country with training in aspects of cancer research ranging from biostatistics and epidemiology to envionrmental chemical carcinogenesis and mechanisms of carcinogenesis, so that they can return to their own country to implement and develop programmes in cancer research or cancer control. At the beginning of 2005, given the widespread possibilities for training in cancer research for students in developed countries, the programme was refocused and reorganized in an attempt to make a unique contribution in this area by giving priority to junior scientists from low- or medium-resource countries who are engaged in research in medical or allied sciences, and wish to pursue a career in cancer research. Training is now offered in any of the Agency's research Groups in Lyon and the duration of the fellowship has been extended to two years.

The Fellowships Selection Committee met twice in Lyon during the 2004-2005 biennium to review applications; the members of the Committee are given below.

In 2004, among a total of 44 candidates, 28 were evaluated by the full Selection Committee and 8 finally awarded; in 2005 under the new programme format, 21 applications were received of which 13 were evaluated by the full Selection Committee and 8 fellowships finally awarded. The list of fellows is given in Table 1.

Fellowship Selection Committee

2004	2005
Dr David Goldgar (IARC) Responsible Officer	Dr Paolo Boffetta (IARC) Responsible Officer
Dr Lucio Luzzatto (Italy)	Dr Carlo La Vecchia (Italy)
Dr Kenneth Nilsson (UICC Representative)	Dr Edith Olah (Hungary)
Dr Edith Olah (Hungary)	Dr Petra Peeters (The Netherlands)
Dr Tikki E. Pangestu (WHO Representative)	Mr Martyn Plummer (IARC)
Dr Petra Peeters (The Netherlands)	Dr Curzio Rüegg (UICC Representative)
Dr Alain Puisieux (France)	Dr Sean Tavtigian (IARC)
Dr Ze'ev Ronai (USA)	Dr Andreas Ullrich (WHO Representative)
Dr Peter Swann (UK) (Chairperson	
Dr Keiji Wakabayashi (Japan)	
Dr Elisabete Weiderpass-Vainio (IARC)	

The Italian Association for Cancer Research continued its generous support of the Fellowships Programme, providing a total of 100, 000 over the two-year period.

Postdoctoral fellowships at IARC

The IARC in-house postdoctoral fellowships programme, spanning from 1998 to 2004, was merged into the new Fellowship Programme in 2005. In 2004, from a total of 27 eligible applications received from 13 countries, 5 postdoctoral fellowships were awarded (see Table 2). These Fellows contributed significantly to IARC's research activities and received good training and experience, thus enhancing the prospects for their future scientific career.

Visiting Scientist Award

In 2004, this Award was given to Dr Christine Friedenreich (Alberta Cancer Board, Calgary, Alberta, Canada), who spent a year in the Hormones Team, Nutrition and Hormones Group and in 2005 to Dr Gajalakshmi Vendhan (Epidemiological Research Center, Chennai, Tamil Nadu, India), who will spend one year in the Gene-Environment Epidemiology Group.

Expertise Transfer Fellowship

With the reorganization of the Fellowship Programme, a new "Expertise Transfer Fellowship" was introduced in 2005 to enable an established and experienced investigator to spend from six to twelve months in an appropriate host institute in a low- to medium-resource country in order to transfer knowledge and expertise in a research area relevant for the host country and related to the Agency's programmes. The first selection will take place in 2006.

Table 1. Research Training Fellowships awarded in 2004 and 2005

Name	Country of Origin	Host Country
2004		
BACKVALL, H. V.	Sweden	USA
BOUKHERIS, H.	Algeria	France
CHIGANCAS, V.	Brazil	France
FASERU, B.	Nigeria	Finland
JAKS, V.	Estonia	Sweden
OLSEN, A. H.	Denmark	UK
PENDINO, F.	France	Norway
ZUO, J.	People's Republic of China	UK
2005		
AL-ZOUGHOOL, M.	Jordan	
BABIKYAN, D.	Armenia	
DAR, N.A.	India	
DE CARVALHO, L.V.	Brazil	
RAZA, S.A.	Pakistan	
SAPKOTA, A.	Nepal	
SHIEKH, I.H.	India	
SZYMANSKA, K.	Poland	

Master's / Ph.D. Programme

The Master's/Ph.D. fellowship programme is a new feature of the programme, introduced in 2005. This aims to provide an M.Sc. and/or a Ph.D. to students from low- and medium-resource countries working in areas of cancer research relevant to prevention. The fellowships are organized in collaboration with a number of international Universities and are tenable at IARC, with joint supervision. 12 applications from candidates in 6 countries were received in response to the first announcement.

Table 2. In-house postdoctoral fellowships awarded in 2004

Name	Country of Origin
2004	
LOIZOU, J.	UK
MCKAY, J.D.	Australia
LIM, M. K.	Republic of Korea
HSU, C.	USA
HOAREAU-ALVES, K.	France

IARC Seminar Series

IARC's formal seminar series was introduced in 2004 to provide a more structured framework for training of junior staff and for communication among scientists. Attendance at the seminars forms part of the on-going training programme.

Trainees, students, postdocs and senior visiting scientists at IARC

In addition to the fellowship programme and in keeping with the Agency's mission to provide education and training in the field of cancer research, as well as to provide appropriately qualified persons with training and experience in cancer research and related support areas at IARC in positions that will provide some complementary support to the Agency's activities. IARC welcomes a substantial number of trainees, students, postdocs and visiting scientists each year (between 60 and 70), who come either with outside funds or who are funded in part or in total by the Agency.

The health and safety of all those working at IARC being an on-going preoccupation, the application and admission procedure for these categories of non-staff was reviewed in 2005, taking into account vaccination requirements for those coming to work in the Agency's laboratories, as well as the necessity for all newcomers to follow basic safety training on arrival. This resulted in a new application form and new guidelines being drawn up which will enter into effect on 1 January 2006, and should benefit all who are working at IARC.

Training Courses

During 2004 and 2005 three courses were held within the core programme, hosting 277 participants, of whom half were financially supported by IARC. This brings the total number of courses organized since the start of the programme in 1968 to 122 and the total number of attendees to 4972. In addition, the Descriptive Epidemiology Group organized a range of courses on cancer registration and descriptive epidemiology and the Screening Group on screening and treatment to prevent cervical cancer in less developed countries.

The Courses Programme was remodelled in 2005, with the IARC Summer School in Cancer Epidemiology and Biostatistics being established as the focal point, aiming to stimulate research in cancer epidemiology by improving scientific knowledge and developing skills among researchers worldwide. Special attention is given to low- and middle-income countries. By helping to develop local expertise in cancer epidemiology and by strengthening research institutions through international collaborations, IARC aims to enhance cancer prevention.

International courses on cancer epidemiology

Tonga (Nuku'Alofa), Pacific, 17-28 May 2004

The course, organized in collaboration with Massey University and the Ministry of Health, Tonga, was attended by 44 participants from 14 countries. The teaching team comprised 2 IARC staff, 2 local and 4 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 provided by the organizers helped 12 participants to attend. The course directors were Neil Pearce (New Zealand) and Sunia Foliaki (Tonga).

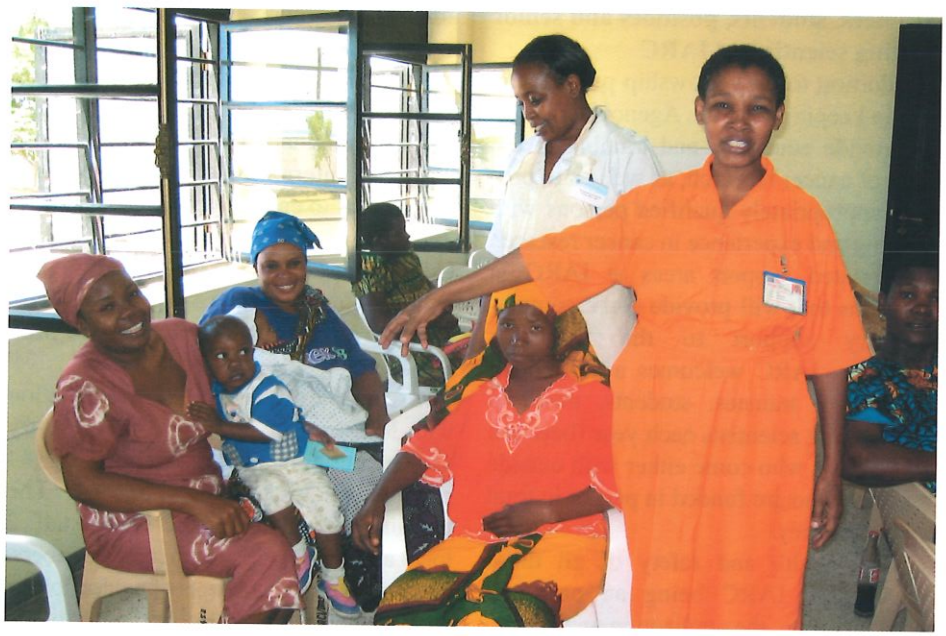
Specialized courses

Sixth international course on molecular epidemiology

Nashville, TN, United States, 7-10 June 2004

The sixth international course on molecular epidemiology was organized in collaboration with Vanderbilt University, the Vanderbilt-Ingram Cancer Center (NCI/-CCC) and the International Epidemiology Institute. It was attended by 46 participants.

Theory class at cervical cancer screening and treatment course in Xiangyuan, People's Republic of China. September 2004



Auxiliary nurse with women waiting to be screened. Cervical cancer screening and treatment course, Dar-es-Salaam, Tanzania. July 2004

IARC summer school on cancer registration and applications in epidemiology

The eighth Summer School on Cancer Registration took place in Lyon on 19 April 7 May 2004, following on the usual model, with the first three weeks devoted to formal training at IARC followed by 3 days at cancer registries in Europe, Brazil and India, gaining practical experience of registration activities. The course organizer was Eva Démaret (IARC). There were 20 participants from 15 countries. The course participants were supported by grants from the US National Cancer Institute, the UICC, the WHO Regional Office for Africa (AFRO), IARC, and the Alliance for Cervical Cancer Prevention (ACCP).

European Network of Cancer Registries courses

The ENCR has organized training courses of five types, covering general registration, statistical methods, coding, EUROCIM use (with special emphasis on the time trends analysis module), and automation in cancer registration.

One course on cancer registration was held in Lyon, France in 2005 with support from the Cancéropole Lyon Auvergne Rhône-Alpes (course organizer: Lorenzo Simonato, Italy). Twenty-seven participants from 9 countries attended.

Courses on screening for cervical cancer

IARC regularly organizes training courses on screening and treatment to prevent cervical cancer in less developed countries. These courses are entirely funded by the Alliance for Cervical Cancer Prevention (ACCP) through the Bill & Melinda Gates Foundation and are designed for health workers, nurses and doctors.

In 2004, three cervical cancer screening courses were organized, in Bamako, Mali, Dar-es-Salaam, Tanzania, and Xiangyuan, People's Republic of China. These were attended by a total of 94 participants from 5 countries.

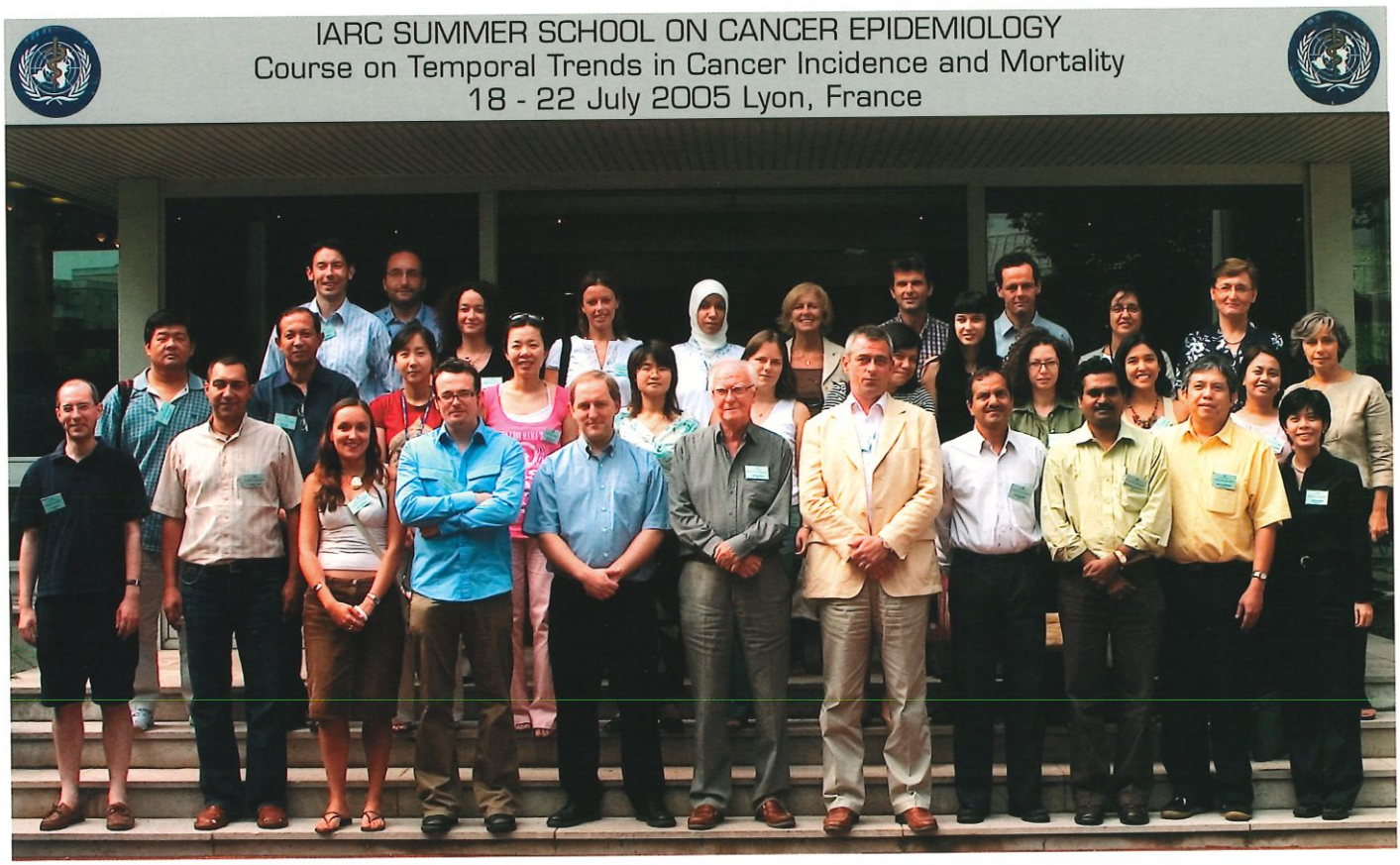
Dr N. Keita, Course director, (CHU Donka, Conakry, Guinea) teaching nurses at a cervical cancer screening course in Bamako, Mali. February 2004

CanReg4/ICD-O-3 courses

Cancer registrars using the registry software CanReg were trained in the use of the CanReg4 programme and of ICD-O-3. During 2004, courses were held in Turkey and in Cameroon, training a total of 60 registrars from 9 countries.

IARC Summer School in Cancer Epidemiology and Biostatistics

In 2005, the Summer School on Cancer Epidemiology and Biostatistics was established, and provided training for 188 participants from 53 countries via a range of modules from basic to advanced epidemiological topics. The course took place on 27 June - 22 July 2005. The Summer School is composed of regular modules on cancer registration, descriptive and analytical cancer epidemiology which are to be repeated every year, as well as specific modules on epidemiological applications or methodological subjects, to be addressed in ad hoc courses. In 2005, the guest lecturers in the regular modules were John Young (United States) and Hans Storm (Denmark). The two parallel courses on specific topics were on environmental cancer epidemiology and temporal trends in cancer incidence and mortality. The course directors for the environmental cancer epidemiology course were Tony Fletcher (United Kingdom), Paolo Boffetta (IARC) and Frederica Perera (United States). The course director for the temporal trends in cancer incidence and mortality course was Michael Hills (United Kingdom).



Division of Administration and Finance

OFFICE OF DIRECTOR OF ADMINISTRATION AND FINANCE

Director of administration and finance
Ms Valerie Hay (until March 2004)
Mr Michael Johnson (from April 2004)

Administrative assistant
Ms Virginie Vocanson

Assistant (Documents)
Ms Agnès Meneghel

Clerks
Ms Audrey Alenda
(until September 2004)
Ms Michelle Lauro
(from February 2005)
Ms Sophie Sibert-Dardenne

ADMINISTRATIVE SERVICES OFFICE

Administrative services officer
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Administrative assistant
Ms Sophie Servat

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Ms Fabienne Lelong

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Ms Anne-Magali Maillol
(from September 2005)

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Mr Michel Bazin
Ms Dimitrina Bertrand
(September–December 2005)
Mr Jean-Paul Bonnefond
Ms Odile Drutel
Mr Jean-François Durand-Gratian
Mr William Goudard
Mr Michel Javin
Ms Rita Kibrisliyan
Ms Géraldine Lett
(until September 2005)
Ms Michèle Marsal
Ms Linda Monnerat
Mr Ludovic Ripert
Ms Laetitia Van Cotthem
(February–September 2004)

PERSONNEL OFFICE

Personnel officer
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Assistant
Ms Eve El Akroud

Social adviser
Mr Henri Paraton

Support staff
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Ms Isabelle Poncet

Trainee
Ms Helene Lau (until October 2004)

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(July 2004–February 2005)
Mr Philip Knoche (from January 2005)
Mr Satish Sapra (April 2004–July 2004)
Mr Raul Thomas (until March 2004)

Finance officer
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Administrative assistants
Mr Charles Augros
Ms Wira Fèvre-Hlaholuk
(until March 2005)
Ms Madeleine Ongaro

Support staff
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Ms Françoise Florentin
Mr Dominique Hornez
Ms Nathalie Lamandé
Ms Danielle Lombardo
(until October 2005)
Mr Thomas Odin
Mr Franck Rousset
Ms Adèle Seguret

Trainee
Ms Patricia Martinez

IARC Governing and Scientific Councils

IARC's work is overseen by two governing bodies, the Governing Council and the Scientific Council.

Governing Council
The Council consists of delegates from the 16 Participating States which direct and support the Agency. The Director-General of WHO is an ex officio voting member of the Governing Council. The Council oversees the scientific programme of the Agency and its execution. It elects the Director and determines the biennial budget. The Council meets once a year in Lyon, usually in the week before the World Health Assembly in Geneva. The Chairperson of the Governing Council prepares the meeting together with the secretariat and advises the Director throughout the year.

Scientific Council
The Scientific Council reviews the scientific activities of the Agency and advises the Director on research strategies, especially in setting priorities for future projects. The Scientific Council's reports for 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 2004-2005, the IARC Governing Council voted a regular budget of US$37.4 million. Of this, about 79% were allocated 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 2002-2003 biennium, approximately 40% of the Agency's overall expenditure were financed by extra-budgetary funds.

Participating States and Representatives at IARC Governing Councils

Forty-Fifth Session 13-14 May 2004

Canada
Dr J. Larivière, Chairperson
Health Canada

Dr N. Berman, Alternate
Centre for Chronic Disease Prevention and Control

Australia
Mr B. Eckhardt
Department of Health and Ageing

Ms J. Quigley, Alternate
Department of Health and Ageing

Belgium
Mme A.-M. Sacré-Bastin
Service public fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement

Denmark
Dr S. Loiborg
Ministry of the Interior and Health

Dr J. Olsen, Alternate
University of Aarhus

Finland
Dr J. Virtamo
National Public Health Institute

France
Dr G. Lenoir
Institut Gustave Roussy

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Mme M.-F. Chedru, Alternate
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Germany
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Switzerland
Dr D. Hartmann
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Dr D. Dunstan
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Mr D. Smith, Alternate
Director of Finance

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Dr A. von Eschenbach
National Cancer Institute

Dr G.S. Davis, Alternate
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Dr J. Harford, Rapporteur
National Cancer Institute

World Health Organization
Dr J.W. Lee
Director-General

Dr C. Le Galès-Camus
Assistant Director-General

Dr C. Sepulveda
Coordinator – Programme on Cancer Control

Mrs J. McKeough
Office of the Legal Counsel

Observers
Dr L. Borysiewicz - Outgoing Chairman, Scientific Council

Dr J.D. Potter - Incoming Chairman, Scientific Council

Dr N. Gray - UICC Representative

External Audits
Mr S. Fakie & Mr G. Randall

Forty-sixth Session (Extraordinary) 4-5 November 2004

Netherlands
Dr J.-W. Hartgerink, Chairperson
Ministry of Health, Welfare and Sport

Japan
Dr Y. Fukuda, Vice-Chairperson
Ministry of Health, Labour and Welfare

Dr Kaoruko Kitamura - Alternate
Ministry of Health, Labour and Welfare

United Kingdom of Great Britain and Northern Ireland

Dr Diana Dunstan, Rapporteur
Medical Research Council

Mr D. Smith - Alternate
Medical Research Council

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Mr B. Lennon
Department of Health and Ageing

Belgium
Dr Margaret Haelterman
SPF Santé publique, Sécurité de la Chaîne alimentaire et Environnement

Canada
Dr J. Larivière
Health Canada

Dr Heather Bryant - Alternate
Institut de Recherche en Santé du Canada

Denmark
Professor J. Olsen
University of Aarhus

Finland
Professor P. Puska
National Public Health Institute – KTL

France
Professeur G. Lenoir
Institut Gustave Roussy

M. F. Werner - Alternate
Institut national du Cancer

Dr J. Dufriche - Alternate
Ministère de la Santé

M. G. Delvallée - Alternate
Ministère des Affaires étrangères

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Norway
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The Norwegian Board of Health

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Norwegian Centre for Health Services

Spain
Dr G. Lopez-Abente
Centro Nacional de Epidemiologia

Sweden
No representative

Switzerland
Professor D. Hartmann
Federal Office of Public Health

United States of America
Dr J. Harford
National Cancer Institute

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Dr R.J. Coates - Alternate
US Department of Health and Human Services

World Health Organization
Dr I. Smith
Adviser to the Director-General

Scientific Council members/Observers
Professor J.D. Potter
Chairman, Scientific Council
Dr H. Autrup
Vice-Président, Scientific Council
Dr J. Baselga (unable to attend)
Professor J. Bénichou
Dr W. Boecker,
Professor L.K. Borysiewicz
Dr A. Burny
Dr G.G. Giles
Dr J. Jiricny
Dr E. Lund
Dr S. Narod (unable to attend)
Dr M. Pierotti
Dr Pirjo Pietinen
Professor B.A. Ponder
Dr R. Toftgård
Dr Flora van Leeuwen
Dr. H. Van Oyen
Dr K. Wakabayashi

International Union Against Cancer
Dr I. Mortara - Executive Director

Forty-seventh Session 12-13 May 2005

Netherlands
Dr J.-W. Hartgerink, Chairperson
Ministry of Health, Welfare and Sport

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RIVM

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Department of Health and Ageing

Professor J. Hopper - Alternate
The University of Melbourne

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Federal Public Services Public Health

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Centre for Chronic Disease Prevention

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National Public Health Institute

France
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Institut National du Cancer

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The Norwegian Health Services

Spain
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Swedish Research Council – Medicine

Switzerland
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Dr Stephanie Zobrist - Alternate
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Medical Research Council

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US Department of Health and Human Services

Ms Lisa Spratt
US Department of State

World Health Organization
Dr R. Beaglehole
Director, Chronic Diseases and Health Promotion

Mrs Joanne McKeough
Office of the Legal Counsel

Dr A. Ullrich
Programme on Cancer Control

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Dr J.D. Potter - Chairman, Scientific Council
Ms Isabel Mortara (unable to attend)
UICC Representative

Members of Scientific Council (2004)

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Chairperson
Imperial College of Science,
United Kingdom

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Dr H. Autrup
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Denmark

Dr J. Baselga
Vall d'Hebron University Hospital
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Dr J. Bénichou
CHU de Rouen
France

Dr W. Boecker
Westphalian Wilhelms University
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University of Zürich
Switzerland

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Hutchinson/MRC Research Centre
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Australia

Dr R. Tofgård
Department of Bioscience at Novum
Sweden

Dr Flora van Leeuwen
The Netherlands Cancer Institute
The Netherlands

Dr W. Wakabayashi
National Cancer Center Research Institute
Japan

Meetings/Seminars organized at IARC

2-4/02/2004
40th Session of IARC Scientific Council

5-6/02/2004
Future directions of genetics programme

10-17/02/2004
IARC Monographs, Volume 87, Lead and Lead Compounds

19-20/02/2004
Sixth meeting on Cancer Mortality Atlas of Europe

4-5/03/2004
Gene-Rad-Interact meeting

10-12/03/2004
Errors in doses meeting

11/03/2004
Breast cancer project meeting

18/03/2004
Interactions of gene-endocrine disruptors (Eds) in infertility and cancer

24/03/2004
Case-control study of lung cancer and leukaemia among nuclear industry workers

29-30/03/2004
Cervical cancer screening in Eastern Europe

13-14/05/2004
45th Session of IARC Governing Council

17/05/2004
Prostate cancer screening

24-25/05/2004
DDRC-NCI-IARC studies of esophageal cancer in North-Eastern Iran

27-29/05/2004
EPIC-Elderly Project meeting

2-9/06/2004
IARC Monographs, Volume 88, Formaldehyde, 2-Butoxyethanol and Propylene Glycol mono-*t*-butyl Ether

7-8/06/2004
INTERPHONE – Occupational exposure subcommittee meeting

24-25/06/2004
European Component of NCI Cohort Consortium on Breast and Prostate Cancer and Hormone-Related Gene Variants

28-29/06/2004
Gene-Rad-Interact meeting

12-14/07/2004
Review of IARC animal facilities and laboratory research

30-31/08/2004
INTERPHONE – Mobile phone exposure task group meeting

2-3/09/2004
Study of cancer risk among European asphalt workers: Nested case-control study of lung cancer – Meeting of the Study Group

10/9/2004
International BRCA1/2 Carrier Cohort Study Meeting

23-24/09/2004
Meeting of National Cancer Institute Directors

27-29/09/2004
EPIC Steering Committee

29/09/2004
EPIC Working Group on Breast Cancer

04/10/2004
Epihealth-Russia Project Meeting

04/10/2004
Tobacco control in Russia

05-12/10/2004
IARC Monographs, Volume 89, Smokeless Tobacco and Some Related Nitrosamines

08/10/2004
DNA double strand break repair and cell-cycle checkpoint

13/10/2004
Environmental PAH Exposure, Genetic Susceptibility and Lung Cancer in Xuan Wei

13/10/2004
EUROTIS (European Thyroid Cancer Study) Planning Meeting

14/10/2004
Evaluation of genetic susceptibility for non-Hodgkin lymphoma in the Interlymph

03/11/2004
Colorectal linkage consortium (CoReGenes collaborative Group)

4-5/11/2004
46th Session (Extraordinary) of the IARC Governing Council

09/11/2004
Epigenetic regulation of NF-kB-dependent gene expression

09/11/2004
Approaches to complex pathways in molecular epidemiology

18-20/11/2004
NATO-CCMS meeting

22-23/11/2004
Cancer Incidence in Five Continents Editorial Meeting

25/11/2004
Natural history of HPV infection in the cervix

29-30/11/2004
Meeting of Study Group on Environmental Exposures and Lymphoid Neoplasms

07/12/2004
IARC Ethical Review Committee

16-18/12/2004
IARC Monographs Advisory Group on Air Pollution and Cancer

21/12/2004
Tumor suppressor function of the Tip60 histone acetyl-transferase

17/01/2005
Trends in Regional Variation in Epidemiology

17-18/01/2005
Working Group on Risk of Skin Cancer & Exposure to Artificial UV Light

17-18/01/2005
Discussions on age period cohort trends of cervical adenocarcinoma in Europe

18/01/2005
Statistical estimates of the number of stem cells repopulating the marrow following bone marrow transplantation

18/01/2005
A no-intercept hierarchical regression model for meta-analysis of epidemiologic dose-response data

19/01/2005
HPV screening in developed and developing countries

21/01/2005
Breast cancer - from traditional to molecular epidemiology

21/01/2005
The future for Cancer Descriptive Epidemiology - a SWOT analysis: Strengths, Weaknesses, Opportunities and Threats

24/01/2005
MicroRNAs: Tiny regulators with a global impact

24-26/01/2005
Interviewer Training Session for the Asphalt nested case-control study

27/01/2005
Genetic diversity may explain geographic variations in the oncogenic potential of hepatitis B virus

31/01/2005 - 01/02/2005
Epidemiology & Biology Cluster (EBC) Review for Scientific Council

31/01/2005 - 01/02/2005
29th ENCR Steering Committee Meeting

2-3/02/2005
41st Session of IARC Scientific Council

07/02/2005
Cancéropôle

15-22/02/2005
IARC Monographs, Volume 90, Human Papillomaviruses

16-18/02/2005
INTERPHONE Study - Analyses Task Group

23/02/2005
HPV and cervical cancer in China

28/02/2005
Cancéropôle

28/02/2005-01/03/2005
Working Group on Avoidable Causes of Cancer

07/03/2005
Réunion de préparation pour la Réunion 'ASCENSION' du Groupe de Coordination pour l'Epidémiologie et l'Enregistrement du Cancer dans les Pays de Langue Latine (GRELL)

07-08/03/2005
Governing Council Strategy Development Sub-Committee

18/03/2005
Cancéropôle

21-23/03/2005
First meeting of IARC Working Group on Avoidable Causes of Cancer

22/03/2005
Aurora kinases and cancer: to be or not to be an oncogene

01/04/2005
Genome-wide association studies

04/04/2005
Verbal autopsy in India

04/04/2005
Endogenous hormones and breast cancer risk

04-06/04/2005
14ème Séminaire d'Enseignement de Biologie de la Peau

05/04/2005
Epidemiology of prostate cancer: methodological issues in genetic association studies

05/04/2005
Malaria, HIV and Cancer in Eastern and Central Africa

07-08/04/2005
Apport de la génomique et de la protéomique en cancérologie pulmonaire

12/04/2005 Geographical variations in the distribution of HPV genotypes: implications for vaccination and HPV screening tests

12/04/2005
Epidemiological aspects of virus-related cancers in the setting of acquired immunodeficiencies

13-14/04/2005
Cellule souche : de la cellule à la biothérapie

18-22/04/2005
UNEP/ILO/WHO International Chemical Safety Card Review meeting

02/05/2005
Testicular cancer aetiology: current and future hypotheses

02-03/05/2005
Interphone Study - Analyses Task Group Meeting

03/05/2005
Chipping away at health risk assessment: where is the genetics/genomics revolution taking us?

03/05/2005
Functional Testing of DNA Repair and the Risk of Cancer

04-06/05/2005
Advisory Group to recommend updates to the Preamble to the IARC Monographs

05/05/2005
Impact of tobacco smoking, alcohol drinking and body mass index on total cancer risk: data from a population-based prospective study in Japan (JPHC Study)

10/05/2005
40th Anniversary of the IARC - International Scientific Symposium and Lectures

12-13/05/2005
47th Session of IARC Governing Council

18/05/2005
Current developments and perspectives of HPV-specific vaccines

18-19/05/2005
EUROSKIN International Workshop "The Burden of Skin Cancer"

27/05/2005
A clinical proteomic approach in neuro-oncology

31/05/2005
The International Tobacco Control Policy Evaluation Project: Evaluating the Policies of the Framework Convention on Tobacco Control

03/06/2005
Interphone Study - Exposure Assessment Sub-committee Meeting

03/06/2005
IARC Ethical Review Committee

06/06/2005
HPV and head and neck cancer in Latin America

06-07/06/2005
Interphone Study - Final Full Study Group Meeting

07-14/06/2005
IARC Monographs, Volume 91: Oestrogen-progestogen replacement therapy and oral contraceptives

07-08/06/2005
Second meeting of the case-control study of lung cancer among European asphalt workers

08/06/2005
Interphone Study - Analysis Task Group Meeting

08/06/2005
On genome-wide association studies in family-based designs: Genomic-screening and control using the set data set

10/06/2005
Cancer risks for germline mutations in mismatch repair genes: a population-based study

15/06/2005
Exploring mechanisms relating energy balance and cancer

20-21/06/2005
European Guidelines for Quality Assurance in Cervix Cancer Screening

21-23/06/2005
MECC Joint Registration Project Steering Committee Meeting

24/06/2005
Inflammatory Breast Cancer Meeting

27/06/2005
Promising translational research for glioma treatment

27/06/2005 - 01/07/2005
Course on "Cancer Registration: Principles and Methods" as part of the IARC Summer School on Cancer Epidemiology

27-29/06/2005
Working Group on Risk of Skin Cancer and Exposure to Artificial Ultraviolet Light

30/06/2005 - 01/07/2005
Working Group on Avoidable Causes of Cancer – Methodological Subgroup

04-08/07/2005
Course on "Methods in Descriptive Epidemiology" as part of the IARC Summer School on Cancer Epidemiology

06/07/2005
Brainstorming meeting on Childhood Cancer

07/07/2005
Genotype and Phenotype in Li-Fraumeni Syndrome

07-08/07/2005
Priorities in Tobacco Research

11-15/07/2005
Course on "Methods in Analytical Epidemiology" as part of the IARC Summer School on Cancer Epidemiology

11-12/07/2005
Meeting on EUROFIR project

18-22/07/2005
Course on "Environmental Cancer Epidemiology" as part of the IARC Summer School on Cancer Epidemiology
Course on "Temporal Trends in Cancer Incidence and Mortality" as part of the IARC Summer School on Cancer Epidemiology

19/07/2005
Molecular Epidemiology of Upper Aerodigestive Tract Cancers

19/07/2005
Gene-Environment Interaction in the Aetiology of Human Cancer in the Post-Genomic Era

21/07/2005
Serological evidence for associations of human papillomavirus and cancer

29/07/2005
Cohort study of HPV persistence in Hawaii

22/08/2005
Visit of Korean Delegation

25/08/2005
Introducing HPV vaccine: Planning for the challenges

06/09/2005
Mechanisms of Mutagenesis by Environmental Carcinogens

16/09/2005
GENE-RAD-RISK Project Board meeting

19-20/09/2005
30th ENCR Steering Committee Meeting

Internal IARC Seminars
(started in 2005)

11/01/05
"Childhood cancer in Europe: the ACCIS project" by Dr Eva Steliarova
"High density genome wide linkage analysis in a large Tasmanian prostate cancer pedigree" by Dr James McKay
"Smoking, alcohol and risk of Hodgkin lymphoma" by Mr Hervé Besson

25/01/05
"Role of papillomaviruses in human carcinogenesis" by Dr Massimo Tommasino
"Cancer incidence in Bhopal: 15 years after Bhopal gas accident" by Dr Rajesh Dikshit
"Looking for genetic modifiers of BRCA1 and BRCA2 related breast cancer" by Dr David Hughes

08/02/2005
"TP53 mutations in human cancer: mutagenesis versus biological selection" by Dr Pierre Hainaut
"Serum C-peptide levels and breast cancer risk; results from EPIC" by Mr Martijn Verheus
"TP53 promoter methylation in human gliomas" by Dr Vishwa Jeet Amatya

23/02/2005
"Why is the incidence of lymphomas increasing?: initial results from the Epilymph study" by Dr Paul Brennan
"A new model to study the role of HPV in skin carcinogenesis" by Mr Wen Dong
"HPV infection and sexual habits: the IARC Multi-centric HPV Prevalence Survey" by Dr Salvatore Vaccarella

08/03/2005
"Genetic pathways to glioblastoma" by Dr Hiroko Ohgaki
"Juggling data: the discovery of errors" by Dr. Mathieu Boniol
"Gene expression profiling of the insulinomas developed in Men (Multiple Endocrine Neoplasia type 1) conditional knockout mice" by Miss Sandra Fontanière

29/03/2005
"History of Cancer Mapping at IARC" Mr Michel Smans
"TP53 and KRAS mutation load and types in lung cancers in relation to tobacco smoke" Miss Florence Le Calvez
"Assessment of Visual Inspection Approaches to Cervical Screening: A pooled Analysis of IARC/ACCP Multi-Centre Cross-sectional Studies" Mr Richard MUWONGE

12/04/2005
"Physical Activity, Weight Control and Breast Cancer Risk: Epidemiologic Evidence and Biologic Mechanisms" by Dr Christine Friedenreich
"XRCC1 is required for DNA single-strand break repair in human cells" by Dr Reto Brem
"Associations between ocular melanoma and other primary cancers: an international population-based study" by Miss Ghislaine Scélo

26/04/2005
"Current issues for the IARC Monographs" by Dr Vincent Cogliano
"Role of Nbs1 in DNA repair" by Dr Yun-gui Yang
"Cannabis use and Lung cancer: a pooled study in Maghreb" by Mr Julien Berthiller

31/05/2005
"Risk of thyroid cancer following ^{131}I exposure in childhood" by Dr Elisabeth Cardis
"Preservation and banking of biological specimens for molecular epidemiology: principles and methods" by Mrs Elodie Caboux
"Oral hygiene and head and neck cancer" by Miss Neela Guha

15/06/2005
"Screening reduces oral cancer mortality among tobacco/alcohol users: results from a randomised trial in Kerala, India" by Dr Rengaswamy Sankaranarayanan
"The skin human papillomavirus type 38 displays carcinogenic activity" by Dr Rosita Accardi
"How to deal with false positives: False Discovery Rate (FDR) and False Positive Reporting Probability (FPRP)" by Ms Marine Castaing

26/07/2005
"Epigenetics and its impact on cancer" by Dr Zdenko Herceg
"Combined estrogen-progestogen contraceptives and estrogen-progestogen menopausal therapy: outcome of the June 2005 IARC Monographs meeting" by Dr Yann Grosse

13/09/2005
"EPIC Study: Recent results and on going projects" by Dr Rudolf Kaaks

"8-Nitroguanine as a marker for nitrative nucleic acid damage caused by inflammatory oxidants" by Dr Tomohiro Sawa
"Tumor Suppressor Auto-antibodies, Human Papillomavirus Infection, and Cancer of the Head and Neck: A Multicenter Study in Central and Eastern Europe" by Dr Charles Hsu

27/09/2005
"Risk associated with many individually rare missense substitutions in BRCA1" by Dr Sean Tavtigian
"Genetic alterations in primary glioblastomas in Japan" by Dr Takao Fukushima
"Chromosomal aberrations and cancer risk: a multicentric study from Central Europe" by Dr Olga Van Der Hel

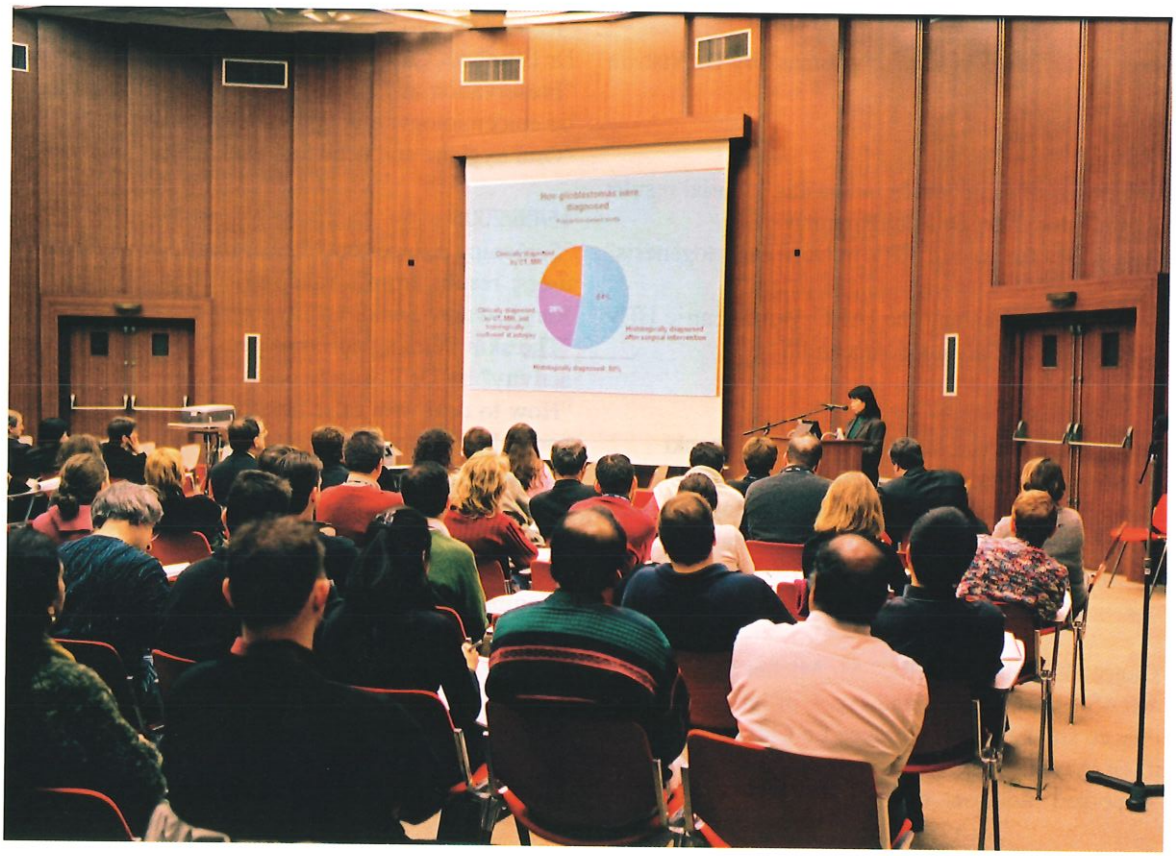
25/10/2005
"Twenty years into The Gambia Hepatitis Intervention Study" by Dr Pierre Hainaut
"The telomere/telomerase system is impaired during the immortalization process induced by the human papillomavirus type 38 E6 and E7 proteins" by Dr Anne-Sophie Gabet
"Genetic susceptibility to nasopharyngeal carcinoma: preliminary results from north african study" by Dr Majida Jalbout

08/11/05
"Cancer attributable to infectious agents - an update" by Dr Paola Pisani
"Role of Poly(ADP-ribose) Glycohydrolase in DNA repair and genomic instability" by Dr Wookee Min
"The relationship between physical activity, anthropometry and endometrial cancer risk: results from the EPIC study" by Ms Anne Cust

22/11/2005
"The International Collaboration of Epidemiological Studies of Cervical Cancer" by Dr Martyn Plummer
"Implication of MyD88 in Ras transformation" by Dr Isabelle Coste
"Plasma and Dietary Carotenoid, Retinol and Tocopherol Levels and the Risk of Gastric Adenocarcinomas in the EPIC Study" by Dr Mazda Jenab

6/12/2005
'Proteomics in Cancer: An Introduction' by Dr Eric Van Dyck
'Development and validation of highly sensitive and specific HPV typing method for epidemiological studies' by Dr Tarik Gheit
'Assessment of the Impact of Recall and Selection Bias in INTERPHONE' by Dr Martine Vrijheid

20/12/2005
"Smoking and cancer" by Dr Vendhan Gajalakshimi
'Role of the RDM1 protein in chromatin metabolism and the cell response to cisplatin' by Mr Dominique Bourgeon
'EPIC Database of Glycaemic index and Glycaemic load values, *Preliminary results*' by Dr Marit Van Bakel



Staff Publications

Aapro MS, Aaro LE, Aro AR, Bergenmar M, Bloch J, Borras Andres JM, Bottomley A, Brug J, Corner J, Evered D, Flechtner H, Geyer S, Greimel E, Hine H, Johansen C, Klep KI, Segnan N, Straif K, Vertio H, de Vries H. Research in the behavioural and social sciences to improve cancer control and care: a strategy for development. A report of an Expert Group. *Eur J Cancer* 2004; 40 316-325

Abkevich V, Zharkikh A, Deffenbaugh AM, Frank D, Chen Y, Shattuck D, Skolnick MH, Gutin A, Tavtigian SV. Analysis of missense variation in human BRCA1 in the context of interspecific sequence variation. *J Med Genet* 2004; 41(7): 492-507

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Accardi R, Oxelmark E, Jauniaux N, De Pinto V, Marchini A, Tommasino M. High levels of mitochondrial large ribosomal subunit protein 40 prevent loss of mitochondrial DNA in null mmf1 Saccharomyces cerevisiae cells. *Yeast* 2004; 21(7): 534-548

Agurto I, Arrossi S, White S, Coffey P, Dzuba I, Bingham A, Bradley J, Lewis R. Involving the community in cervical cancer prevention programs. *Int J Gynecol Obstet* 2005; 89(Suppl 2): S38-S45

Airoldi L, Vineis P, Colombi A, Olgiati L, Dell'Osta C, Fanelli R, Manzi L, Veglia F, Autrup H, Dunning A, Garte S, Hainaut P, Hoek G, Krzyzanowski M, Malaveille C, Matullo G, Overvad K, Tjonneland A, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Palli D, Peluso M, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Lund E, Agudo A, Martinez C, Dorronsoro M, Barricarte A, Chirlaque MD, Quiros JR, Berglund G, Jarvholm B, Hallmans G, Day NE, Allen N, Saracci R, Kaaks R, Riboli E. 4-Aminobiphenyl-hemoglobin adducts and risk of smoking-related disease in never smokers and former smokers in the European Prospective Investigation into Cancer and Nutrition prospective study. *Cancer Epidemiol Biomarkers Prev* 2005; 14(9): 2118-2124

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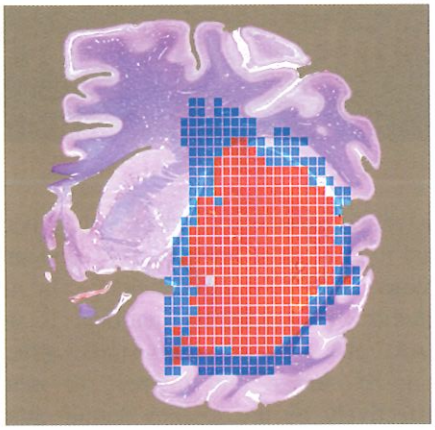
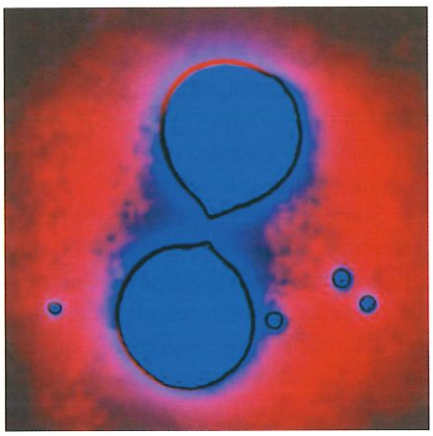
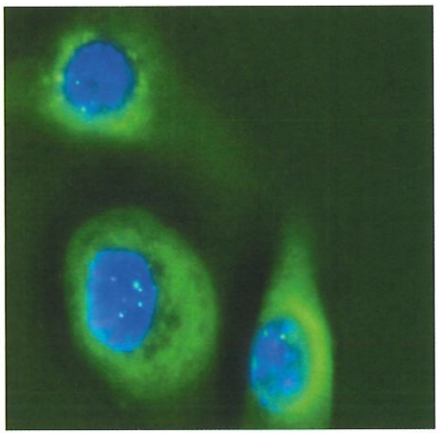
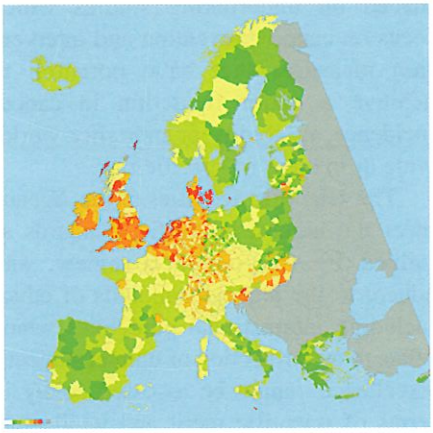
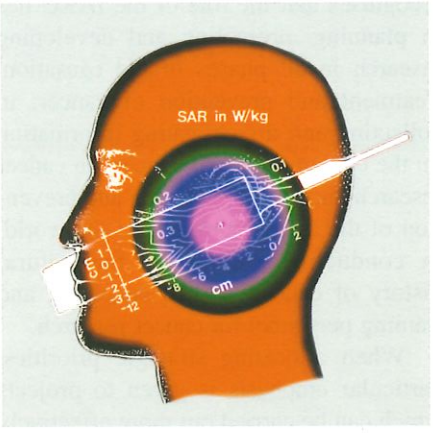










Selected Scientific Highlights, 2004–2005

Introduction

IARC was established by a World Health Assembly Resolution in September 1965. Since then, the world-wide pattern of cancer has undergone significant changes. Notably, the numbers of new cases diagnosed each year has more than doubled around the world, reaching a total of nearly 11 million new cases each year. The epidemic of tobacco-related cancers has developed since the founding of the Agency: it has peaked in some countries but is still rapidly increasing in many low- and medium-resource countries. Today, in marked contrast to the situation forty years ago, the majority of human cancers arise in the developing world.

The Agency's tasks are outlined in its Statute, which remains virtually unchanged since its foundation forty years ago, and whose guiding principle is to promote international collaboration in cancer research. Specifically, the Statute recognises that the role of the IARC lies in planning, promoting and developing research in all phases of the causation, treatment and prevention of cancer; in collecting and disseminating information on the epidemiology of cancer, on cancer research and on the causation and prevention of the disease throughout the world; in conducting studies on the natural history of cancer; and in educating and training personnel for cancer research.

When allocating strategic priorities, particular emphasis is given to projects which can be carried out more effectively through international collaboration than at a national level. IARC also prioritises studies which require a multidisciplinary approach, which has been established among the staff of the Agency and its scientific partners, in particular the potential to have close integration of epidemiology and laboratory science in its studies. Given its international focus, IARC also gives priority to studies which can be carried out uniquely or more effectively by the Agency acting either alone or in collaboration with other international or national bodies and on topics which take advantage of the geographical and human diversity of cancer to give insights into causes and mechanisms and provide a basis for population-based interventions.

A particular focus of IARC's scientific activities is on cancers which contribute significantly to the human cancer burden or which provide particular insights into causes and mechanisms or are common in specific populations (e.g. in developing countries, certain ethnic groups, children, migrants). Emphasis is placed on undertaking studies which focus on cancer prevention and intervention measures that have potential to achieve a major reduction in cancer incidence, morbidity or mortality worldwide or in areas of specific risk.

The scientific activities of the Agency meet the highest scientific standards as judged by rigorous peer-review, and adhere to the highest standards of ethics including international guidelines which relate to the protection of human subjects. Excellence cannot be assessed solely in terms of scientific merit and intellectual challenge – other important dimensions include applicability and public health relevance.

The global cancer burden was estimated to have doubled in the last 25 years of the twentieth century and this rate of increase will continue in the first quarter of the current century, due to the growth and ageing of the world's population, unless effective preventive strategies are identified and implemented urgently. The Regions of the world which will be most effected by this change will be the low- and medium-resource countries, many of which are currently facing high levels of communicable diseases and are short of the resources needed to cope with this increasing burden of cancer and other non-communicable diseases.

Some selected highlights of the IARC scientific programme during 2004-2005 are presented in this Review. This clearly indicates areas of research where IARC has been active and successful, describes the scope of activities covered by the Agency's scientific programme and the importance of partnerships developed with the international cancer scientific community.

The importance of IARC activities in cancer prevention research, its Monographs programme, the descriptive epidemiology programme and its education and training activities are known and recognised world-wide. In the year ahead, and beyond, IARC shall continue to forge new scientific collaborations with partners around the world in order to conduct research relevant to the prevention of cancer.

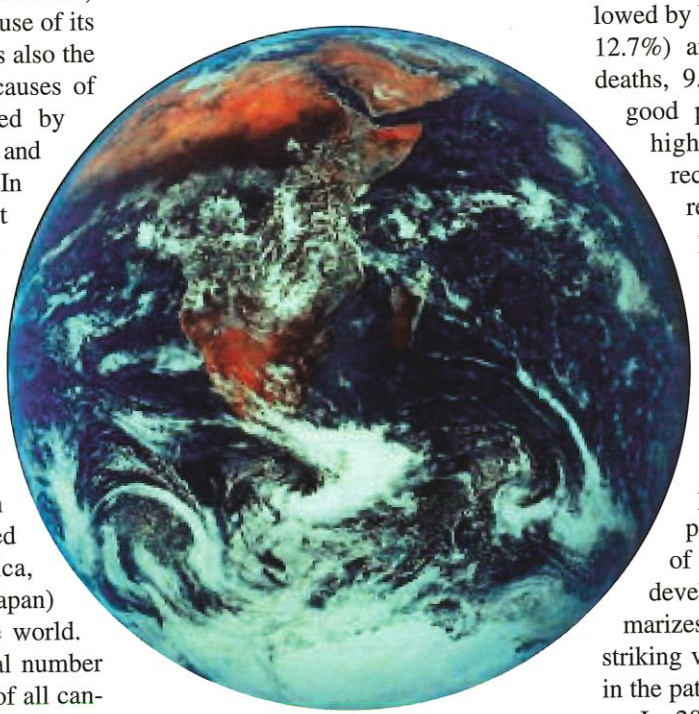
Dr Peter Boyle
Director
January, 2006

Global Burden of Cancer

Estimates of the burden of cancer in terms of incidence (number of new cases occurring), mortality (number of deaths) and prevalence (persons alive with the disease) are essential basic information to allow priorities for disease control to be established.

IARC has estimated that in 2002, on the basis of the most recent available data (*Ferlay *et al*, 2004; Parkin *et al*, 2005), there were in total 10.9 million new cases, 6.7 million deaths and 24.6 million persons alive with cancer (within five years of diagnosis). The most common cancers in terms of incidence were lung (1.35 million), breast (1.15 million) and colorectal (1 million). Because of its poor prognosis, lung cancer was also the most common cancer among causes of death (1.18 million), followed by stomach cancer (700,000 deaths) and liver cancer (598,000 deaths). In terms of prevalence, the most common cancers are breast cancer (4.4 million women surviving five years after diagnosis), colorectal cancer (2.8 million persons) and prostate cancer (2.4 million men).

Figure 1 shows the ranking of cancers in terms of incidence and mortality, for men and women in the developed (Europe, North America, Australia/New Zealand and Japan) and developing regions of the world. Overall, some 53% of the total number of new cancer cases and 60% of all cancer deaths occur in developing countries. In men, prostate cancer is now the most common form of cancer diagnosed in the developed regions (513,000 cases, 19% of all new cases), but only sixth in the developing countries (165,000 cases, 5.3%) where lung cancer ranks first (481,000 cases, 15%). In women breast cancer is by far the most frequent cancer worldwide, with an estimated 636,000 new cases diagnosed in the developed regions (27.4% of the total) and 514,000 in developing countries (18.8%).



Mortality reflects the fatality of the different cancers, and in men lung cancer remains the most common cause of death with an estimated 424,000 deaths in the developed regions (27.4% of the total number of deaths), and 423,000 in less developed countries (18.8%). Breast, lung and colorectal cancers account for 42.6% of the total deaths in women in developed countries, while cancer of the uterine cervix ranks first in developing countries, with an estimated 234,000 cancer deaths (13.5% of the total), followed by breast cancer (221, 000 deaths, 12.7%) and stomach cancer (170, 000 deaths, 9.6%). Because of their rather good prognosis together with their high incidence, breast, colon-rectum and prostate cancers represent around 50% of the total prevalent cancer cases in developed regions. In contrast, in developing countries, cancers of the liver, stomach and oesophagus are more common but are associated with poor prognosis, so that despite the four times smaller population (1.2 billion compared with 5 billion), about 58% of the total prevalent cases live in developed countries. Figure 2 summarizes these results and illustrates the striking variations from region to region in the patterns of occurrence of cancer.

In 2002, the world population was estimated to be around 6.2 billion, and it will reach about 8.1 billion by 2030 (United Nations, 2003). A 38% increase in the population of the less developed

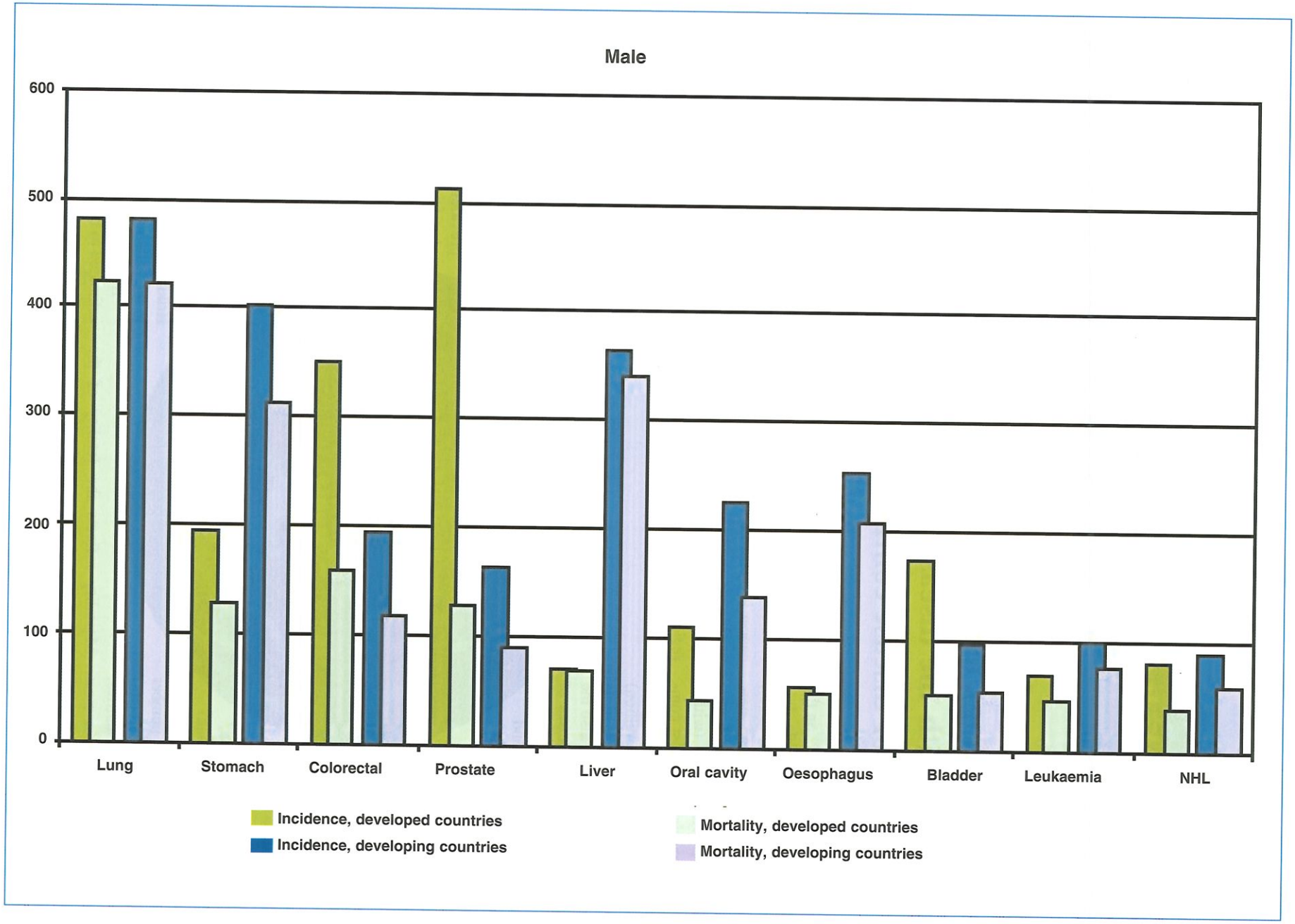


Figure 1. Cancer incidence and mortality (number per thousands) for men and women in Europe, North America, Australia/New Zealand and Japan and developing regions of the world

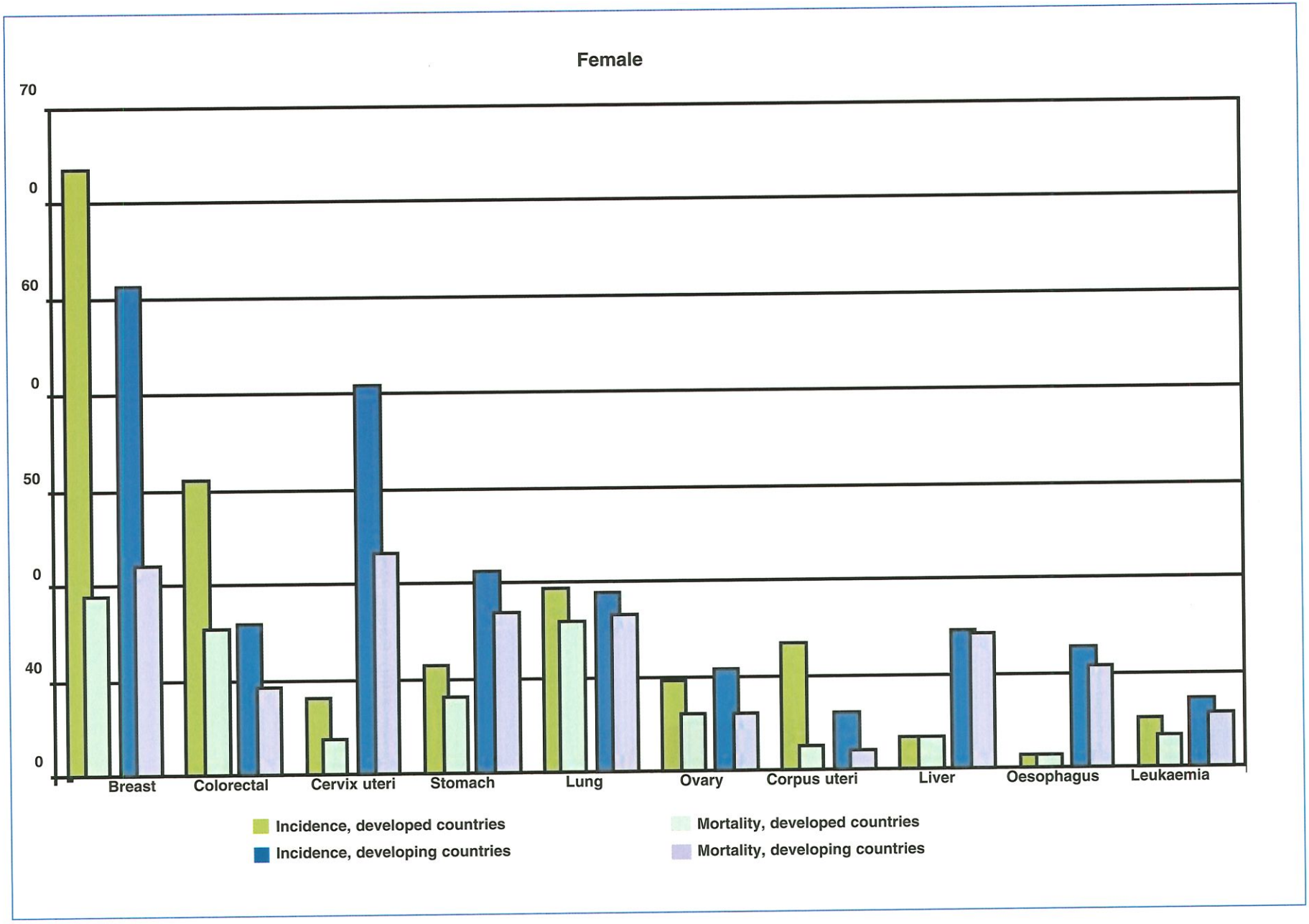


Figure 1 (cont'd) Cancer incidence and mortality (number per thousands) for men and women in Europe, North America, Australia/New Zealand and Japan and developing regions of the world

countries is expected over this period, while in the more developed areas, the increase will be limited to 1%. Cancer affects mainly older age groups and during the period 2002–2030, the proportions of people over age 65 are projected to increase from 5.2% to 10%, and from 14.5% to 22.6% in developing and developed areas, respectively. Since, as noted above, there are already slightly more cancer cases and deaths occurring in less developed than in developed countries, and the greatest demographic changes will take place in the developing areas, more and more of the future cancer burden will shift to these countries, and will be supported by the elderly populations of both areas (*Parkin *et al*, 2001). Table 1 shows the predicted numbers of new cases of and deaths from cancer, based on demographic changes and time trends. With no change in current rates, cancer could kill more than 12 million people by 2030, and if the rates increase by 1% annually, this figure will reach more than 16 million. Preventive measures will play an increasing role in cancer control programmes during the coming decades: control of tobacco smoking and screening for breast cancer and for cervical cancer in developing countries remain the major challenges and could have a great impact in reducing the global burden of cancer.

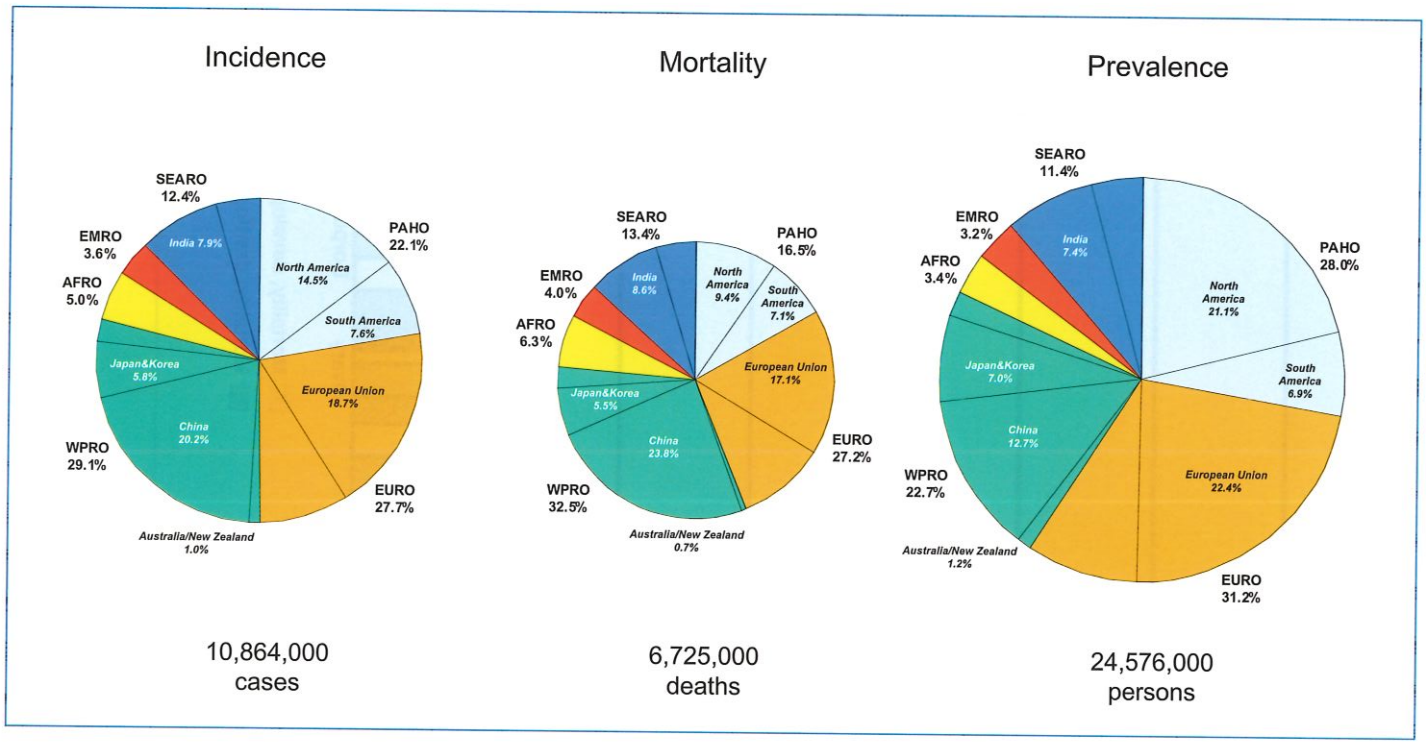


Figure 2. Incidence mortality and prevalence in the six WHO regions

AFRO: Africa; EMRO: East Mediterranean; EURO: Europe; PAHO: Pan-American; SEARO: South-East Asia; WPRO: Western Pacific

Table 1. Estimated (2002) and projected numbers (millions) of cancer cases and deaths, all cancers, both sexes

Region	2002		2030*		2030**	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
World	10.9	6.7	19.2	12.4	25.4	16.4
More developed	5.0	2.7	7.2	4.0	9.5	5.2
Less developed	5.8	4.0	12.0	8.5	15.9	11.2
Africa (AFRO)	0.5	0.4	1.0	0.8	1.3	1.0
Europe (EURO)	3.0	1.8	4.1	2.6	5.4	3.4
East Mediterranean (EMRO)	0.4	0.3	0.9	0.6	1.2	0.8
Pan-America (PAHO)	2.4	1.1	4.7	2.3	6.2	3.0
South-East Asia (SEARO)	1.3	0.9	2.6	1.8	3.5	2.5
Western Pacific (WPRO)	3.2	2.2	5.9	4.3	7.8	5.7

* No change in current rates

** With 1% annual increase in rates

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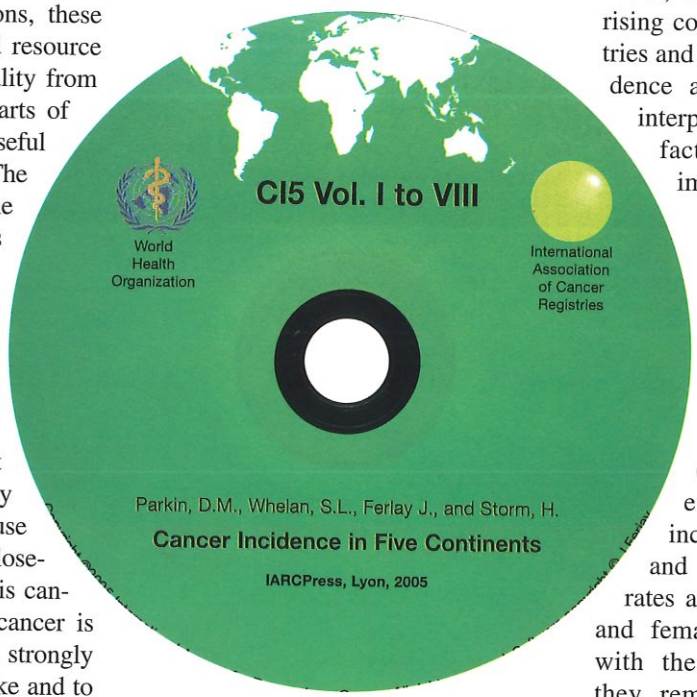
Time Trends

The data published in successive volumes of *Cancer Incidence in Five Continents* together with the WHO mortality data are now available on-line at the IARC web site (http://www-dep.iarc.fr).

Incidence data are collected by cancer registries which may cover entire national populations or regions (*Parkin, Whelan *et al*, 2005). They provide the most direct information about cancer risk. Mortality data have been compiled for very long time periods and are available for many countries (WHOSIS). They provide an easily interpretable measure of the outcome of cancer. Although the quality varies considerably within countries or regions, these data form a unique centralized resource on the incidence of, and mortality from major cancer types in many parts of the world, and are especially useful for the study of time trends. The following examples review the four most frequent cancers worldwide (*Ferlay, Bray *et al*, 2004; *Parkin, Bray *et al*, 2005) using tables and graphs extracted from the IARC web site.



Lung Cancer

Lung cancer is the commonest cancer in the world today (*Ferlay *et al*, 2004), and because of its poor prognosis, mortality closely parallels the occurrence of this cancer. The major cause of lung cancer is tobacco smoking, and the risk is strongly related to age of starting to smoke and to prevalence of smoking. Thus trends in age-specific mortality rates by period of birth are of particular interest. Figure 1 compares France and the UK, showing the effect of smoking habits: rates are rising in French men and women of almost all generations, with a stabilization of the risk confined to older men. In the UK, these rates have been declining in men since the generation born around 1911 when the maximum prevalence of smoking was reached, so that the all-age mortality has been declining since 1976. In women, who took up smoking later, the declines are confined to younger age groups (*Parkin, 1989). These figures illustrate the need for effective tobacco control programmes in Europe, particularly addressed to young women (*Boyle & Ferlay, 2004).

Breast Cancer

Breast cancer is estimated to be the leading cancer in women (*Ferlay, Bray *et al,* 2004), but there is a wide divergence between incidence and mortality. Cumulative incidence rates (age 35–74 years) are increasing in all countries (Figure 2), although to greatly differing extents. Mortality increased until the mid-1980s, then declined in some European countries, Australia and the USA (Figure 3). Although relatively lower, mortality from breast cancer is rising continuously in developing countries and in Japan. These patterns of incidence and mortality are difficult to interpret because of the interaction of factors such as screening and improvements in treatment.

Colorectal cancer

As for breast cancer, higher colorectal cancer incidence is associated with higher socioeconomic status. In countries of higher incidence rates are either stabilizing or decreasing (*Boyle & Ferlay, 2005). However, in Japan, a dramatic increase is observed in both males and females. In general, incidence rates are rising slowly in both males and females in developing countries, with the exception of India, where they remain stable (*Parkin, 1994). For mortality, the countries with the largest increase are those of Eastern Europe and Japan, while decreases are observed in high-rate countries of Western Europe and the USA (*Boyle & Ferlay, 2005).

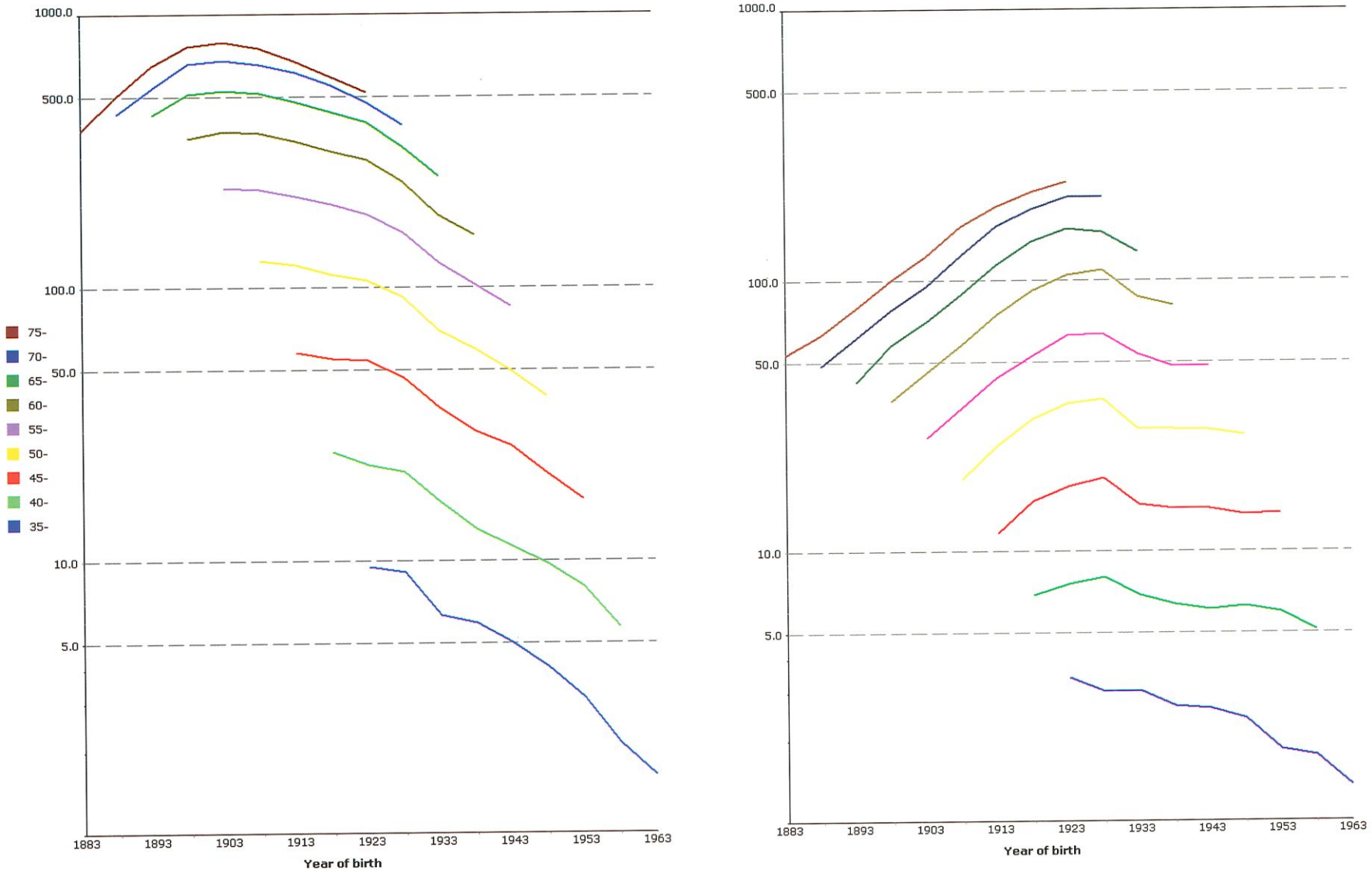


Figure 1. Lung cancer mortality by period of birth (1883–1963) UK, male and female

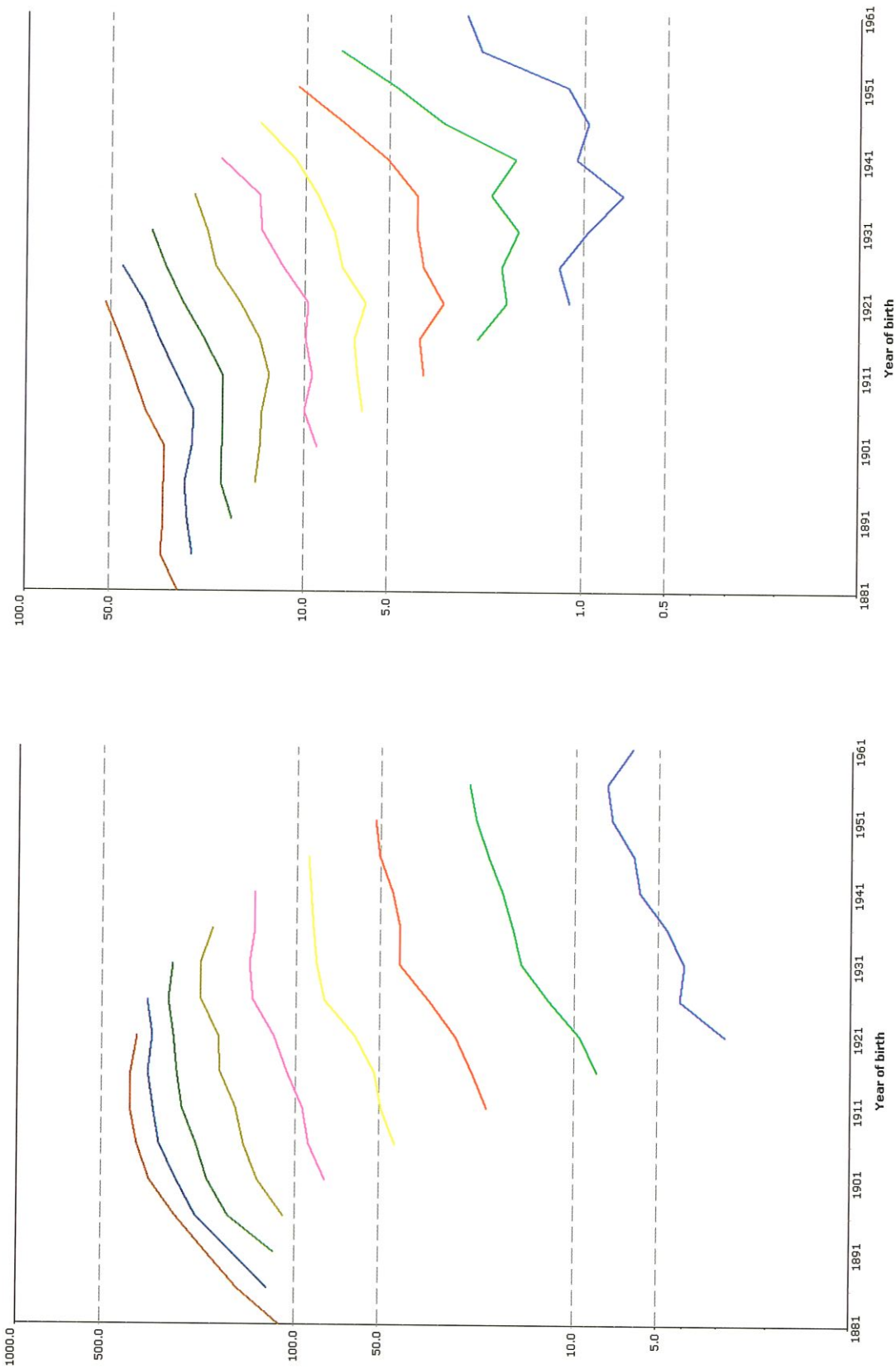


Figure 1 (cont'd) Lung cancer mortality by period of birth (1883–1963) France, male and female

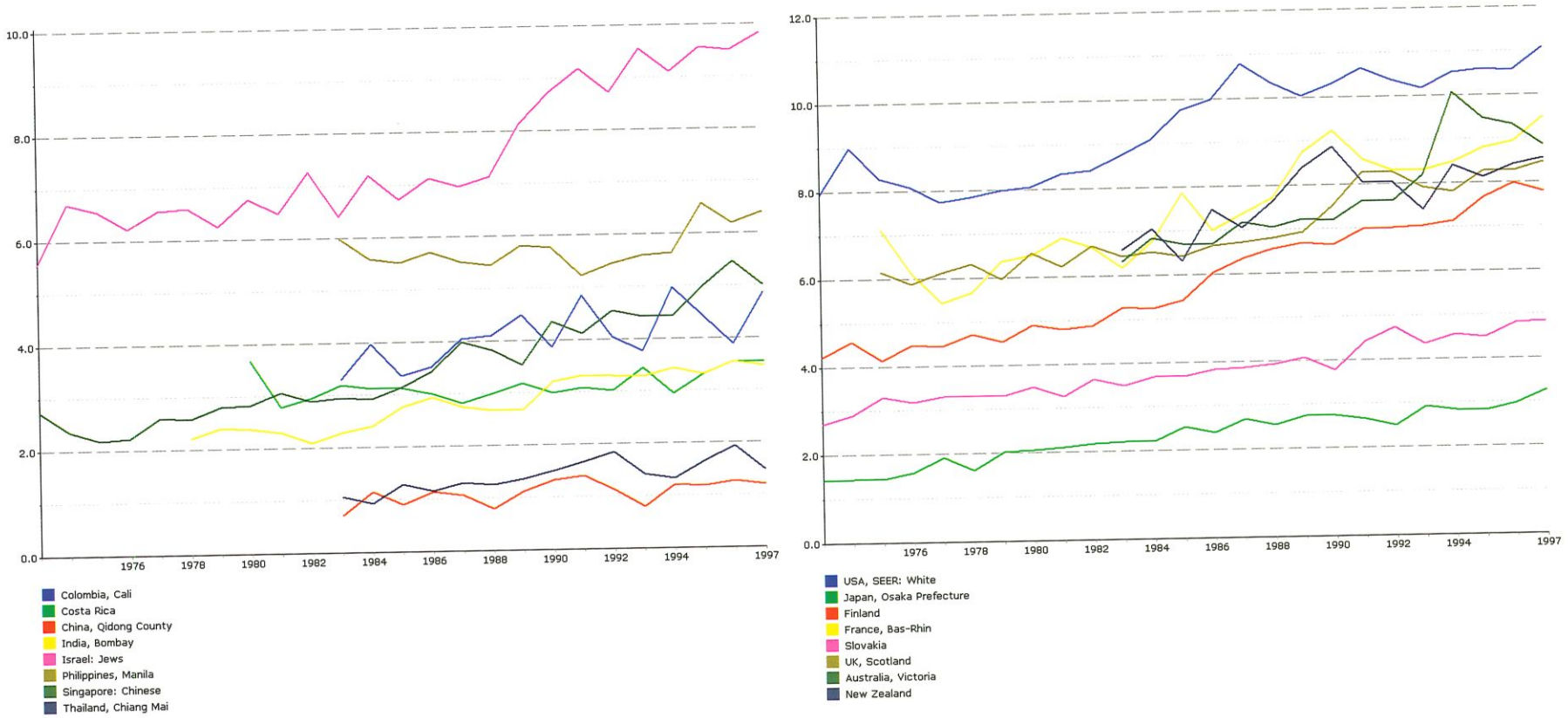


Figure 2. Breast cancer cumulative incidence 1973–97

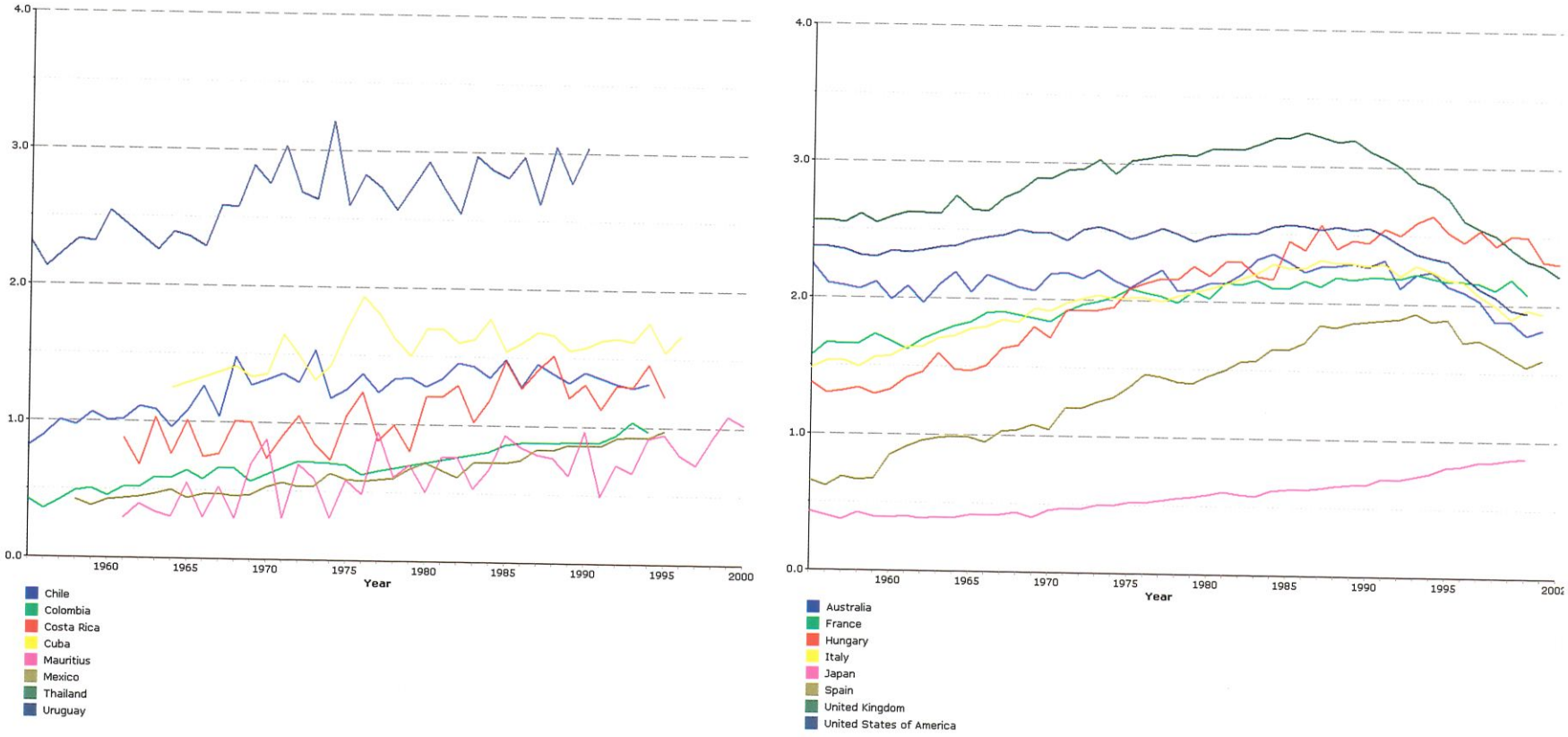


Figure 3. Breast cancer mortality 1953–2000, age 35–74 years (per cent)

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Geography of Cancer Death in Europe

Mapping of cancer mortality rates provides insight into patterns of geographical distribution of cancer.

A first atlas of cancer mortality in Europe (*Smans *et al*, 1992) was published by IARC in 1992. A new atlas (*Boyle & Smans, 2006), to be published in 2006, has now been prepared using more recent mortality data (1993–97) for 28 European countries. Age-adjusted rates for most common cancers were calculated for small geographical units (equivalent to NUTS3 in the European Union) and compared using a gradient of rates on a relative scale throughout Europe. Figure 1 presents the distibution of lung cancer mortality rates in Europe for the period 1993–97 in men and women.

Lung cancer

As a result of the rapid decrease in rates following implementation of prevention policies in the Nordic countries, the map for males shows a group of low rates for these countries (*Ferlay *et al*, 2004; *Parkin *et al*, 2005). In contrast, there is a clear geographical cluster of high rates for males in North-East France, Belgium and The Netherlands and rates remained high in the Eastern European countries.

The high lung cancer rates seen in the UK in the 1992 atlas have diminished on the latest maps, although the rates in males have remained high in large cities such as Glasgow, Liverpool and Newcastle.

For both sexes, a clear south-to-north gradient of rates is evident within Italy, with more affluent parts of Italy having the highest rates.

Women started smoking tobacco later than males and this change occurred first in the UK, Denmark and the Nordic countries. The map of lung cancer among females reflects this development, with a clear south-to-north gradient in lung cancer burden. In view of the changing consumption of tobacco in Europe, with the percentage of women who smoke decreasing in the Nordic countries and increasing dramatically in Southern Europe (for example, Spain (Shafey *et al*, 2004), a change in the current picture of

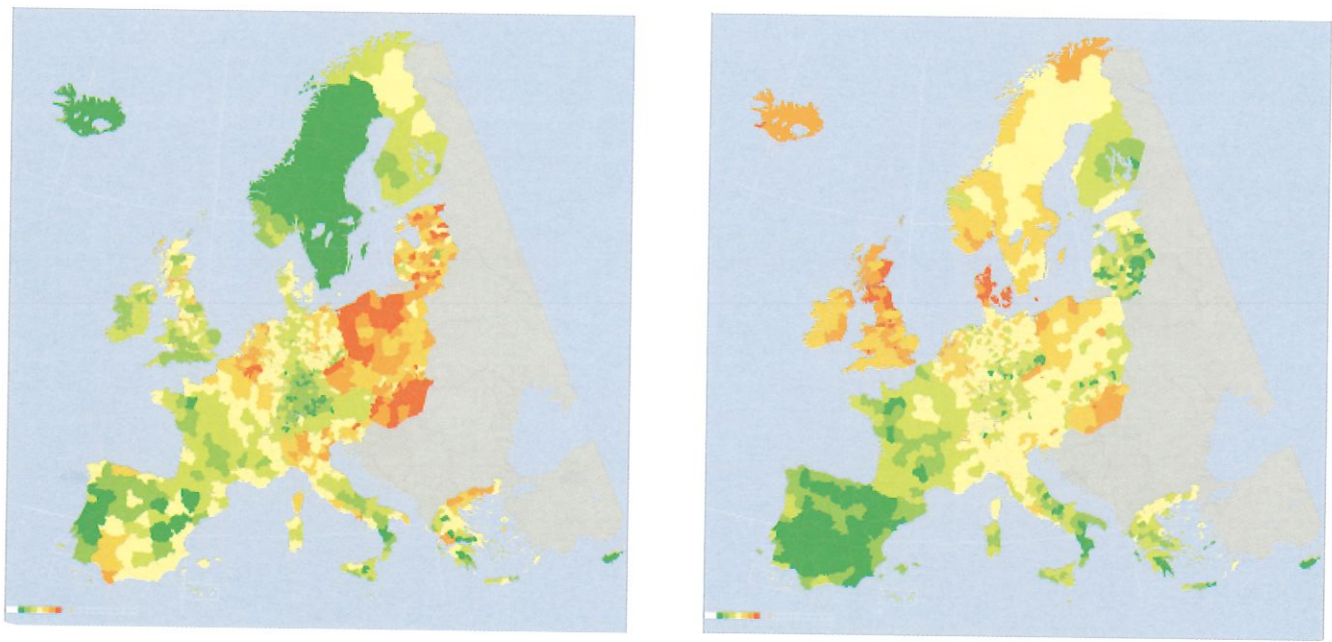

Figure 1. Map of lung cancer mortality among men (left) and women (right) in Europe (1993–97) (relative scale)

rates in Europe can be expected, with inversion of this south-to-north gradient (*Boyle *et al*, 2003).

Breast cancer

The distribution of breast cancer mortality rates in Europe shows a concentration of higher rates in the UK, Ireland, Belgium, The Netherlands, Denmark and most of Germany. Lower rates tend to be seen towards the edges of the map (Figure 2). This pattern is unlikely to be due to classification differences between countries, since national boundaries are hard to distinguish on the map, but rather is probably related to wide variations in demographic characteristics such as age at first pregnancy, number of children per woman and dietary habits across Europe. The pattern has not changed compared with the previous atlas, suggesting that the risk factors for breast cancer still present the same geographical distribution in Europe (*Smans *et al*, 1992).

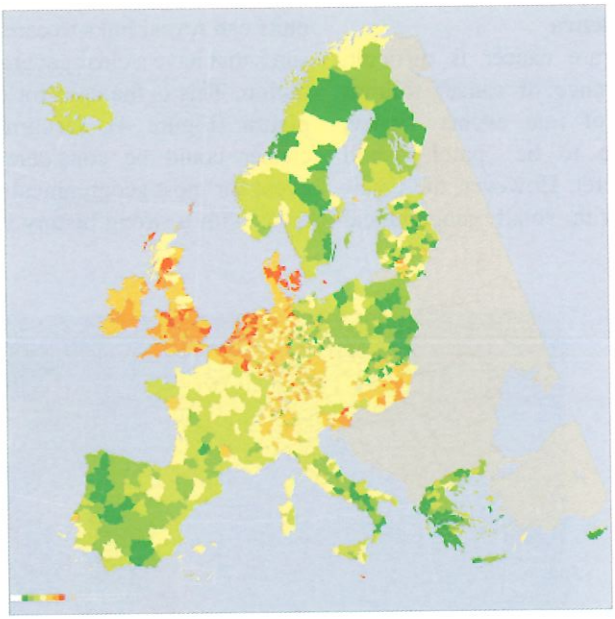

Figure 2. Map of breast cancer mortality among women in Europe (1993–97) (relative scale)

Stomach cancer

The long-term decrease in stomach cancer mortality rates in most countries (*Ferlay *et al*, 2004; *Parkin *et al*, 2005) has been related to improvements in food preservation and nutrition, and linked to the socioeconomic status of countries. These differences are reflected in the maps of mortality rates for both males and females (Figure 3). Whereas rates for males are twice those of females, the geographical distribution is very similar, suggesting that similar risk factors affect both sexes. Central European countries still present the highest mortality rates and within Germany, there is a clear difference in rates between the two pre-reunification Republics. This pattern is likely to dissipate as economic conditions improve in Central Europe.

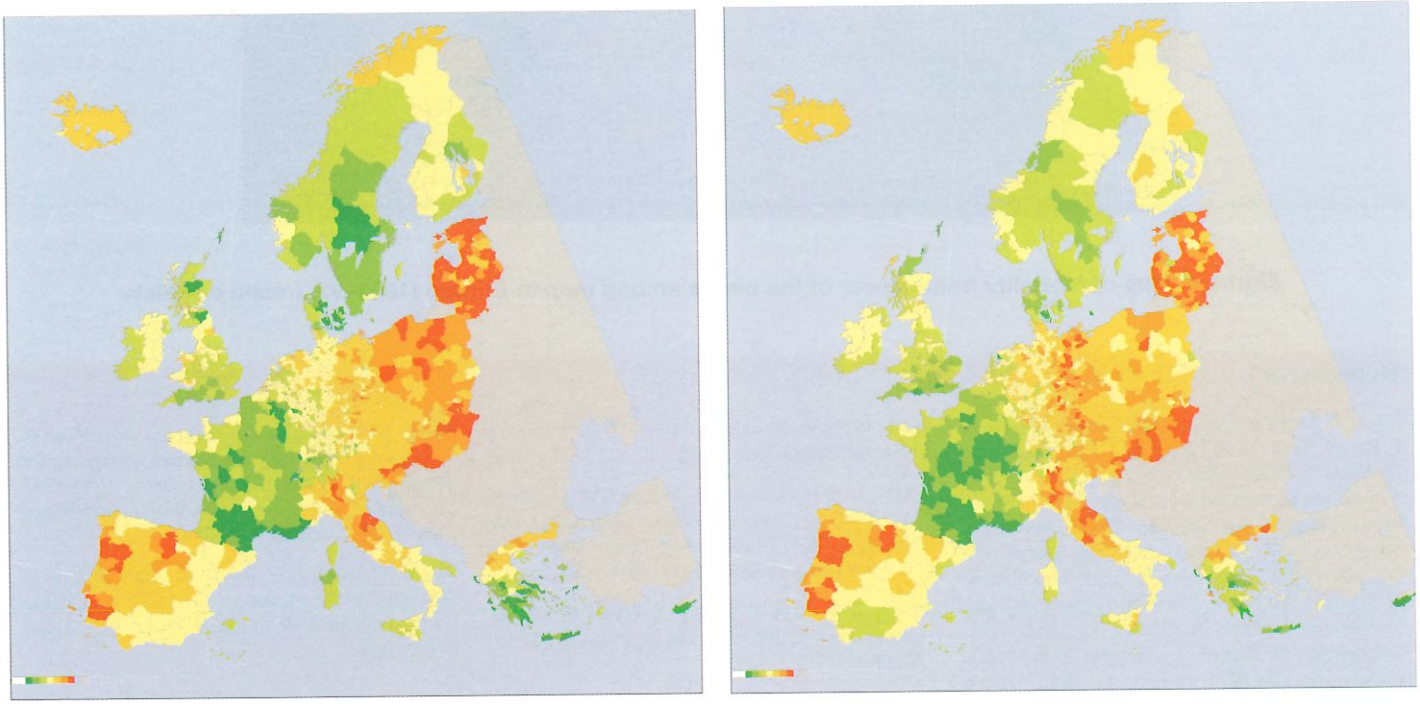

Figure 3. Map of stomach cancer mortality among men (left) and women (right) in Europe (1993–97) (relative scale)

Cancer of the pleura

Mapping of a rare cancer is difficult, since the occurrence of cancer follows statistical laws of rare events. Hence, maps are liable to be "patchy" and difficult to interpret. However, the precision obtained with small geographical units can reveal links to carcinogen exposures that have a clear geographical distribution. This is the case for cancer of the pleura (Figure 4). Occurrence of this cancer could be considered a random event for most geographical units, but for areas with a strong history in ship-building such as Vestfold (south of Oslo), Genoa and Newcastle, rates of cancer of the pleura are the highest in Europe, presenting a clear geographical picture of places where a relatively high proportion of the population was exposed to asbestos.

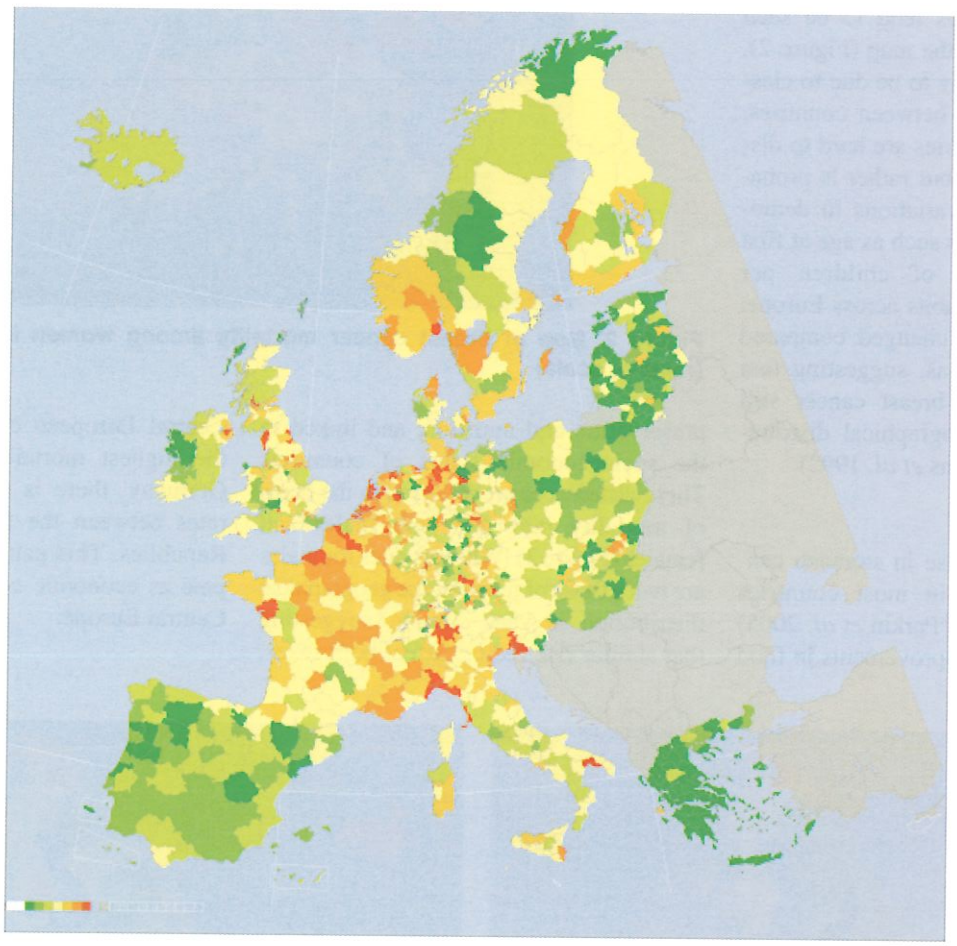

Figure 4. Map of mortality from cancer of the pleura among men in Europe (1993–97) (relative scale)

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Tobacco

Tobacco currently accounts for 5 million deaths per year, and estimates remain at 10 million per year by 2030 based on current projections of tobacco use (Jha & Chaloupka, 1999).

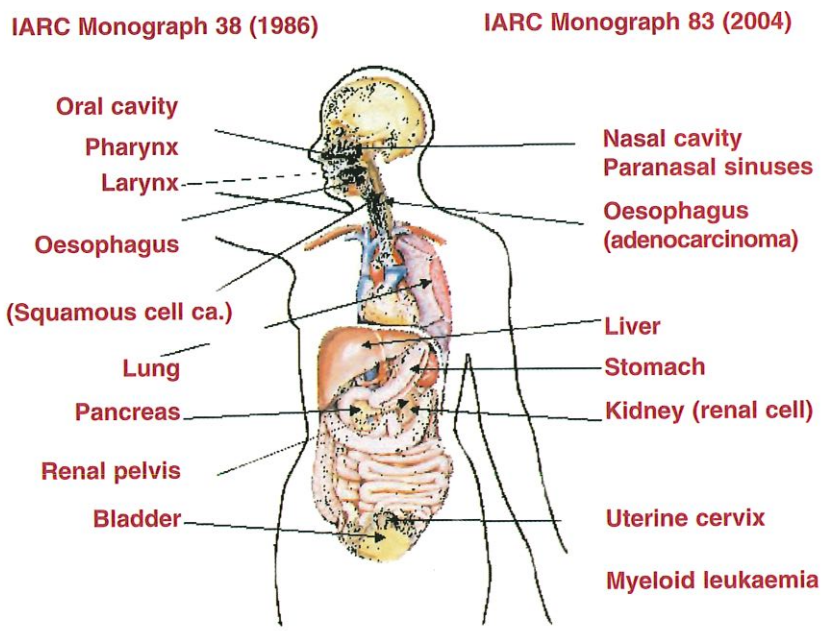
The majority of these deaths are from cancer, heart disease, and pulmonary disease – and all of them preventable.

In addition, the majority of these deaths will occur in the developing world, as the more developed nations improve their tobacco control with increased smoking cessation and decreased teenage initiation. Unfortunately, it is also in the more developing nations and in women that the tobacco multinationals are focusing their marketing efforts.

In 2004, IARC published a pivotal Monograph, *Volume 83: Tobacco Smoke and Involuntary Smoking (*IARC, 2004*)*. In this 1400-page meticulous review of the data, several important conclusions were reached by the Working Party. First, it was concluded that tobacco smoke was a Group I carcinogen, which it had previously been classified as in the 1986 Volume 38. However, in this current review, several additional cancers were found to be attributable to tobacco. In addition to the cancers of respiratory and upper digestive tracts, bladder, renal pelvis and pancreas which were identified in 1986, cancers of the nasopharynx, nasal cavity and paranasal sinuses, liver, ureter, stomach, kidney, uterine cervix and myeloid leukaemia were added with the 2004 review.

Volume 83 was also critically important in declaring involuntary smoking a Group I carcinogen. The Working Party found sufficient evidence for exposure to involuntary smoking to cause lung cancer in humans. This finding is of significant importance to support the numerous regulations and legislations that require scientific support for new laws that have been promulgated around the world. Ireland became the first smoke-free country in 2004 – eliminating smoking even in their famed pubs. They were followed by Norway, Malta, New Zealand, Italy and Sweden in 2005. More localities and nations are reviewing the data and considering laws to further restrict exposure to secondhand smoke. The findings that involuntary smoking is a Group I carcinogen has played a very significant role in these discussions.

To add further support to the findings of Volume 83, Richard Doll *et al* published a remarkable paper in the *British Medical Journal* that reviewed a 50 year follow-up of a study on male British physicians (Doll, Peto *et al.*, 2004). This study began in 1951 and its early results were influential in demonstrating that cigarette smoking caused lung cancer in 1954. With the 50-year follow-up, this study confirmed the IARC findings of increased oral and laryngeal cancers from cigarette smoking (Doll, Peto *et al,* 2005). In



addition, this paper demonstrated the improvement in mortality with smoking cessation, even later in life, but states that previous estimates of cigarette usage had under-estimated its harm. Currently, one-half to two-thirds of continuing smokers will die from their tobacco use. This information reinforces even more strongly the need for better tobacco control.

Another pivotal study published in 2005 with 14.5-year follow-up was the Lung Health Study (LHS) with 5887 smokers with airway disease (Anthonisen *et al,* 2005). This trial demonstrated that patients who quit smoking had significantly fewer deaths than continuing smokers, including fewer lung cancers. This is the first study that has demonstrated that providing a smoking cessation intervention results in fewer lung cancer. Between the Doll cohort study and this LHS, it is clear that smoking cessation must be provided as significant mortality can be avoided.

In February 2005, the first public health treaty ever written became international law (FCTC, 2005). 168 countries had signed on to the Framework Convention on Tobacco Control (FCTC) and it has been ratified by the requisite 40 countries. Since then, over 110 countries have ratified the FCTC and the formal Conference of the Parties will meet in February of 2006 to begin implementation of the Convention. This FCTC is a remarkable treaty that works to strengthen global tobacco control through 38 Articles, including restrictions on advertising, smuggling, taxation, youth access, environmental tobacco smoke, research and education needs, etc. An example of one of the pictorial warnings is demonstrated in Figures (Health-Canada, 2005) Such visual warnings have been demonstrated to be significantly more likely to lead to people desiring to quit smoking than the older, more standard warning labels that are currently in place (Hammond *et al*, 2004). It is critical for everyone interested in decreasing the morbidity and mortality from tobacco, whether from cancer or other tobacco related diseases, to not only be familiar with the FCTC, but work to help fulfill its complete implementation. The Tobacco and Cancer Group at IARC will be working to provide the research necessary to support the FCTC.

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Alcohol Drinking

Alcohol drinking is an important cause of cancer and other chronic diseases.

A causal link was established several decades ago between alcohol drinking and cancers of the oral cavity, pharynx, oesophagus and liver (*IARC, 1988). Recently, evidence has accrued in favour of causal associations with colorectal and breast cancers.

Several studies have provided evidence, although not fully consistent, of an association between elevated intake of alcohol, and increased risk of colorectal cancer. When the results of these studies were combined in a meta-analysis, a moderately increased risk of colorectal cancer was detected, with a dose–response relationship for increasing amounts of alcohol consumption (Corrao *et al,* 1999). A subsequent pooled analysis of eight cohort studies also reported a dose–response relationship between colorectal cancer risk and the amount of alcohol consumed (Cho *et al,* 2004). The pooled analysis and meta-analysis did not detect any differences in the type of alcoholic beverage consumed or the level of risk of colon vs. rectal cancer. Potential confounding by low intake of protective dietary factors, notably folate, was controlled for in most of the recent studies and does not seem to explain the increased risk among drinkers. Thus it is reasonable to conclude that though the effect may be moderate, there does appear to be a causal relationship between alcohol consumption and colorectal cancer risk.

With respect to breast cancer, an association with alcohol consumption has been reported fairly consistently in numerous studies. The strongest evidence comes from a pooled analysis of 53 epidemiologic studies with 58,515 cases and 95,067 controls, which resulted in an increase in breast cancer risk of 7.1% for each additional 10 grams per day increase in alcohol intake (Figure 1) (Hamajima *et al,* 2002). Differences in risk due to alcohol beverage types have not been observed (Singletary *et al*, 2001). The association is consistent among both premenopausal and postmenopausal women. It is likely that both overweight and heavy alcohol drinking act on breast cancer risk through mechanisms involving hormonal level or metabolism.

For other cancers, including cancers of the stomach, pancreas, kidney and bladder, a causal association is suspected, but the current evidence does not permit a definite conclusion.

The importance of alcohol as a human carcinogen is often underestimated. A recent estimate made at IARC of the burden of alcohol-related cancers indicated in a total of 390,000 cases of cancer worldwide, representing 3.6 % of all cancers (5.2 % in men, 1.7 % in women) (Table 1). It is worth noting that among women breast cancer is the main contributor to the burden of alcohol-related cancer.

There is growing evidence that the risk of cancer among drinkers is modulated by genetic factors. Research has focused in particular on variants in genes involved in alcohol metabolism (Figure 2). Alcohol dehydrogenases (ADHs) are enzymes involved in the oxidation of ethanol to acetaldehyde. Subsequent oxidation of acetaldehyde to acetate is catalysed by the enzymes aldehyde dehydrogenase (ALDH). The efficiency in converting ethanol to acetaldehyde, and subsequent conversion to acetate, is largely determined by the *ADH* and *ALDH* gene families, with potential inter-individual differences in acetaldehyde exposure due to the

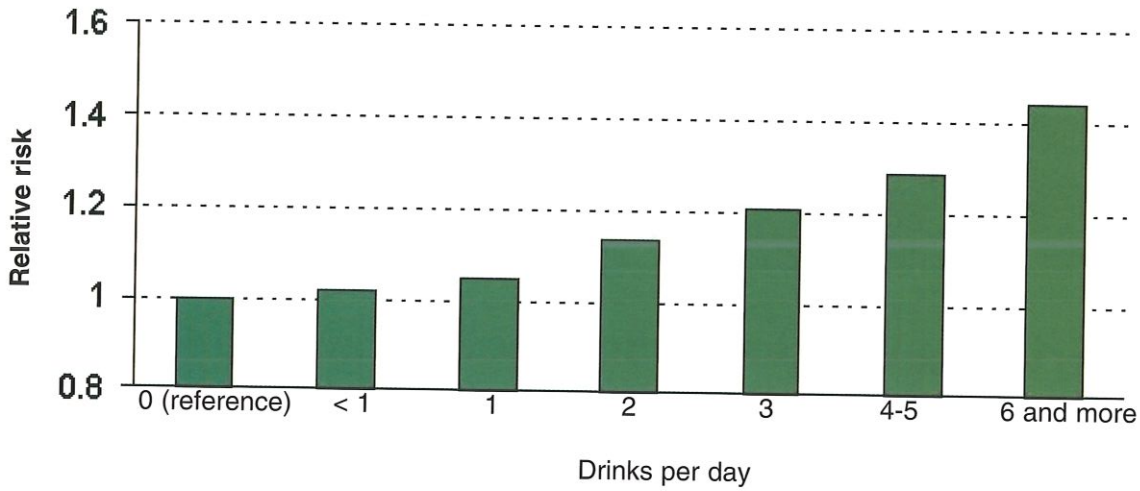

Figure 1. Relative risk of breast cancer for alcohol intake. Results of the pooled analysis of 53 epidemiological studies (Hamajima *et al.*, 2002)

Table 1. Number of cases of cancer occurring in 2002, in men and women, attributable to alcohol drinking

Men			Women		Total	
	AF%	Cases	AF%	Cases	AF%	Cases
Oral cavity, pharynx	38.8	109,500	10.9	13,300	30.4	122,800
Oesophagus	25.0	79,000	4.5	6,600	18.5	85,500
Colon and rectum	4.6	25,200	1.7	7,800	3.2	33,000
Liver	12.2	53,800	2.9	5,400	9.4	59,100
Larynx	25.3	35,200	7.3	1,500	23.0	36,700
Breast (women)	NA	NA	4.5	51,900	4.5	51,900
Total	5.2*	302,600	1.7*	86,400	3.6*	389,000

AF%, fraction of cancers attributable to alcohol drinking

* Denominator comprises all cancers

NA, not applicable

presence of common genetic variants with a functional role.

The functionally important polymorphisms for *ADH1B* are Arg48His in exon 3 and Arg370Cys in exon 9; that for *ADH1C* is Ile350Val in exon 8. The *ADH1B* 48His and the ADH1C 350Val alleles encode for enzymes which result in the 'fast' metabolism of ethanol. Small-scale studies in Asian populations have shown that the *ADH1B* 48His allele is associated with an increased risk of esophageal cancer (Yokoyama *et al,* 2003); and in a pooled analysis of seven published case-control studies conducted by IARC, which included 1,325 cases and 1,760 controls, no increased risk of head and neck cancer for the *ADH1C* Ile350Val polymorphism (*Brennan *et al,* 2004) was shown. The *ALDH2* gene contains several polymorphic sites: the best studied is an inactive *ALDH2* Gln487Lys polymorphism, resulting in homozygote carriers who are unable to oxidize acetaldehyde and heterozygote carriers who do so inefficiently, resulting in a toxic reaction including flushing, increased heart rate, and nausea, upon intake of alcohol. The *ALDH2* 487Lys allele, is frequently observed in Asian populations, where it has been shown to be associated with an increased risk of upper aerodigestive tract cancer (Yokoyama, 2003), but it is rare in Europeans, among whom other, less studied polymorphisms, are prevalent.

Cytochrome P-450 2E1 *(CYP2E1)* also oxidizes ethanol into acetaldehyde. Several polymorphisms with functional

relevance have been identified, but the available studies do not consistently suggest a effect on the alcohol-associated risk of cancers of the head and neck, esophagus and liver.

Alcohol-related cancer is an important field of research, in which IARC is active in several key aspects, including elucidation of the carcinogenic effect of specific types of alcoholic beverages (in particular home-made liquors), the identification of genetic variants interacting with alcohol in determining cancer risk, and the coordination of consortia of molecular and epidemiological studies of alcohol and cancer.

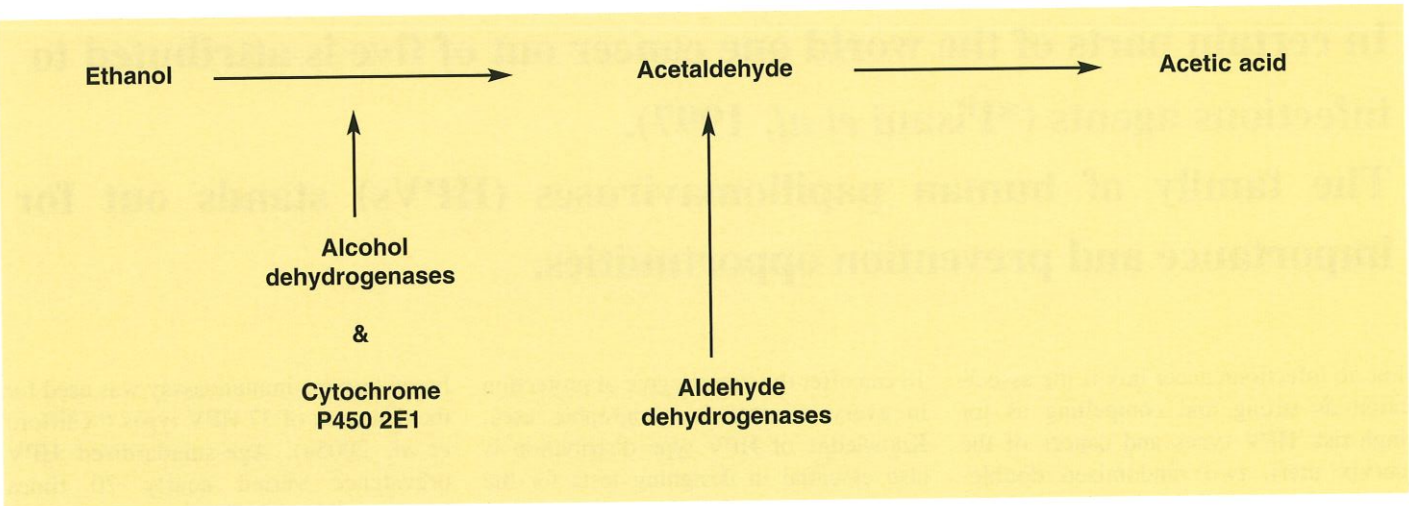

Figure 2. Genes involved in alcohol metabolism

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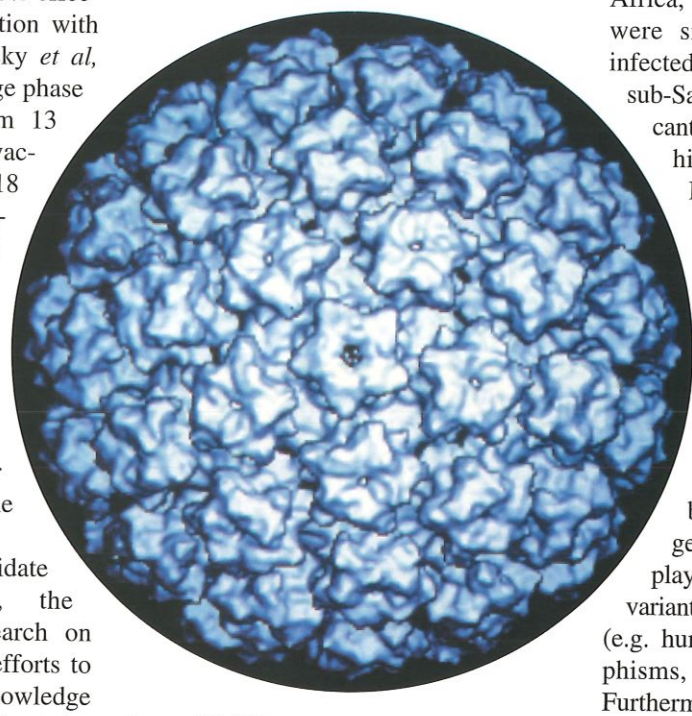
Human Papillomavirus Infection

In certain parts of the world one cancer out of five is attributed to infectious agents (*Pisani *et al,* 1997).
The family of human papillomaviruses (HPVs) stands out for importance and prevention opportunities.

For no infection/cancer link is the association as strong and compelling as for high-risk HPV types and cancer of the cervix uteri; two randomised double-blind placebo-controlled trials involving more than 2,000 young women have shown that both of the vaccine candidates currently available are at least 90% effective in protecting against infection with the targeted HPV types (Koutsky *et al,* 2002; Harper *et al*, 2004). A large phase 3 trial of 12,000 women from 13 countries have shown that the vaccine against HPV6, 11, 16 and 18 has over 100% efficacy in preventing precancerous lesions caused by the corresponding HPV types (Lowndes *et al*, 2005). Future findings from additional trials of HPV vaccines, involving nearly 60,000 women should lead to marketing of HPV vaccine in 2006 or 2007 in many countries of the world (Washam, 2005).

With promising HPV candidate vaccines on the horizon, the International Agency for Research on Cancer (IARC) has intensified efforts to fill the remaining gaps in the knowledge on HPV. Until we know more about the distribution of HPV types in low- and middle-resource countries, we cannot be certain that the current vaccine candidates including the high-risk types HPV16 and 18 can offer the same degree of protection in every country or geographic area. Knowledge of HPV type distribution is also essential in designing tests for the early detection of cervical lesions and monitoring vaccine effectiveness (*IARC, 2005).



Over 15,000 women without cervical lesions were, therefore, randomly selected from the general population of 13 areas in four continents and a highly sensitive GP5+/6+ polymerase chain reaction-based enzyme immunoassay was used for the detection of 37 HPV types (*Clifford *et al*, 2005a). Age-standardised HPV prevalence varied nearly 20 times between populations. Although both overall HPV prevalence and HPV16 prevalence were highest in sub-Saharan Africa, HPV-positive women in Europe were significantly more likely to be infected with HPV16 than were those in sub-Saharan Africa, and were significantly less likely to be infected with high-risk HPV types other than HPV16 and/or low-risk HPV types (Figures 1 and 2). Women from South America had HPV-type distribution in between those from sub-Saharan Africa and Europe, and heterogeneity between areas of Asia was significant.

Differences in the relative prevalence of HPV types might be related to the complex geographical and biological interplay between different HPV types or variants and host immunogenetic factors (e.g. human leukocyte antigen polymorphisms, Hilde-sheim *et al,* 2002). Furthermore, HPV16, the most oncogenic HPV type, seems to be less influenced by immune status than are other HPV types (Strickler *et al,* 2003). This finding, coupled with impairment in cellular immunity in some of the populations

studied (e.g. through chronic cervical inflammation, parasitic infection, malnutrition, and, more recently, human immunodeficiency virus infection), could somehow contribute to a higher penetrance of HPV types other than HPV16. However, regional heterogeneity decreases with increasing severity of lesions as HPV16 becomes increasingly dominant (*Clifford *et al,* 2003a; *2003b; *2005b).

To further elucidate which HPV types are the strongest predictors of the risk of cervical intraepithelial neoplasia grade 3 and cancer, we compared our three large systematic reviews on the distribution of HPV types in low-grade squamous intraepithelial lesions (LSILs, 8308 women from 50 studies, *Clifford *et al*, 2005b), high-grade squamous intraepithelial lesions (HSILs, 4338 women from 52 studies, *Clifford *et al,* 2003a) and squamous cell cervical carcinoma (SCC, 10,058 women from 85 studies, *Clifford et al, 2003b). Only HPV16 and 18 were found more frequently in SCC than in LSILs, whereas HPV26, 39, 51, 56 and 73 were at least 10 times more common, and HPV53 and 66 were approximately 30 times more common, in LSILs than in SCC (*Franceschi *et al,* 2005, Figure 3). These findings suggest priorities for inclusion of HPV types in vaccines and screening tests (*Franceschi *et al,* 2005, Figure 3).

In order to reassess all of the available evidence on the carcinogenicity of HPV, 25 scientists from 12 countries met at IARC in February of 2005 (*Cogliano *et al*, 2005). In addition to HPV16 and 18 (*IARC, 1995) the Working Group concluded that HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 can lead to cervical cancer and are to be considered carcinogenic to humans.

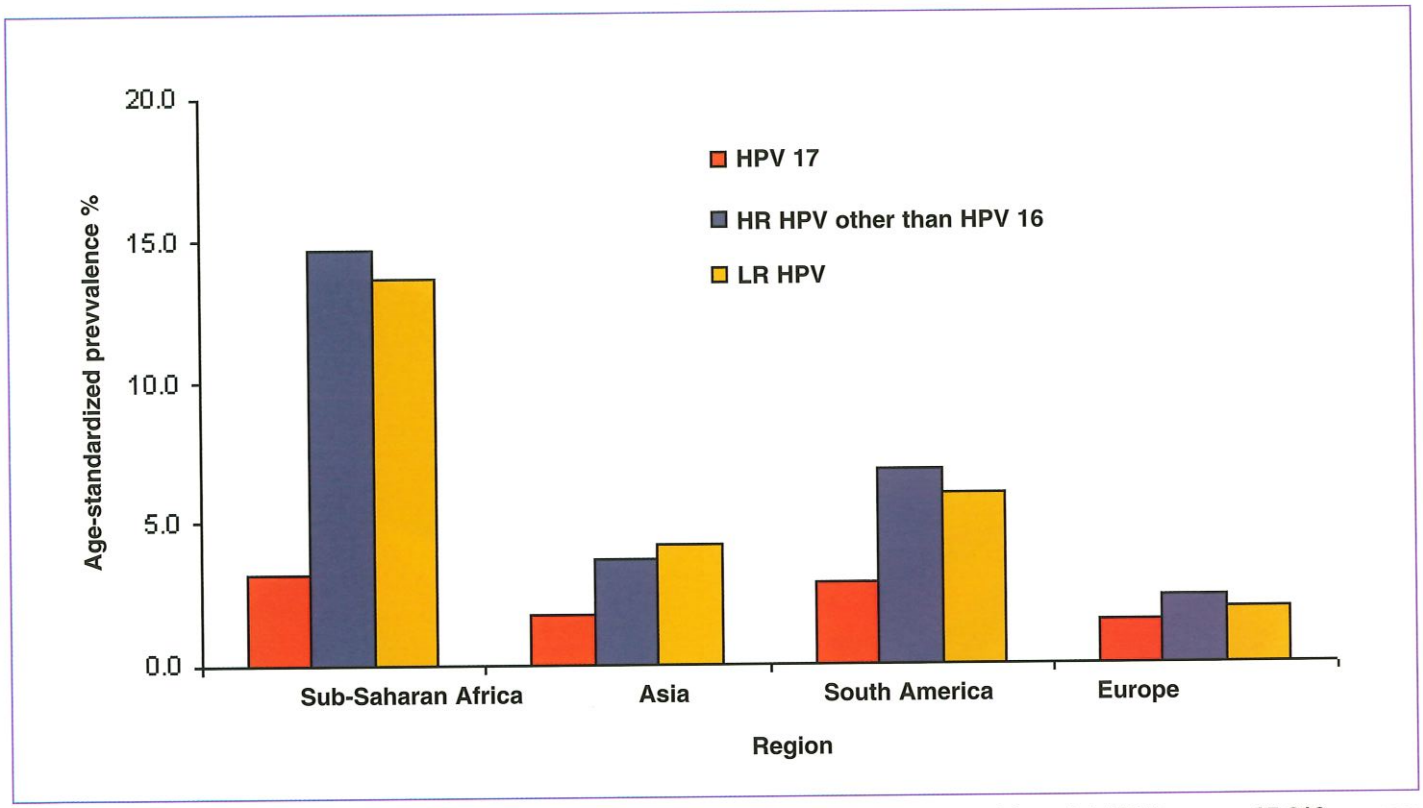


Figure 1. Age-standardised prevalence of HPV16, high-risk HPV other than HPV16 and low-risk HPV among 15,613 women without cervical abnormalities in the IARC HPV Prevalence Surveys by region
From *Clifford *et al.*, 2005a

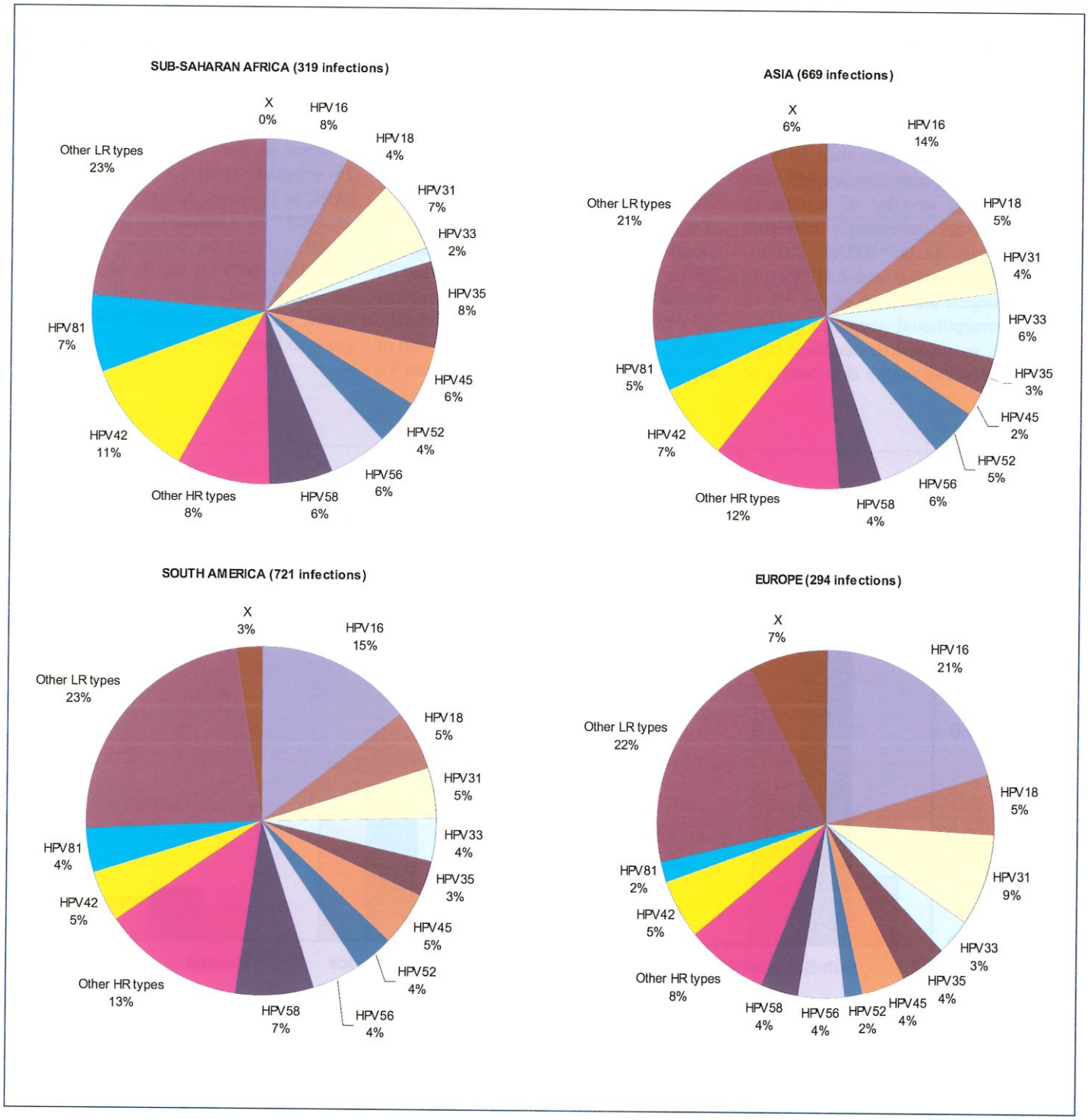


Figure 2. Human papillomavirus (HPV) infections by type and region in the IARC HPV Prevalence Surveys
From *Clifford *et al,* 2005a

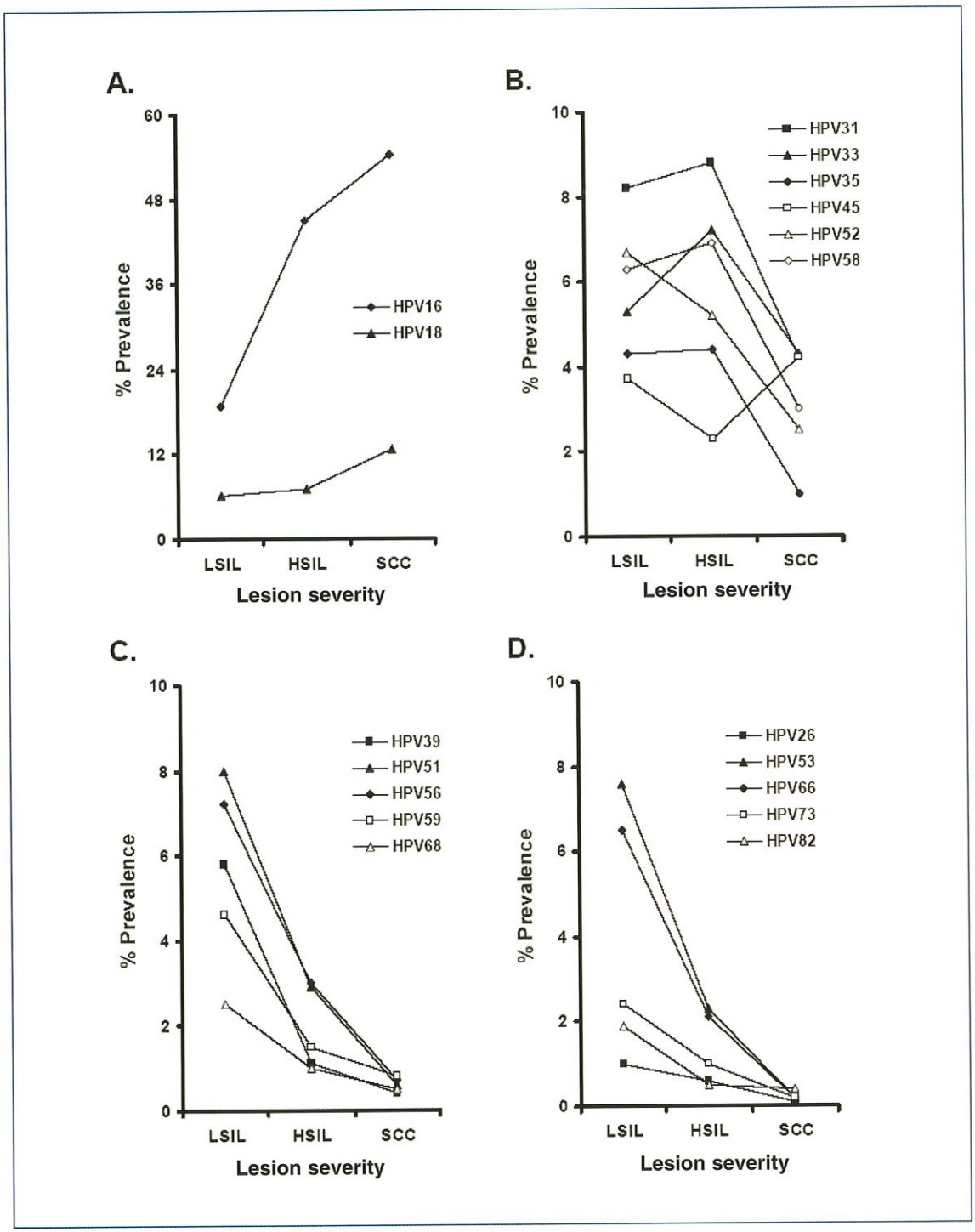


Figure 3. The 13 HPV types included in the Food and Drug Administration (FDA)-approved HPV test kit are shown in A-C: A. HPV16 and 18, B. HPV types present in 1-5% of SCCs (HPV31, 33, 35, 45, 52 and 58), and C. HPV types present in less than 1% of SCC (HPV39, 51, 56, 59 and 68). The five HPV types not currently included in the FDA-approved test set, as discussed by Schiffman *et al,* 2005 (HPV26, 53, 66, 73 and 82), are shown in D. LSIL = low-grade squamous intraepithelial lesions; HSIL = high-grade squamous intraepithelial lesions; SCC = squamous cell carcinoma.
From Franceschi *et al,* 2005.

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Gambia Hepatitis Intervention Study: 20 years of activity

Hepatocellular carcinoma (HCC) is the most frequent form of primary liver cancer and is a major cause of death in sub-Saharan Africa and Eastern Asia.

The main etiological factor in these regions is chronic infection with HBV, namely the chronic carrier status. Other factors that contribute to the etiology of primary liver cancer in these regions include other hepatitis viruses (HCV) and dietary exposure to aflatoxins, a group of mycotoxins that are natural contaminants of the staple diet. The latter have a multiplicative effect on the risk of developing HCC.

The Gambia Hepatitis Intervention Study (GHIS) is a collaborative undertaking by the International Agency for Research on Cancer (IARC), The Government of the Republic of The Gambia and the Medical Research Council of the United Kingdom (MRC). At various points in the study, funding was also received from several sources, notably the Swedish Medical Research Council and the Government of Italy. This programme was launched in 1986 with the objective of evaluating the efficacy of hepatitis B (HB) vaccination in childhood for the prevention of HB infection, chronic liver disease and hepatocellular carcinoma (HCC) in a population at high risk (GHIS Study Group, 1987). The implementation of GHIS involves three overlapping phases. During phase I (1986–1990), HB vaccine, approved by the World Health Organization, was phased into the Gambian Expanded Programme on Immunization (EPI) over a four-year period from July 1986 to February 1990. Two groups of children were recruited, one of about 60,000 children who received all EPI vaccines (BCG, DPT polio, measles, yellow fever), and the other of a similar number of children who received all vaccines plus HB. Since February 1990, HB vaccination has been offered to all newborns as part of the EPI in The Gambia. During Phase ll (1991–1997), the efficacy of HB vaccine against infection and chronic carriage was estimated through longitudinal and cross-sectional surveys in selected groups of HB-vaccinated and unvaccinated children. Phase lll (initiated in 1998) consists in long-term follow-up through cancer registration, using HCC as primary end-point.

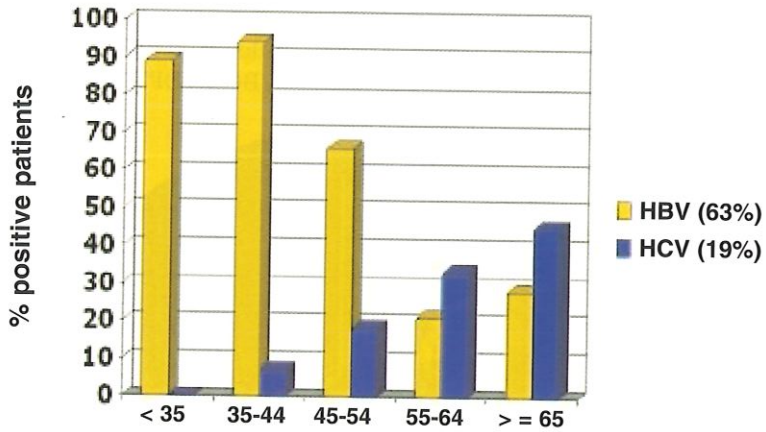
The GHIS cohort includes a total of 124,577 subjects, 61,065 of whom received HB vaccine. Detailed cross-sectional studies have demonstrated that by 10 years of age, the vaccine efficacy is of 83% against infection, and of 94% against chronic HB carriage. Despite waning antibody titres, the protection against carriage remains high into adolescence. A National Cancer Registry (NCR) was set up at the initiation of the project to identify and record data on cancers of all types occurring in The Gambia (*Bah *et al,* 2001). The cases are ascertained in public or private health departments with support of National Health Laboratory and Histopathology Services. For HCC diagnosis, clinical criteria, ultrasonography and alpha-feto-protein measurement are used in combination according to a protocol validated against histology in Senegal. The

final outcome of GHIS will be evaluated through record linkage between HCC cases in the NCR and the GHIS database of vaccinated and unvaccinated children.

The proportion of HCC attributable to HBV and HCV infections was assessed in a recent case–control study on 197 incident cases of HCC and 405 matched, hospital-based controls (Kirk *et al*, 2004). HBV carriage was present in 63% of HCC cases and 16% of controls while 19% of HCC cases were HCV seropositive compared to 3% of controls. Increased HCC risk was strongly associated with chronic HBV (OR 18; 95%CI 10–32), HCV (OR 21; 95%CI 8–54) and dual infection (OR 35; 95%CI 4–350). Strikingly, HBV carriage was found in over 80% of patients aged less than 35 years old. This proportion decreased in older age groups, and HCV became the more prevalent infection in patients older than 50 years old (see below). Taken together, the three case–control studies suggest that between 60 and 80% of HCC under age 50 is attributable to HBV. In parallel, molecular analysis demonstrated an increased risk of HCC associated with several polymorphisms in genes involved in the metabolism and detoxification of aflatoxin, as well as in the repair of aflatoxin–DNA adducts (Kirk *et al*, 2005)

In 2004, experts of the IARC Scientific Council carried out a comprehensive review of GHIS achievements, as well as a re-assessment of GHIS predicted outcomes. Twenty years after it was conceived, the design of the GHIS appears to have well resisted the trial of time and field experience. On the basis of all evidence available, we are in a position to confirm that the major end-point of the study, the evaluation of the protective efficacy of childhood HB vaccine against HCC, will be reachable between 2017 and 2020, slightly earlier than the initial assumption of an overall follow-up of 35 to 40 years (GHIS, 1987). The final success of this unique, long-term endeavour will depend upon the continuing development of a sustainable infrastructure for cancer detection, diagnosis and registration, for monitoring viral infections, and for performing record linkage. These infrastructures will not only contribute to the final research outcome of GHIS, but may also provide a backbone for the development of other interventions aimed at preventing cancer and better managing patients in the context of a low-resource African country. Finally, the strategy adopted for the development of GHIS provides a model for the introduction of new vaccines in the EPI of African countries.

HBV (HbSAg) and HCV in HCC patients from The Gambia



Bars indicate, for different age groups of patients with liver cancer, the proportion of patients with HBV or HCV.

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Vegetables and Lung Cancer

Previous case-control and cohort studies have provided consistent evidence for a protective role of vegetable consumption against lung cancer, with the evidence being most apparent for green cruciferous vegetables such as broccoli and cabbage (WCRF, 1997). Such vegetables are rich in isothiocyanates (ITC), which have been shown in animal studies to have strong chemopreventive properties against the development of lung cancer, and are therefore likely agents for explaining the protective effect observed in humans (Hecht, 1996). However, in a recent IARC review of the evidence of cruciferous vegetables, interpreting a definite protective effect against any type of cancer was not possible given the small size of available studies and potential for confounding from other dietary sources (*IARC, 2004). One way to overcome the problem of confounding is to adopt a Mendelian randomization approach (Davey *et al*, 2003). ITCs are thought to be eliminated by glutathione-S-transferase enzymes, most notably GSTM1 and GSTT1 (London *et al*, 2000; Fowke *et al,* 2003). Both *GSTM1* and *GSTT1* genes have null alleles with homozygous null genotypes resulting in no enzyme being produced. Individuals who are homozygous for the inactive form of either one or both genes are likely to have higher ITC concentrations due their reduced elimination capacity. Furthermore, and implicit in the Mendelian randomization approach, the role of *GSTM1* and *GSTT1* genes are likely to be independent of other dietary and lifestyle factors, reducing the possibility of confounding from these sources.

In order to clarify the role of cruciferous vegetable consumption in preventing lung cancer, and their interaction with *GST* genotypes, we investigated this relationship in a case-control study of 2141 cases and 2168 controls in 6 countries of Central and Eastern Europe, a region which has a traditionally high level of cruciferous vegetable consumption. Incident cases and comparable hospital or population controls were recruited from 15 centres in Poland, Slovakia, Czech Republic, Romania, Russia and Hungary

using an identical protocol and questionnaire (Scélo *et al,* 2004). All subjects completed a detailed standardized lifestyle and food frequency questionnaire that had been piloted in all centers prior to use. The dietary component of the questionnaire comprised 23 foods of which 3 were cruciferous vegetables (cabbage, and brussel sprouts/broccoli combined). A blood sample was also obtained for all individuals and genotyping for *GSTM1* and *T1* was conducted.

An overall protective effect was observed for 'at least weekly' consumption of cruciferous vegetables compared to 'less than monthly' (adjusted odds ratio (OR) = 0.78, 95% confidence interval (CI) 0.64-0.96). When stratified by GST status, any protective effect of high cruciferous vegetable consumption was restricted to those who were *GSTM1* null (OR=0.67, 95% CI 0.49-0.91), *GSTT1* null (OR=0.63, 95% CI 0.37-1.07), or both *GSTM1* and *T1* null, (OR=0.28, 95% CI 0.11-0.67) (Figure 1). No protective effect was observed for those who were *GSTM1* and T1 positive, with a moderate non-significant protective effect for those who had only one null genotype (OR=0.88, 95% CI 0.65-1.21). The interaction between *GSTM1* null/*GSTT1* null versus other *GSTM1*/-*GSTT1* groups and cruciferous vegetable consumption was significant (p=0.03). Similar results were observed separately for cabbage and broccoli/brussel sprout consumption, after adjusting for the other, suggesting an independent protective effect of both sources of cruciferous vegetables.

These results provide strong evidence for our a *priori* hypothesis that the protective effect of cruciferous vegetables is most apparent among those who have low levels of circulating GST enzymes due to possession of null alleles for *GSTM1* and T1 genes. They are also supported by findings from several other smaller studies of lung cancer, breast cancer and colorectal adenomas that find an increased protective effect of cruciferous vegetable among *GSTM1* and *T1* null carriers (Hecht, 1996). It is however not possible to make definitive conclusions

from any of these individual studies due to their limited sample size [the three previous studies of lung cancer, based in Shanghai, Singapore and Texas, comprised a total of 968 cases and 1362 controls] (London *et al,* 2000, Zhao *et al*, 2001; Spitz *et al*, 2000). Taking into consideration the size of the protective effects that have been reported in this and other studies, which are likely to have been substantially diluted by measurement error, they raise the prospect of an important chemopreventative effect for cruciferous vegetables in general, and isothiocyanates in particular. We are currently conducting further studies in other populations in order to confirm these findings.

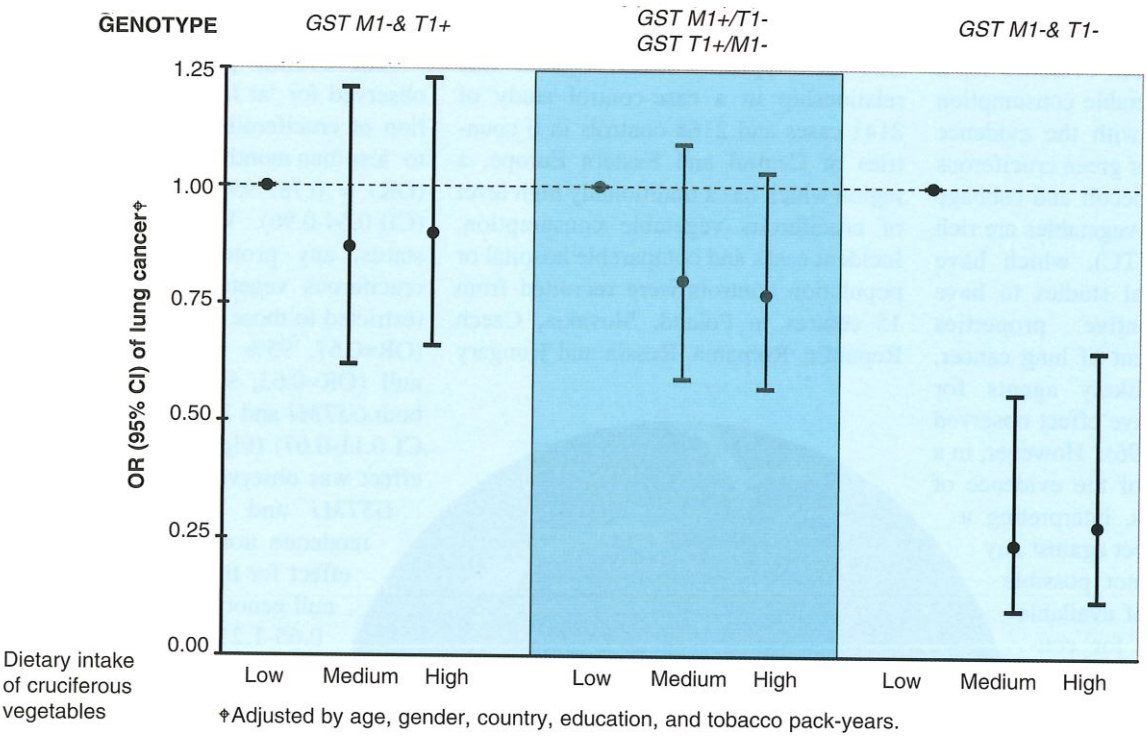

Figure 1. Mendelian randomization: effects of cruciferous vegetables on lung cancer by *GSTM1* and *T1* polymorphisms

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Ionising Radiation

Ionising radiation is one of the most studied and ubiquitous carcinogens in our general environment.

Guidelines for ionising radiation protection have existed, at the multinational level, since the 1940s. The main basis for radiation risk estimates, however, is the study of the Japanese survivors of the atomic bombings – a population exposed primarily at high dose-rates – while the primary public health concern is the protection of persons with relatively low-dose, protracted exposures such as are received by the public in the general environment and by workers occupationally.

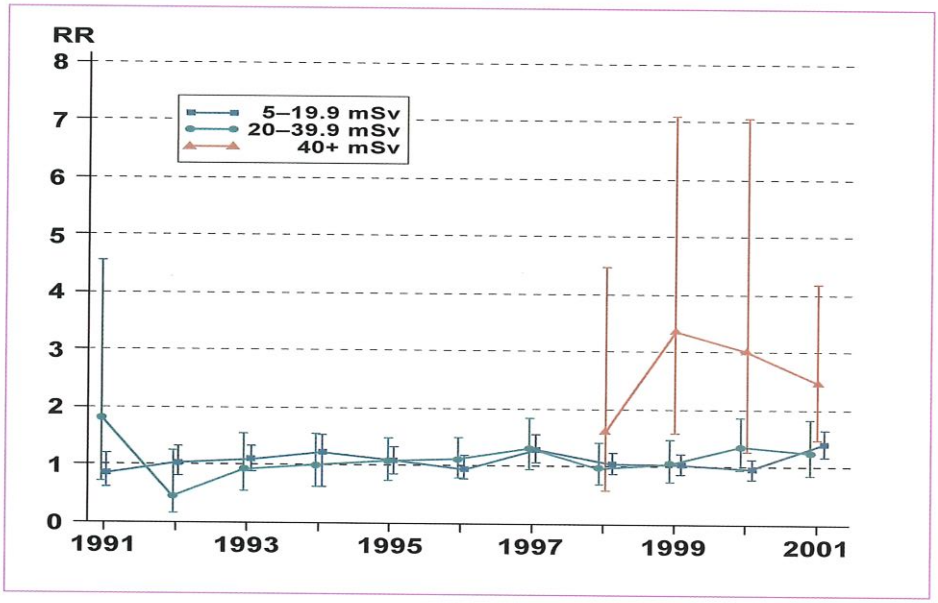
The use of data from the atomic bomb survivors to estimate the effects of the relatively low-dose rate chronic exposures of environmental and occupational concern necessitates the use of controversial models to extrapolate risks from high to low doses, from high to low exposure rates, and from acute exposures to protracted or chronic exposures. Resolution of this controversy requires answering a number of outstanding questions in ionising radiation research and protection today, namely the effects of:

- exposure pattern – in particular low doses, low dose-rates and protraction and fractionation of exposures
- radiation type – in particular specific radionuclides, such as ^{131}I
- factors which may modify radiation-induced risks (including age at exposure, sex, genetic differences and other host and environmental factors).

An International Collaborative Study of Cancer Risk among Radiation Workers, a retrospective cohort study of cancer mortality among nuclear industry workers in 15 countries, has been conducted in order to provide precise direct estimates of risk after protracted low-dose exposures and to strengthen the scientific basis of radiation protection. The first results have been published (*Cardis *et al*, 2005 – BMJ). Analyses included 407, 391 workers individually monitored for external radiation with a total follow-up of 5.2 million person-years. The excess relative risk for cancers other than leukaemia was 0.97 per Sv (95% CI, 0.14 to 1.97). This estimate, from the largest study of nuclear workers ever conducted, is higher than, but compatible with, risk estimates used for radiation protection. Analyses indicate that, although confounding by smoking may be present, it is unlikely to explain all of this increased risk. The results suggest that there is a small excess risk of cancer at the low doses and dose-rates typically received by nuclear workers. This is consistent with the conclusions of the recent report of the US National Academy of Sciences BEIR VII Committee (2005), of which Dr Cardis was a member, that support a simple proportionate relationship at low doses between radiation dose and cancer risk.

Dose reconstruction team in front of the Chernobyl Power Plant, Ukraine

The Chernobyl experience has provided a unique opportunity to learn about the effects of exposure to doses from radioactive iodines on thyroid cancer risk. A large



Time trend in breast cancer RR by average cumulative dose category in territories of Belarus and Ukraine contaminated by the Chernobyl accident (doses lagged by 5 years; age at exposure <45) (Pukkala *et al*, in press)

number of epidemiological studies of thyroid cancer have been carried out in Belarus, Russia and Ukraine since the accident. Although the majority of studies are ecological, they have clearly shown an association between thyroid cancer incidence in young people and average dose to the thyroid.

A population–based case–control study of thyroid cancer in young people, jointly coordinated by RAD and the Sasakawa Memorial Health Foundation (SMHF) of Japan, has been carried out in the regions of Belarus and Russia most contaminated by the Chernobyl accident. The objectives were to evaluate the risk of thyroid cancer related to exposure to ^{131}I in childhood and adolescence and the role of environmental and host factors that may modify radiation–induced thyroid cancer risk. These include age at exposure, stable iodine intake, genetic background and reproductive history. The first results have been published (*Cardis *et al,* 2005 – JNCI). The study included 276 cases with thyroid cancer and 1300 controls, all aged younger than 15 years at the time of the accident. Individual doses were estimated for each subject. A strong dose-response relationship was observed ($P<.001$). For a dose of 1 Gy, the estimated odds ratio varied from 5.5 (95% CI 3.1-9.5) to 8.4 (95% CI 4.1-17.3), depending on the model. The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas than elsewhere. Administration of potassium iodide as a dietary supplement reduced this risk by a factor of 3. These results have important public health implications: stable iodine supplementation in iodine-deficient populations may substantially reduce the risk of thyroid cancer related to radioactive iodines after accidental releases and medical exposures in childhood.

An ecological study of breast cancer incidence was also conducted in regions of Belarus and Russia, suggesting an increased risk of breast cancer in young women in the most contaminated districts (see above figure, Pukkala *et al*, in press).

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IARC Monographs Evaluations

The first step in cancer prevention is to identify the causes of human cancer. The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* is a series of scientific reviews that since 1971 has evaluated more than 900 agents and identified more than 400 of them as potentially carcinogenic to humans.

Group 1	*Carcinogenic to humans*	109 agents
Group 2A	*Probably carcinogenic to humans*	65 agents
Group 2B	*Possibly carcinogenic to to humans*	242 agents

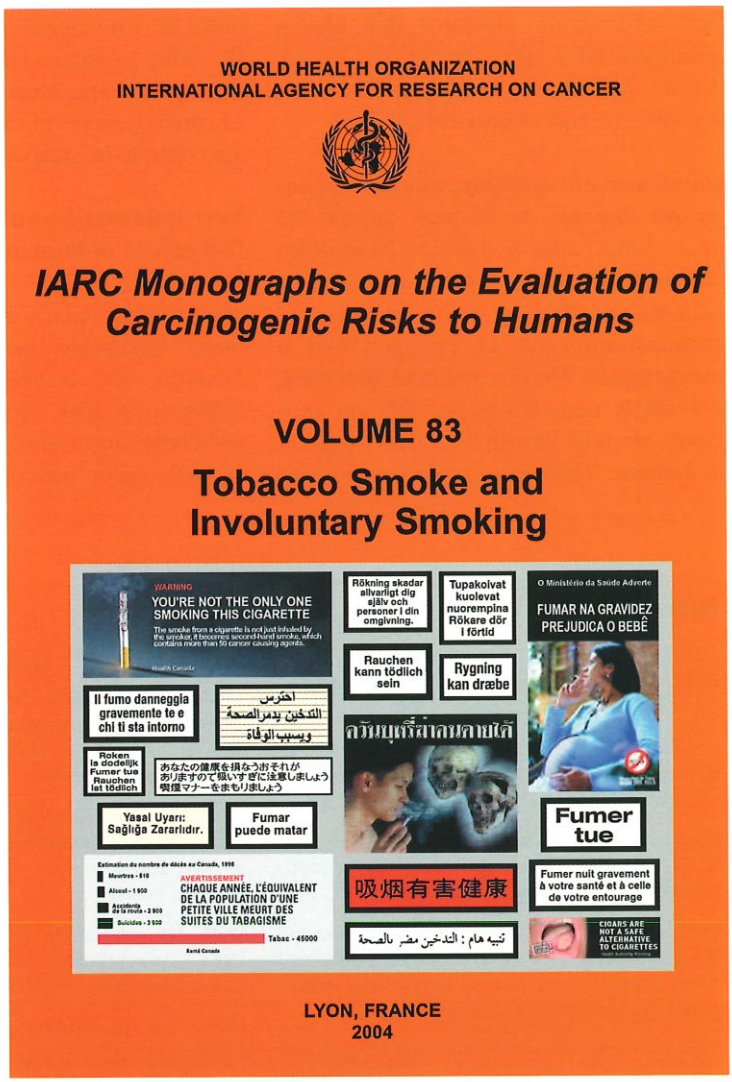
During the 2004-2005 biennium, the *IARC Monographs* identified several new known causes of human cancer and provided additional information about other previously identified carcinogens.

Newly identified causes of human cancer

Several agents were newly identified as *carcinogenic to humans* (Group 1) during the biennium. The diversity of these agents reflects the breadth of the programme and shows that there are still human carcinogens that remain to be identified.

Formaldehyde. Common sources of formaldehyde exposure include vehicle emissions, particle board and similar materials found in buildings and furniture, and carpets. Based on new epidemiological studies, formaldehyde is now known to increase the risk from nasopharyngeal cancer. There is also strong evidence that occupational exposure to formaldehyde is associated with leukaemia, a new finding that has attracted considerable attention.

Tobacco-specific nitrosamines (NNN and NNK). Nitrosamines are formed during the curing and processing of tobacco and also during smoking. The most abundant



strong carcinogens in smokeless tobacco products, NNN and NNK, were evaluated as *carcinogenic to humans,* based on a combination of experimental, mechanistic, and epidemiological evidence.

Human papillomaviruses. HPVs infect human mucosal and cutaneous tissue. Persistent infection with a carcinogenic HPV type is found in virtually all cases of cervical cancer, the second-leading cancer in women worldwide. Nearly 80% occur in developing countries without effective screening programs. Previously, only HPV types 16 and 18 had been associated with an increased risk of cervical cancer. New evidence is now *sufficient* to support a causal role also in cancers of the vulva, vagina, penis, anus, oral cavity, and oropharynx; thus, known cancer risks are no longer limited to the genital area or to women. In addition, current information indicates that eleven additional HPV types (types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) also increase the risk of cervical cancer.

Combined estrogen-progestogen menopausal therapy. At its peak around the year 2000, approximately 20 million women in developed countries were using menopausal therapy that involves co-administration of an estrogen and a progestogen. These combined therapies, previously regarded as *possibly carcinogenic*, are now known to be *carcinogenic to humans*. There is a consistent increase in the risk of breast cancer among current and recent users. This risk increases with duration of use and exceeds that in women taking estrogen-only therapy. There is also an increased risk of endometrial cancer when progestogens are taken fewer than 10 days per month.

Benzo[a]pyrene. Polycyclic aromatic hydrocarbons are formed during the incomplete combustion of organic material. Environmental sources of PAHs include industrial and urban air pollution, tobacco smoke, and diet; diet is frequently the major source of exposure in non-smoking, non-occupationally-exposed populations. High occupational exposure can occur during the conversion of coal to coke and coal tar, and during the processing and use of coal tar-derived products. Benzo[a]pyrene, a PAH commonly used as an indicator of PAH exposure, was evaluated as *carcinogenic to humans* based on its ability to induce tumours in many animal species and because the mechanisms of carcinogenesis in experimental animals also operate in exposed humans.

New information on previously identified causes of human cancer

In addition to HPV types 16 and 18, several other agents that had been previously identified as *carcinogenic to humans* were re-evaluated because new information had become available on additional cancer sites. The carcinogenicity of each agent was re-affirmed, demonstrating the robust and definitive nature of the classification *carcinogenic to humans.*

Smokeless tobacco. Hundreds of millions of people are addicted to smokeless tobacco, and use by young people is increasing in many regions of the world. Smokeless tobacco was previously known to increase the risk of oral cancer. New evidence is now sufficient to conclude that there is also an increased risk of pancreatic cancer, the first time that cancer risks have been established at sites distant from where smokeless tobacco is used.

Combined estrogen-progestogen oral contraceptives. Worldwide, over 100 million women – about 10% of all women of reproductive age – now use combined hormonal contraceptives. The proportion who has ever used them is much higher, exceeding 80% in some developed countries. Combined oral contraceptives were previously known to increase the risk of liver cancer. New evidence is now *sufficient* to conclude that current and recent users also have increased risk of breast cancer, and an increased risk of cervical cancer that increases with duration of use. At the same time, the risks of endometrial cancer and ovarian cancer are decreased. These findings highlight the need for each woman who uses these products to learn about the risks and benefits and to discuss them with her doctor.

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Breast Cancer Screening

Breast cancer is the most frequent cancer in women world-wide. The number of new cases is increasing, particularly in developing countries.

Breast cancer was diagnosed in 1.15 million women and over 400,000 deaths from breast cancer were reported in women world-wide in 2002 (*Ferlay *et al*, 2004). In high resource countries, population-based breast cancer screening using mammography has been demonstrated to lower breast cancer mortality and is recommended as a public health policy for breast cancer control (*IARC, 2002). In low-resource countries in which mammography is not feasible, improving awareness and clinical early detection linked with treatment are important to control breast cancer and thereby reduce the burden of the disease in the population. Evaluation of this approach is currently underway in a randomized trial in India.

Experience in the implementation of population-based mammography screening programmes underlies the importance of quality assurance in screening in general and breast cancer screening in particular. Despite the high cumulative incidence of breast cancer, the vast majority of women participating in a given round of a screening programme (ca. 99% in normal risk populations) will not have detectable breast cancer. Thus, the sensitivity of the screening procedure must be very high, in order to identify those women who may benefit from early detection. Furthermore, unnecessary examinations and treatment resulting from false-positive screening tests, and adverse effects of the screening test and any other examinations performed to assess abnormalities must be kept to a minimum.

Comprehensive quality assurance guidelines for breast cancer screening based on mammography have been developed in the Europe Against Cancer Programme (Perry *et al*, 2001) with the aim of optimising the benefits of screening while avoiding adverse effects on the health status of screening participants. The scope of the EU guidelines encompasses the entire screening process from invitation to management of screen-detected lesions because the net balance between benefit and harm of screening is affected by each step in this process. A fourth, revised edition of the EU guidelines will be published in 2006 (Fig 1). In addition to new physico-technical aspects (digital mammography) it will underscore the complex organisational and multidisciplinary aspects of mammography screening and particularly the need for effective screening programmes to be integrated into a routine health care infrastructure capable of delivering high quality diagnosis and treatment. Thus, the EU breast screening guidelines have been expanded to include diagnosis of symptomatic disease and requirements for specialist breast units for management of both screen-detected and symptomatic breast cancers.

Key general elements of the quality assurance and best practice recommendations in the EU Guidelines include:

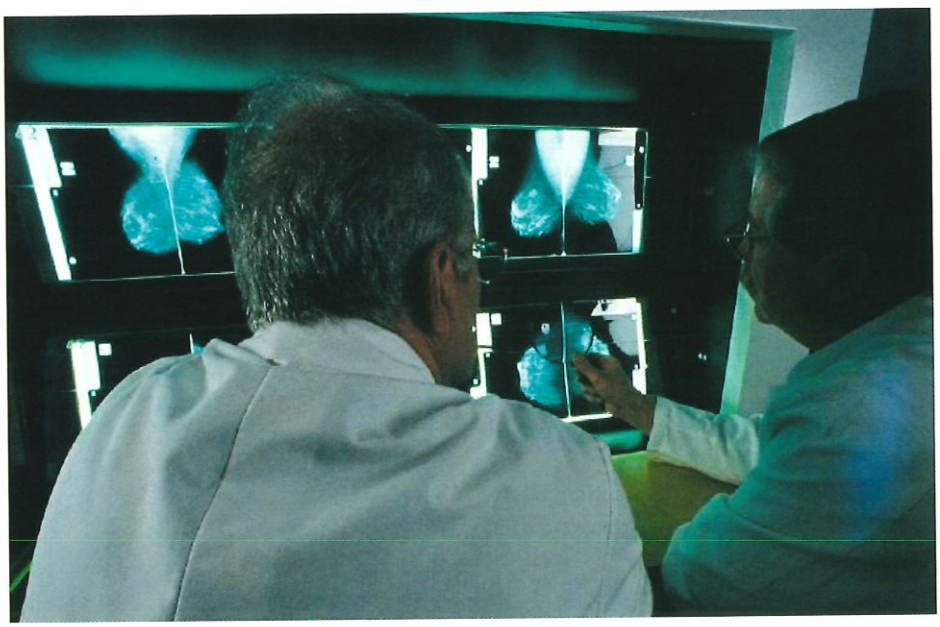

Image provided by Dr Hans Junkermann, Senologische Diagnostik, University Hospital, Heidelberg

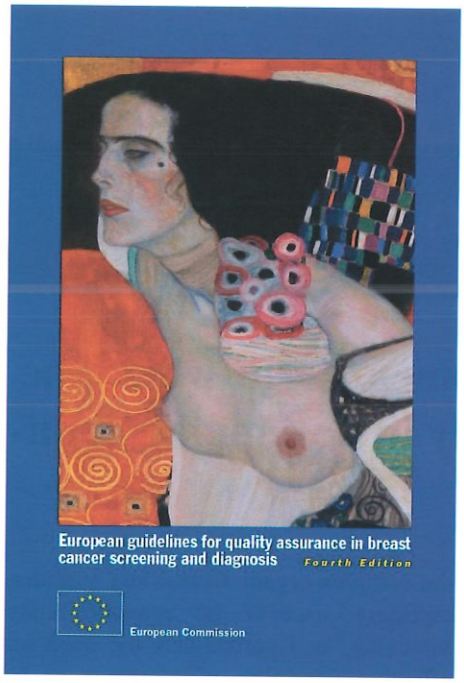

Figure 1. European guidelines for quality assurance in mammography screening (Fourth edition, in preparation)

- population-based invitation to screening
- training of all staff, particularly: radiographers, radiologists, pathologists and surgeons
- specialisation of personnel
- observance of volume levels
- multidisciplinary team working, including above staff as well as breast care nurses or psychologically professionally trained persons and medical oncologists/radiotherapists
- targets, performance indicators and regular audit
- organization of preoperative and postoperative multidisciplinary conferences
- avoidance of mixing of screening and symptomatic women
- complete and accurate recording of all relevant data for evaluation
- accreditation of units meeting quality standards

A basic tenet of the EU guidelines is that quality assurance must be applied to all steps in the screening process (not just to the screening test):

- invitation,
- performance of the screening test
- reading of mammograms
- further diagnostic work-up of women with suspicious results
- treatment of women with screen-detected lesions

More specific requirements for quality assurance of breast cancer screening include:

- adequate information presented in an appropriate and unbiased manner in order to allow a fully informed choice as to whether to attend
- extensive quality assurance protocols for equipment and technical performance in conventional and digital mammography
- interpretation of screening mammograms by two independent readers
- standardization of pathology procedures and reporting
- standardization of data collection and monitoring
- comprehensive protocols for non-technical quality assurance
- nomination of a given professional responsible for overall unit performance and with the authority to maintain standards and outcomes by suspending inadequate elements if necessary

Development of the European guidelines on the quality assurance of mammography screening in the European Breast Cancer Network (EBCN) and cooperation of experts, programme administrators, health care planners and advocates through the EBCN has played a key role in the expansion of population-based breast cancer screening programmes across Europe. In the current EU Member States and EFTA countries only 6 regional mammography screening programmes were operational in 1989. By 2005 national coverage has been achieved in 12 countries and regional coverage in 9 countries (Fig. 2).

An example of the technical errors which can be avoided by following the recommendations in the EU guidelines is shown in Figs. 3 a and b. Part of the breast tissue (2 cm) is missing on the craniocaudal (CC) film on the right in Fig. 3 a because the breast was not sufficiently pulled forward when the mammogram was taken. Although it is not always possible to expose all of the breast tissue on the CC film, the minimum standard was not initially fulfilled in this case and the mammogram was therefore repeated. Fig. 3 b shows a similar mistake corrected in a screening mammogram: the tumor near the edge of the film on the right was not detected until the CC view was repeated after correct positioning of the breast.

Further substantial improvement in breast cancer care can be expected from delivery of breast surgery in specialist units because the majority of breast cancer cases are diagnosed in women not attending screening programmes. Thus, the EU guidelines include quality

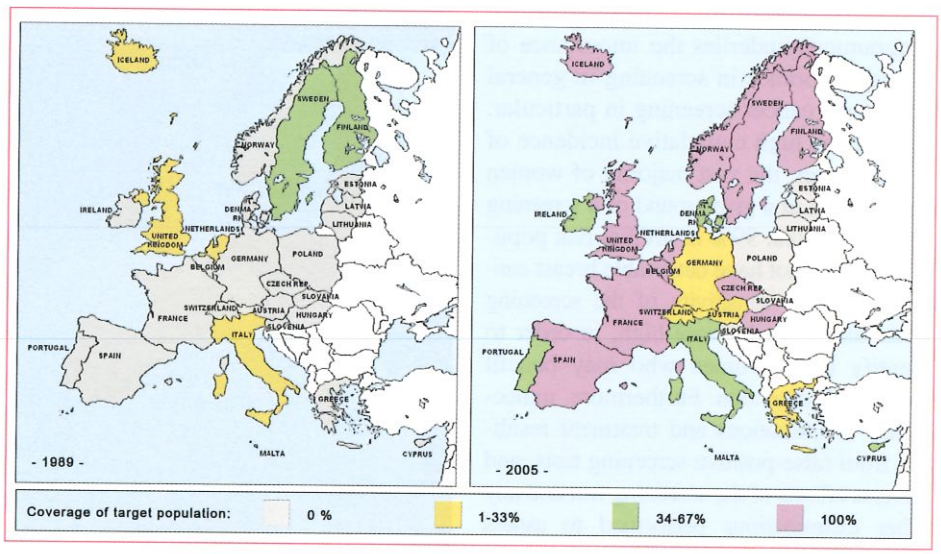

Figure 2. Mammography screening programmes based on EU guidelines in current EU member states and EFTA countries

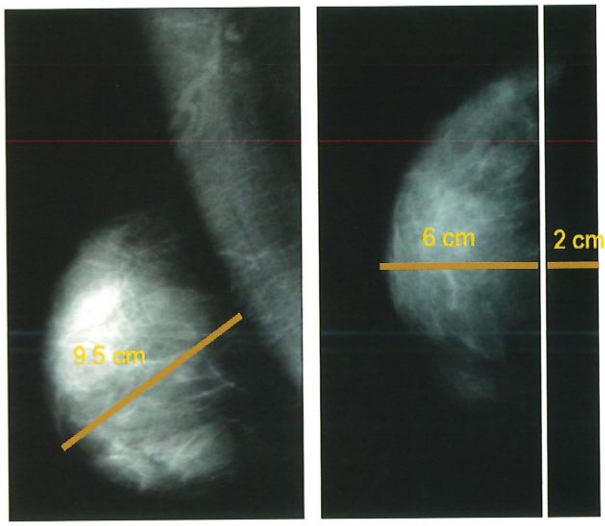

Figure 3a. Part of the breast (2 cm wide) is missing on the CC film near the chest wall because the breast was not sufficiently pulled forward when the X-ray was taken.
(Images provided by courtesy of Dr Margrit Reichel, Wiesbaden)

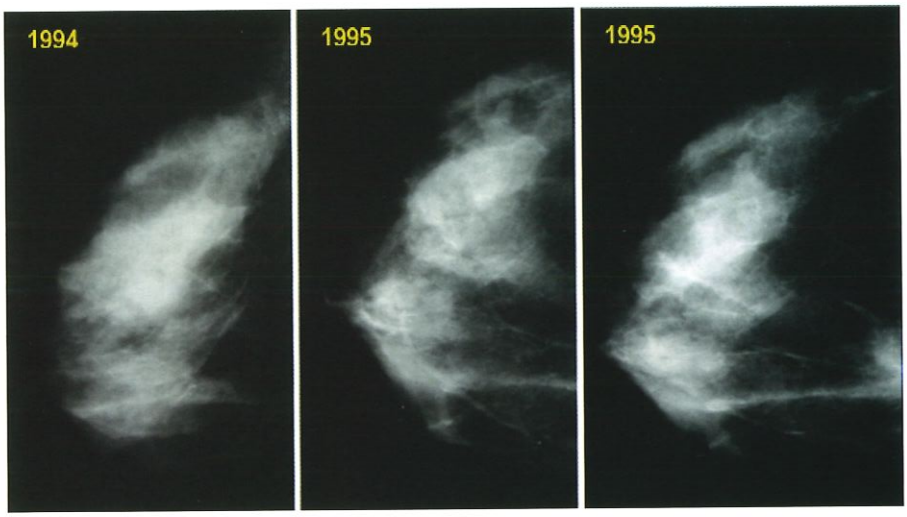

Figure 3b. The CC view shows a tumor which was previously missed because the breast was not sufficiently pulled forward when the X-ray was taken.
(Images provided by courtesy of Dr Margrit Reichel, Wiesbaden)

standards for specialist breast units which apply regardless of whether cancer is diagnosed in a screening programme or in a symptomatic setting. For example:

- Breast surgery should be performed by specially trained surgeons in specialist units providing a minimum of 150 primary breast cancer operations annually
- Each breast surgeon should perform a minimum of 50 primary breast cancer operations per year
- Clinical, imaging and pathology findings of all women requiring breast surgery should be discussed and documented in regular pre-operative and post-operative meetings of the full multi-disciplinary team (radiologist, radiographer, pathologist, surgeon, nurse counsellor and medical oncologist/radiotherapist)
- Patient support must be provided by specialist breast care nurses or appropriately psychologically professionally trained persons with expertise in breast cancer
- Continuous monitoring of outcomes and regular audit are essential for maintaining high quality

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Cervix Cancer Screening

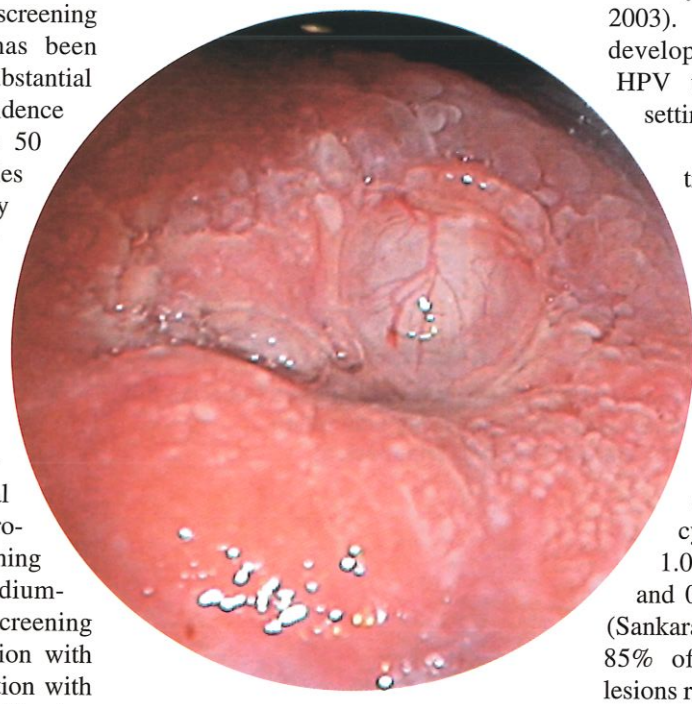
Cervical cancer continues to be the most common cancer among women in many low- and medium-resource countries in South Asia, South-East Asia, sub-Saharan Africa and Latin America.

World-wide cervix cancer accounts for 493,000 new cases and 274,000 deaths annually, more than 80% of which occurs in developing countries. Many parts of the world lack screening programmes and the disease is still predominantly diagnosed in locally advanced stages with 5-year survival less than 50%.

Organized or opportunistic screening with conventional cytology has been primarily responsible for the substantial reductions in cervical cancer incidence and mortality during the last 50 years in high-income countries (*IARC, 2005). However, in many low- and middle-income countries screening is yet to be effectively implemented or has failed to reduce cervical cancer burden (*IARC, 2005).

Advances in screening

In view of the sub-optimal performance of cytology in several settings and the challenges in introducing organized cytology screening programmes in low- and medium-resource countries, alternate screening methods such as visual inspection with acetic acid (VIA), visual inspection with acetic acid using low-level magnification (VIAM), visual inspection with Lugol's iodine (VILI) and HPV testing for accuracy in detecting high-grade cervical intraepithelial neoplasia (CIN 2 and CIN 3) have been widely evaluated in China, India, Thailand, Mali, Burkina Faso, Guinea, Congo, Niger, Uganda, Kenya, Zimbabwe, South Africa, and Peru (*IARC, 2005; *Sankaranarayanan *et al*, 2005a, *Sankaranarayanan *et al*, 2005b). The results from these studies indicate that VIA had similar or higher sensitivity than conventional cytology offered in the same settings, but lower specificity. Low-level magnification did not improve the test qualities of naked eye VIA (*Sankaranarayanan *et al*, 2005a). VILI was found to have a higher sensitivity than VIA but similar specificity in many studies (*Sankaranarayanan *et al*, 2005a). Visual testing and reporting results and training methods have been standardized (Blumenthal *et al*, 2005). HPV testing, which is the most reproducible of all screening tests, has shown higher sensitivity but lower specificity than cytology in many settings (*IARC, 2005; Franco, 2003). Efforts are now underway to develop affordable, rapid and simple HPV tests for use in low-resource settings.



Two large cluster-randomised trials are on-going in India to evaluate the efficacy and cost-effectiveness of once-in-a-lifetime screening with cervical cytology or VIA or HPV testing in reducing cervical cancer incidence and mortality (*Sankaranarayanan *et al*, 2004; *Sankaranarayanan *et al*, 2005b). Interim results suggest CIN 2-3 detection rates are similar for cytology, VIA and HPV testing: 1.0% for cytology, 0.7% for VIA and 0.9% for HPV testing ($p = 0.06$) (Sankaranarayanan *et al*, 2005b). Over 85% of the women with high-grade lesions received treatment. Final results in terms of reduction in incidence, mortality and cost-effectiveness are expected from these studies around 2007.

Costing in the context of one of the randomised trials suggest that the cost of detecting a case of CIN2/3 compared to no screening was $522; the additional

cost per additional case detected in the same population with cytology instead of VIA was $1066; HPV testing was dominated (Legood *et al,* 2005) While screening with VIA was the least expensive option, HPV testing may not be a cost effective screening strategy in developing countries at current consumable prices. The know-how and programmatic strategies for establishing cervical screening programmes in low- and medium-resource settings have now been well established (ACCP, 2004).

Cervical cancer screening: women waiting to be screened
(Guinea Conakry – March 2004)

Quality assurance guidelines

It is widely recognized that effective quality assurance is necessary to achieve and maximise the benefits of cancer screening while minimising the adverse effects on the health status of screening participants (*IARC 2005). The effectiveness of routine cervical cancer screening depends on the population coverage and the accuracy of the screening test. Furthermore, health care infrastructure is also needed for the assessment of screen-detected abnormalities and for treatment of women with precursor lesions and invasive cancer. If such infrastructure is lacking, or of insufficient quality and effectiveness, it must be developed to an adequate and self-sustaining level of routine performance. A quality assurance programme for cervical cancer screening must therefore not merely monitor the performance of these critical factors, it must also delineate responsibility for programme results at the local, regional and national levels and provide for adequate response if results are unsatisfactory.

Comprehensive quality assurance guidelines for cervical cancer screening have been developed by the European Cervical Cancer Network in the former Europe Against Cancer Programme (Coleman *et al,* 1993). A second, revised edition of the EU guidelines will be published in 2006. It will include chapters on: 1) epidemiology and principles of organisation; 2) evaluation of evidence of new technologies, including HPV testing, liquid-based and automated cytology; 3) quality assurance in the cytological laboratory; 4) histological diagnosis; 5) management of cervical lesions, and 6) performance indicators. Appendices will deal with: communication with women and health professionals, natural history of HPV infection, and HPV vaccination. Cervical cytology practice guidelines have also been developed by the American Society of Cytopathology (ASC, 2001). The cervical screening guidelines used in low-resource countries have been adapted from the guidelines used in Europe and North America.

Cervical cancer screening: women being registered to be screened
(Nepal – November 2004)

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Oral Cancer Screening

Oral cancer continues to be an important public health problem globally accounting for 274,000 cases and 127,000 deaths annually.

Although largely a preventable disease by avoiding the risk factors such as tobacco and alcohol use, a high occurrence of oral cancer is observed in the Indian sub-continent, Central and Eastern Europe, parts of France, Southern Europe, South America, and Oceania. Oral cancer is the commonest form of cancer and cancer death in men in India. The high-risk in the Indian sub-continent is related to the high prevalence of pan-tobacco (a combination of betel leaf, lime, areca nut and sun-cured tobacco) chewing in the population. World-wide, oral cancer has one of the lowest survival rates. The 5-year survival rates in high-risk Asian countries are less than 40% (Figure 1). It is well recognized that survival rates are improved if the disease is detected and treated in its early stages. Hence screening for early cancer is a potential control methodology for oral cancer.

A systematic review on the effectiveness of oral cancer screening was performed by the Cochrane Collaboration using all publications in between 1966 and September 2002. The review concluded that there is no evidence to recommend either inclusion or exclusion of screening programs for oral cancer using visual examination in the general population (Kujan *et al*, 2003; Kujan *et al*, 2005). In addition, the review concluded that no robust evidence exists to indicate whether other screening methods including toluidine blue, fluorescence imaging, or brush biopsy are either beneficial or harmful (Kujan *et al.*, 2003; Kujan *et al.*, 2005).

The results from a recently concluded cluster-randomised, controlled oral cancer screening trial involving 196,000 subjects in Kerala, India indicated that oral visual screening and treatment can result in a 34% reduction in oral cancer mortality among users of tobacco or alcohol or both (*Sankaranarayanan *et al*, 2005). These results extrapolated to the world burden of oral cancer deaths suggest that oral visual screening has the potential to prevent at least 37,000 deaths from oral cancer world-wide annually. In the South Asian region, where a high-risk is observed, about 20,000 premature deaths from oral cancer can be prevented annually by screening. The findings from this trial provide the evidence-base to call for implementation of screening for oral cancer among users of tobacco or alcohol or both in high-risk regions such as South Asia and other high-risk countries (*Sankaranarayanan *et al*, 2005; Mignogna *et al*, 2005).

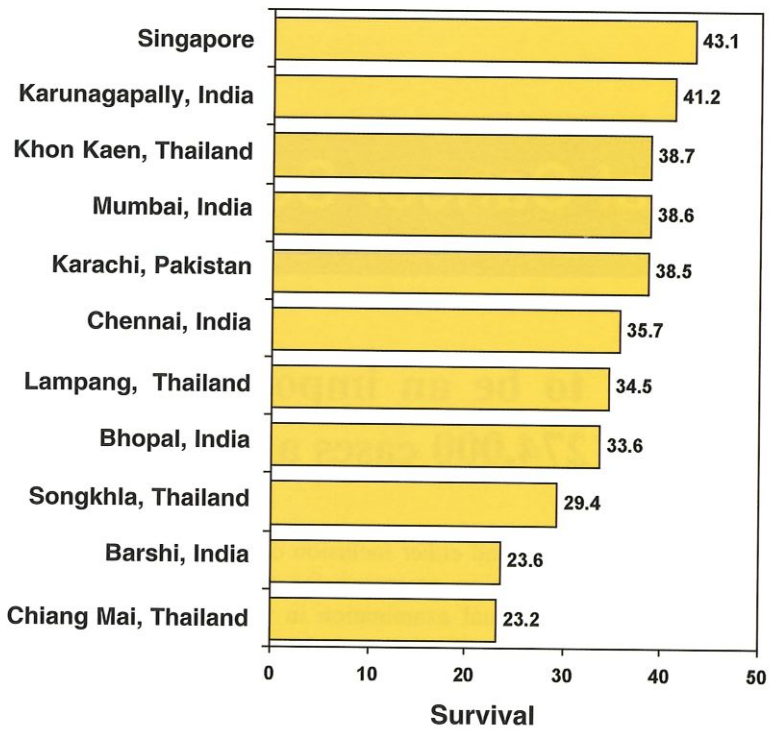

Figure 1. Population-based 5-year relative survival for oral cancer in Asia, 1990-99

Household members being screened for oral lesions (Trivandrum, India)

Betel leaf

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Biomarkers

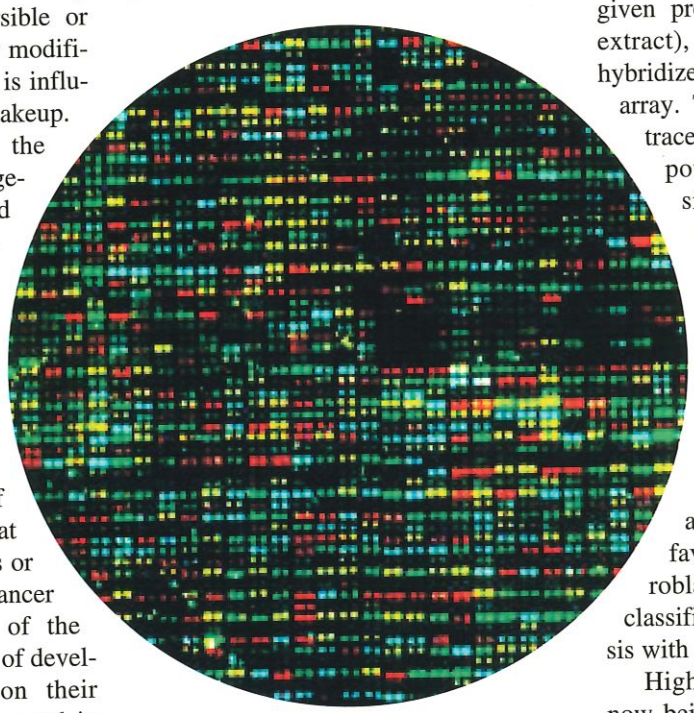
Cancer occurs and develops through the accumulation of molecular and cellular changes that alter a number of cell functions.

What is a biomarker?

Critical steps in this process include acquisition by the cell of enhanced proliferation and unlimited replicative capacity, evasion from apoptosis, relaxed control over genetic and genomic stability, sustained angiogenesis, and local and distant invasion capacities (Hanahan and Weinberg, 2000). Each step is driven by the formation of novel, irreversible or reversible molecular and cellular modifications, the occurrence of which is influenced by the individual genetic makeup. Irreversible changes occur in the form of DNA mutations or epigenetic modifications that are passed by one cell to its progeny, ultimately resulting in cancer. Reversible changes may include, among others, repairable damage to cellular components and untimely or excessive activation or inhibition of specific regulatory pathways. The term "biomarker" refers to any kind of molecular or cellular change that can be measured in cells, tissues or body fluids of non-cancer or cancer subjects, which is indicative of the presence of cancer or of the risk of developing cancer. Depending upon their applications, biomarkers can be used in studies addressing almost every step of cancer occurrence and progression, such as assessment of genetic susceptibility, evaluation of the extent of exposure to environmental or biological risk factors, early detection of pre-cancer or cancer disease, prognosis, and prediction of response to therapy (Maruvada and Srivastava, 2004, Verma, 2004).

Technologies for biomarker analysis

Over the past 10 years, impressive technical progress has taken place in the field of biomarkers, with a considerable impact on our approach to cancer epidemiology, detection, therapy, as well as on the way we carry research on these topics. Until recently, most laboratory methods for assessing biomarkers were quite laborious, expensive and imprecise, so that it was very difficult to apply them to studies on human subjects on a large scale. The advent of novel and high-throughput technologies has greatly facilitated such large scale applications. A typical example of this technical revolution is the DNA microarray. Microarrays consist in small matrices on which thousands of different pieces of single-strand DNA are fixed side-by-side as individual spots. Within a single reaction, it is possible to test the presence in a given preparation (e.g. a cancer tissue extract), of DNA or RNA that can hybridize with any of the spots on the array. The use of specific fluorescent tracers, high resolution imaging and powerful computers allows the simultaneous analysis of each spot on the array and the scoring of hybridization signals at each position. Taken together, these signals will produce a "pattern". Patterns that occur again and again in different specimens of the same type are identified as "signatures". For example, a particular pattern may allow to distinguish between favourable and unfavourable neuroblastomas, providing a potential classifier to predict the patient prognosis with high efficacy (Ohira *et al*, 2005).



High-throughput technologies are now being developed to measure simultaneously many different types of molecular change. Their impact on how molecular information is obtained and exploited is such that new terms are being coined to identify these new approaches. For example, "genomics" is the global study of changes and variations in the

genome; "transcriptomics" addresses global changes in gene expression levels (the set of RNA corresponding to the genes transcribed in any specific cell is called the "transcriptome"). Proteomics studies global changes in protein patterns. "Metabolomics" analyses changes in the production of metabolites in cells, tissues, or body fluids. All these approaches can be combined, making it possible, at least in theory, to determine in the same tumour the genetic status, the set of expressed genes, the patterns of proteins resulting from gene expression, and the variations in metabolites that characterize physiological or pathological changes. To perform these global analyses, "platforms" are being set-up, regrouping the instruments, the know-how and protocols, and the computer capacity for running systematic, large scale testing of many specimens.

IARC and studies on biomarkers

Research on cancer biomarkers has always been a central theme at IARC. Most studies are not only aimed at detecting and measuring biomarkers, but also at better understanding their functional significance. Indeed, interpreting what a biomarker means as a beacon for cancer risk, occurrence of progression, requires a good understanding of the impact of that biomarker on cell behaviour and functions.

On the other hand, one of the keys to success in biomarker application is the coordination of large, multicentric studies in which biospecimens are collected and stored. IARC has a long-standing involvement in developing such studies. Currently, the IARC biobanks house specimens from over 750,000 subjects, including close to 400, 000 subjects of the EPIC study (European Prospective Investigation Into Cancer and Nutrition). Developing and managing such biobanks, and processing the specimens to make them available for various types of molecular analyses, is a prerequisite for application of technologies of the "-omics" type.

Given the heavy technological involvement, IARC is currently re-organizing its activities in the field of biomarkers on a "platform" basis. These platforms are located within different Groups but coordinated through a common laboratory service infrastructure. They not only carry out their own research but also provide service and support to allow the integration of demanding technologies into molecular epidemiological studies developed by other groups. Some of these developments are illustrated below. Other important developments are taking place in the fields of metabolite and hormone detection, protein analysis and molecular pathology.

Molecular biomarkers

Molecular biomarkers encompass many types of change in gene, RNA and protein structure, amount, or intracellular localisation, that occur as a result of damage inflicted by environmental or endogenous carcinogens, or appear during the temporal sequence of events leading to cancer. In brief, these molecular biomarkers can be used as sources of information on the natural history of cancer.

Studies at IARC focus on several types of molecular biomarkers, including gene mutations as biomarkers of exposure to carcinogens, of early cancer detection, or of disease prognosis and prediction. The *TP53* gene offers a textbook example of such an approach. *TP53* encodes a protein, p53, that is present at low levels in all cells of the body but accumulates only in cells exposed to various forms of stress such as DNA damaging stress. After accumulation, the protein acts as a natural "brake" for cell proliferation, and eliminates damaged cells from the pool of cells capable of undergoing cell division. This elimination occurs through different biological processes, preventing the formation of potentially dangerous lesions. As such, p53 is thus one of the main obstacles to cancer development. In many cancer cells, p53 function is destroyed by a variety of mechanisms, the most common being missense mutation of the *TP53* gene. A missense mutation consists in a change in a single pair of bases that alters the coding sequence of the gene, resulting in a mutant protein that differs by only one amino-acid. To date, over 100,000 human tumours have been analysed for mutation in TP53, and all mutations that have been identified are compiled into a world-wide database maintained at IARC (http://www-p53.iarc.fr/index.html). Soon after this database was initiated in the 1990s, it became evident that different types of cancers showed differences in mutation frequency, type and position within the gene. Such tumour-specific mutation patterns may reflect the specific mode of action of the mutagens that have caused the tumours. On the other hand, the mutation may persist in the cancer cells because it perturbs p53 function in a way that suits cancer development in a particular organ (Shi *et al*, 2005). In the first instance, the mutation pattern may be considered as a biomarker of exposure. In the second instance, it may be useful as a

Biobanking at IARC

Left: liquid nitrogen tanks, where specimens from human subjects are preserved at a temperature of –140°C

Right: sets of plastic straws and containers used for specimen storage. Each straw may contain 0.5 ml of sample (e.g. blood)

biomarker for early detection, prognosis or prediction of cancer disease.

Studies on liver cancer provide a good illustration of how *TP53* mutations can be useful as biomarkers. The majority of hepatocellular carcinomas (HCC) detected world-wide occur in sub-Saharan Africa and South–East Asia. This high incidence is explained by the synergy between two important factors of risk for HCC that are highly prevalent in these regions, chronic infection by the hepatitis B virus (HBV) and contamination of the diet by a carcinogenic mycotoxin, aflatoxin (Figure 1). Liver cancers that develop in this context very often contain a single, typical mutation at codon 249 in *TP53*. This mutation is rare in other cancers, as well as in liver cancers from other parts of the world (Szymanska *et al*, 2004).

Recent studies by IARC scientists and their collaborators in Africa and Asia have shown that the mutation at codon 249 occurred very early on in the process of cancer development, and was even detectable at very low levels in subjects who do not have a clinically detectable liver cancer (Lleonart *et al*, 2005). To detect such low levels, a powerful methodology using mass spectrometry has been set up and used to search for very small amounts of mutant in the blood of normal subjects who are chronic carriers of HBV and exposed to aflatoxin. The extreme sensitivity and specificity of the methods allow mutant DNA to be detected even when it represents less than 0.1% of the DNA fragments present in the blood. Measuring this mutation may provide a good, individual marker of mutagenic exposure to aflatoxin. Furthermore, it may also allow to identify the individuals who are at high risk of developing a cancer of the liver, thus focusing preventive and clinical intervention on the population groups that most need it. In parallel, molecular studies are conducted in the laboratory to understand how the codon 249 mutant perturbs liver cells, with the ultimate goal of finding a new therapeutic approach to neutralize it. Indeed, it should be possible to design pharmacological agents that specifically target those cells harbouring a p53 mutant. Destroying these cells at an early stage may allow their eradication even before their evolution into a full-blown cancer lesion.

In cancers of other organs than the liver, however, the analysis of *TP53* mutations is much more complex because mutations occur at many different positions within the gene. To facilitate the analysis of a large series of specimens, IARC has set up a collaboration with a group based in Estonia to develop, test and validate a new type of DNA microarray. In comparison against classical techniques, this new array was shown to perform better in terms of sensitivity, speed, and cost (Le Calvez *et al*, 2005). This new method is now ready for application to large scale studies, such as the case-control studies developed by several groups at IARC.

Genetic biomarkers

Although all human beings share the same, global genome, there are a large number of variations from one individual to the other. These inherited sequence variants may play a role in susceptibility to disease, including cancers that are common or rare in the general population. The increased risk they may confer may be anything between modest ($\sim 1.25 < OR \leq 2$) and high ($OR \geq 5$). Over the last decade, testing at-risk individuals for mutations in high-risk susceptibility genes such as *BRCA1, BRCA2* (breast cancer, ovarian cancer), MLH1, and MSH2 (colon cancer) has become an important part of clinical cancer genetics practice because the resulting genotype information influences the medical and surgical management of mutation carriers and can be used to add years to their lives (Armstrong *et al*, 2004, Domchek *et al*, 2003, Lynch and Lynch, 2000, Rebbeck *et al*, 2004, Rebbeck, 2004, Watson *et al*, 2003, Whittemore *et al*, 2004). In contrast, consideration of genotype at modest-risk loci has not yet entered clinical practice. There are two principal reasons for this difference: (i) few modest-risk loci have been conclusively demonstrated, and (ii) individually, such sequence variants do not confer enough of an increase in risk to either motivate or justify available risk management methods.

There are two scenarios in which modest-risk sequence variants may eventually be shown to confer enough risk to impact clinical cancer genetics practice. The first is when there is a strong gene-environment interaction and the second is when a number of individual modest-risk

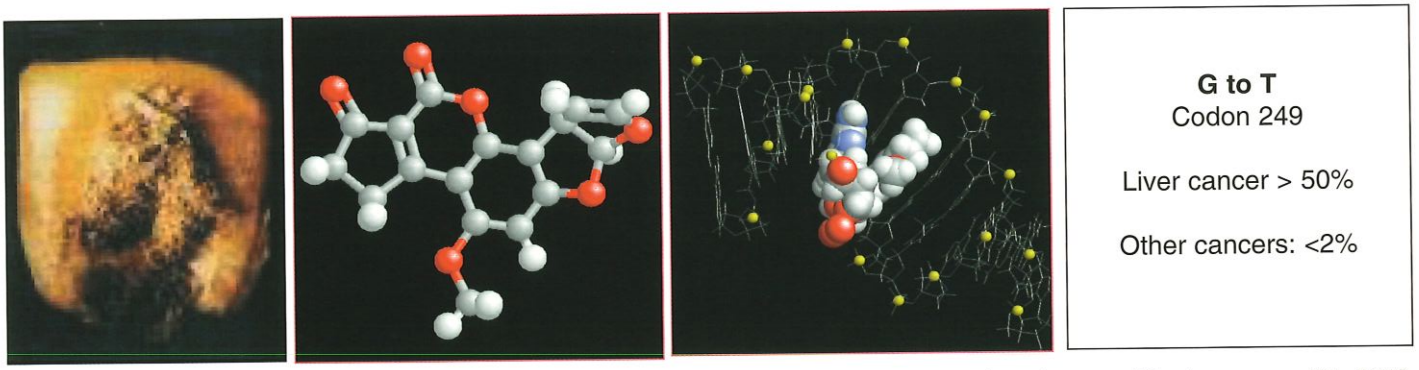


Figure 1. Aflatoxin, a common contaminant for staple diet in many tropical countries, forms adducts on specific DNA positions and generates characteristic mutations at codon 249 in the TP53 gene. These mutations are common in liver cancer in Africa and South-East Asia.
Left to right: contaminated corn, aflatoxin, adduct on guanine in DNA, prevalence of TP53 mutation at codon 249 in liver and other cancers

variants can be combined into a multigenic model that predicts high-risk for individuals who have inherited specific genotype combinations. In principle, the main genes involved in ethanol metabolism, alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) could provide examples of both of these scenarios (see section on Alcohol and Cancer).

Mutation screening data for high-risk susceptibility genes such as *BRCA1, BRCA2*, MLH1 and MSH2 are used in clinical cancer genetics practice to advise patients on their risks of breast, ovarian, colon, endometrial, and other cancers, and on possible risk reduction strategies. State-of-the-art clinical testing methods have a very high sensitivity for clearly deleterious sequence variants such as frameshifts and other protein truncating mutations. But these same methods find many unclassified sequence variants (UCVs). Gene testing centres report both clearly deleterious mutations and UCVs to physicians who in turn report them to patients. But the test reports that include an UCV are ambiguous and create difficulties for both physicians and patients. Over the last several years, considerable effort has gone towards analysis of UCVs, in particular unclassified missense substitutions, with the goal of developing efficient methods to classify many of them as either neutral or deleterious. Recently, Goldgar *et al,* (2004) developed an analytic framework that integrates four different methods of UCV analysis (Goldgar *et al,* 2004). Each of the methods integrated in this framework is an independent estimator of risk, and each is formulated as a likelihood expression. Other research groups have already started to use this framework (Lovelock *et al*, 2005; Wappenschmidt *et al*, 2005), and it should contribute to classification of a considerable number of UCVs over the next few years. One of the methods integrated within Goldgar's framework uses "in silico" sequence analysis to identify groups of unclassified substitutions that are highly enriched for deleterious mutations and other groups that are highly enriched for neutral substitutions (Abkevich *et al*, 2004, *Tavtigian *et al,* 2005), we expect the integrated framework and improved versions of the methods that it combines to prove an efficient, robust, and clinically useful approach to the analysis of UCVs (*Tavtigian *et al*, 2005; *Tavtigian *et al*, in press).

Hormonal Biomarkers

Tumour development is a consequence of mutations in proto-oncogenes and tumour suppressor genes that normally control cell proliferation. The likelihood that mutations become fixed by transmission to daughter cells, in part depends on the rate of cell proliferation, and on the failure of cells to undergo apoptosis (programmed death) (Preston-Martin *et al,* 1990). In addition, the likelihood of proliferating cells to accumulate mutations may also depend on the pool-size of cells maintained in a relatively undifferentiated state, as only non-differentiated cells have the potential to divide. Hormones and growth factors have well-documented roles in maintaining a proper balance between cellular differentiation, proliferation and programmed death. Alterations in endogenous hormone and growth factor metabolism may thus affect the risk of developing cancer. Besides their well-documented roles in regulating cellular differentiation, mitosis and apoptosis *in vitro,* there is abundant evidence from animal experiments and cell or tissue cultures that some of these hormones may favour the selective growth of preneoplastic and neoplastic cells (Dickson and Stancel, 2000; Aaronson, 1991).

Epidemiologists have had a long-standing interest in the sex steroids, especially in relation to cancers of steroid-sensitive tissues or organs such as the breast, endometrium, ovary, and prostate (Henderson *et al*, 1982). Classical hypotheses are that elevated blood concentrations of oestrogens will increase the risk of breast cancer ('oestrogen excess' hypothesis), and that elevated oestrogens in the absence of progesterone will increase risk of endometrial cancer ('unopposed oestrogen' hypothesis). With regard to ovarian cancer, animal studies have suggested that excessive stimulation by luteinizing hormone (LH) follicle-stimulating hormone (FSH) or both may enhance the malignant transformation of entrapped epithelium 'gonadotropin' hypothesis (Cramer *et al*, 1983), either directly, or through the stimulation of ovarian production of androgens or oestrogens (Lukanova and Kaaks, 2005).

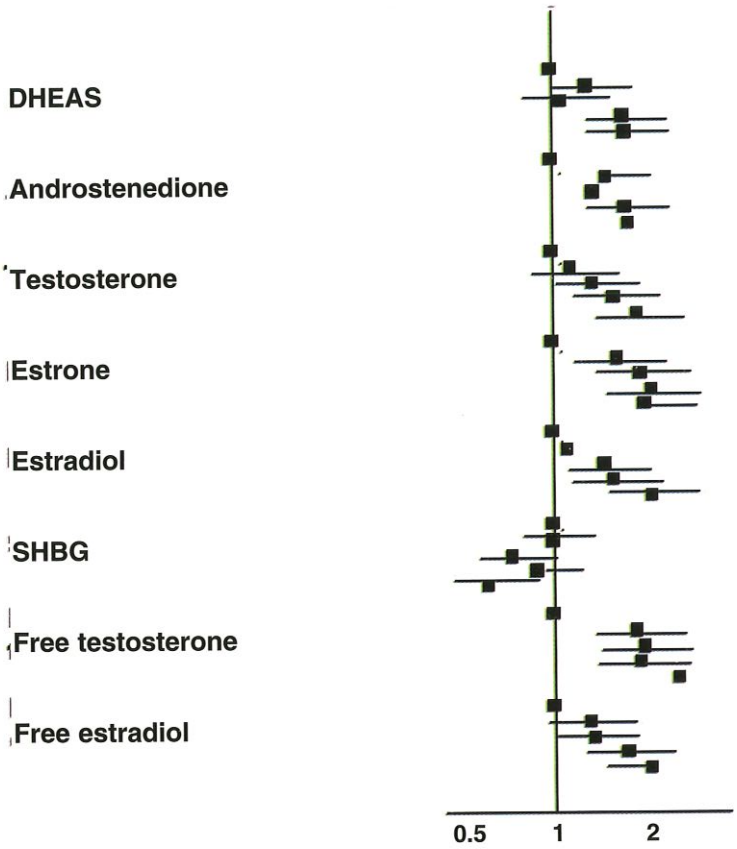
Prospective cohort studies provide the ideal design for epidemiological studies relating blood hormone levels to cancer risk. IARC has collaborations with several major prospective studies world-wide, including cohorts in the USA and Europe, and especially the European Prospective Investigation into Cancer and Nutrition (EPIC). To enhance large-scale studies on hormone metabolism and cancer risk, a specialized hormone assay laboratory was set up. Key results from several studies performed at IARC in prospective cohorts include increased risks of cancer of the breast (*Kaaks *et al*, 2005a, see Figure 2) and endometrium (Lukanova *et al*, 2004a) among postmenopausal women who had elevated blood concentrations of androgens or oestrogens (DHEAS, androstenedione, testosterone) and low concentrations of sex-hormone binding globulin (SHBG). Interestingly, elevated androgen concentrations, and low levels of progesterone during the luteal phase of the menstrual cycle, were also related to increased risk of breast cancer in women of premenopausal age (*Kaaks *et al,* 2005b). While excess body weight could clearly be identified as one of major causes of oestrogen excess among postmenopausal women, the causes for the comparatively elevated androgen levels remain largely unknown, and are an important area of current research. First study results also suggest a possible increase in ovarian cancer risk among premenopausal women with elevated circulating androgens (Lukanova *et al,* 2003; and EPIC unpublished results), which could reflect increased ovarian exposure to luteinizing hormone.

In addition to the sex steroids, there has been increasing interest in the possible roles of insulin, insulin-like growth factor-I (IGF-I) and IGF-binding proteins in tumour development (Khandwala *et al,* 2000). These hormones have tropic effects on a wide variety of tissue types, and are also important regulators of the synthesis and biological availability of

sex steroids, by stimulating steroidogenesis. In addition, the metabolism of insulin and IGF-I is also strongly related to nutrition and energy metabolism, thus making these hormones interesting candidates for explaining relationships between nutritional energy balance and cancer risk. Deregulations in the metabolism of insulin or IGF-I might thus form a metabolic link between a Western lifestyle, characterised by lack of physical activity and excess energy intake, increased levels of bioavailable androgens and oestrogens, and high incidence rates of various forms of cancer that are frequent in industrially developed societies (*Kaaks & Lukanova, 2001). Recent prospective studies conducted at IARC have also shown increased risks of cancers of the colon (*Kaaks *et al*, 2000) and endometrium (Lukanova *et al,* 2004b) among women and men who have elevated blood concentrations of insulin, and reduced concentrations of IGF-binding proteins-1 and -2. In addition, studies have shown direct increased risks of cancers of the prostate (Stattin *et al*, 2004) and colon (Palmqvist *et al*, 2002) among men and women with high blood levels of IGF-I. Besides nutritional lifestyle factors, genetic susceptibility factors have been shown to be important determinants of between-subject differences in their blood levels of IGF-I, and the identification of the specific underlying gene variants is an area of very active research.

In addition to the sex steroids, insulin and the IGF-I system, many other hormones have been postulated to be of potential relevance to cancer development, including, for example, the follistatin/activin/inhibin system, thyroid hormones, and various cytokines. Relating these hormonal and metabolic parameters to cancer risk will remain an important area for future research.

Figure 2. Postmenopausal serum sex steroid and breast cancer risk
The EPIC Study



For each hormone considered, the relative risk (■), and the 95% confidence interval (-■-) are presented by quintiles.

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WHO Classification of Tumours 'Blue Books'

The aim of the WHO blue books is to establish a pathological classification and grading of human tumours that is accepted and used world-wide.

Without clearly defined clinical and histopathological diagnostic criteria, and more recently genetic and expression profiles, epidemiological studies and clinical trials are difficult to conduct. The blue book project was initiated through a resolution of the WHO Executive Board in 1956 and the World Health Assembly in 1957. The first edition was published during 1967–81 by WHO. The second edition was edited in 1982–2002 under the auspices of the WHO Cancer Unit but published by Springer Verlag, Heidelberg. The Series Editor was Dr Sobin, the Armed Forces Institute of Pathology (AFIP) in Washington DC.

The third edition of the WHO blue books has been published by IARC*Press* since 2000. The Series Editors are Dr Paul Kleihues and Dr Leslie H. Sobin (Table 1). In contrast to previous editions, this edition not only covers pathology, but also contains concise sections on epidemiology, clinical signs and symptoms, major genetic alterations and expression profiles, and predictive factors. Diagnostic criteria, pathological features and associated genetic alterations are described in a strictly disease-oriented manner. Consensus/editorial meetings for all ten volumes were held at IARC in 1999–2003. Editing of the first six volumes was completed in 1999–2003 in IARC. In 2004 and 2005, the remaining four volumes were edited by Dr Kleihues, in Zurich, Switzerland, and were published by IARC*Press* (Fig. 1). The third edition has been a great success, being widely distributed among pathologists all over the world.

Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs covers tumours of the kidney, the urinary system, the prostate, the testis and paratesticular tissue, and the penis. Sections on all recognized neoplasms and their variants include new ICD-O codes, incidence, age and sex distribution, location, clinical signs and symptoms, pathology, genetics, expression profiles and predictive factors. *Pathology and Genetics of Tumours of Endocrine Organs* covers tumours of the pituitary, the thyroid and parathyroid, the adrenal gland, the endocrine pancreas and inherited tumour syndromes. *Pathology and Genetics of Tumours of the Head and Neck* covers tumours of the nasal cavity and paranasal sinuses, the nasopharynx, the hypopharynx, larynx and trachea, the oral cavity, oropharynx, and the salivary glands, as well as odontogenic tumours, and tumours of the ear and the paraganglionic system and inherited tumour syndromes. *Pathology and Genetics of Tumours of the Skin* covers keratinocytic, melanocytic, appendageal, haematopoietic, soft tissue and neural tumours, as well as inherited tumour syndromes. In each volume, each entity is extensively discussed with information on clinicopathological, epidemiological, immunophenotypic and genetic aspects of these diseases.

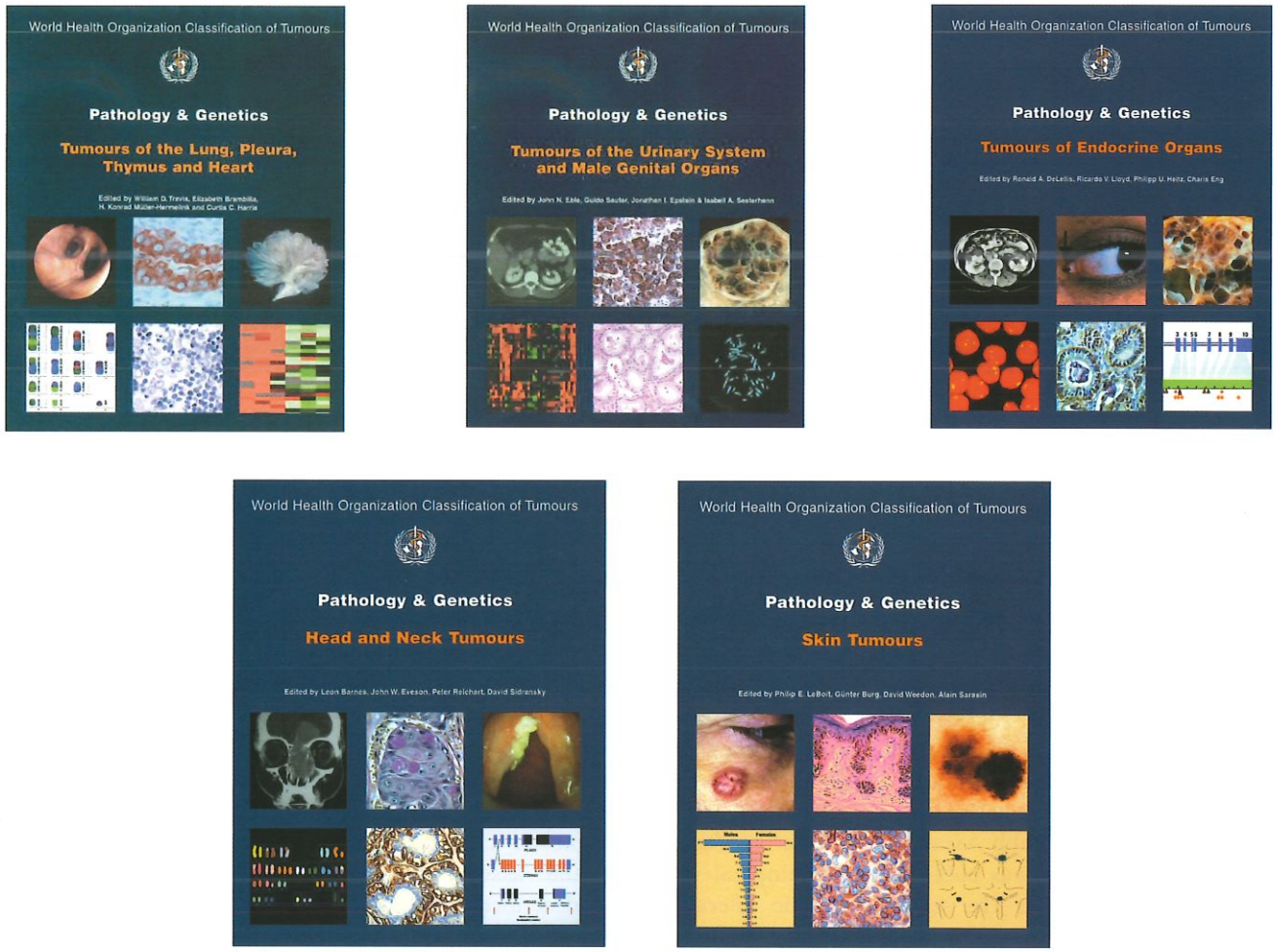


Figure 1. WHO 'blue books' published in 2004–2005

Table 1. World Health Organization Classification of Tumours (WHO Blue Books)

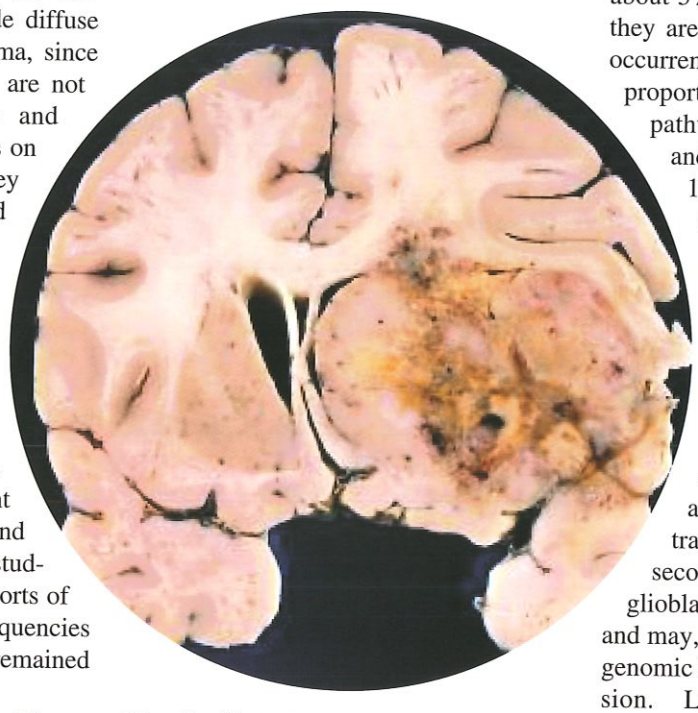
	Title	Editors	Consensus conference	No of contributors	Publication	Pages/ Copies printed
1	Tumours of the Nervous System	P. Kleihues (France), W.K. Cavenee (USA)	July 27-30, 1999	109	Feb. 2000	314 14 000
2	Tumours of the Digestive System	S.R. Hamilton (USA), L.A. Aaltonen (Finland)	November 6-9, 1999	113	Oct. 2000	314 13 000
3	Tumours of Haematopoietic and Lymphoid Tissues	E.S. Jaffe (USA), N.L. Harris (USA), H. Stein (Germany), J.W. Vardiman (USA)	November 8-11, 2000	75	July 2001	361 35 000
4	Tumours of the Breast and Female Genital Organs	F.A. Tavassoli (USA), P. Devilee (The Netherlands)	January 12-16, 2002 March 16-20, 2002	136	Oct. 2003	423 25 000
5	Tumours of Soft Tissue and Bones	C.D.M. Fletcher (USA), K.K. Unni (USA), Fredrik Mertens (Sweden)	April 24-28, 2002	147	Oct. 2002	427 15 000
6	Tumours of the Lung, Pleura, Thymus and Heart	W.D. Travis (USA), E. Brambilla (France), H.K. Müller-Hermelink (Germany), C.C. Harris (USA)	March 12-16, 2003	197	Sept. 2004	342 10 000
7	Tumours of the Urinary System and Male Genital Organs	J.N. Eble (USA), G. Sauter (Switzerland), J.I. Epstein (USA), I.A. Sesterhenn (USA)	December 14-18, 2002	131	March 2004	349 10 000
8	Tumours of Endocrine Organs	R.A. DeLellis (USA), R.V. Lloyd (USA), P.U. Heitz (Switzerland), C. Eng (USA)	April 23-26, 2003	150	Oct. 2004	321 10 000
9	Head and Neck Tumours	L. Barnes (USA), J.W. Eveson (UK), P. Reichart (Germany), D. Sidransky (USA)	July 16-19, 2003	129	June 2005	460 10 000
10	Skin Tumours	P.E. LeBoit (USA), G. Burg (Switzerland), D. Weedon (Australia), A. Sarasin (France)	September 22-25, 2003	150	Nov. 2005	355 10 000

Brain Tumours

Gliomas of astrocytic, oligodendroglial and ependymal origin account for more than 70% of all brain tumours.

Current knowledge on the survival of glioma patients and on factors that are predictive of outcome is based largely on clinical trials on patients with malignant gliomas (anaplastic astrocytoma and glioblastoma). However, clinical trials have a strong bias towards the recruitment of patients with better prognosis, i.e. high preoperative Karnofsky performance score and younger age (Stewart, 2002; Weller *et al.*, 2003). Therapeutic trials have less frequently addressed the outcome of patients with low-grade diffuse astrocytoma or oligodendroglioma, since in many centres, these patients are not subjected to adjuvant radio- and chemotherapy. Similarly, studies on genetic alterations and how they influence response to therapy and survival are usually based on small numbers of patients, often contradictory and difficult to validate. In recent years, it has been established that primary (de novo) glioblastomas and secondary glioblastomas derived from low-grade or anaplastic gliomas develop through different genetic pathways (*Kleihues and Cavenee, 2000). However, these studies, too, were based on small cohorts of selected cases and the relative frequencies of these glioblastoma subtypes remained unclear.

In order to overcome these problems, IARC has conducted a large population-based study on close to 1000 patients combining incidence and survival rates with data on key genetic alterations in astrocytic and oligodendrogliomas in the Canton of Zurich, Switzerland (approx. 1.16 million inhabitants) (*Burkhard *et al*, 2003; *Ohgaki *et al*, 2004; *Ohgaki *et al*, 2005; *Okamoto *et al*, 2004). The following conclusion emerged. (i) Patients with pilocytic astrocytoma (WHO grade I) have an excellent prognosis after surgical intervention (96% 5-year survival), suggesting that adjuvant radio- or chemotherapy is unnecessary in the management of this generally benign neoplasm



(Fig. 1). (ii) In low-grade gliomas (WHO grade II), age and histological type are significant predictors of clinical outcome. TP53 mutations and LOH 1p/19q are genetic hallmarks of astrocytomas and oligodendrogliomas, respectively and these alterations are mutually exclusive (*Huang *et al,* 2004). (iii) The prognosis of glioblastoma patients at the population level is even worse than generally assumed from clinical trials, with less than 2% surviving more than 3 years. Through the entire age range, higher age is the strongest predictor of poor outcome (Fig. 2). (iv) Secondary glioblastomas originating from low-grade or anaplastic astrocytoma are rare, accounting for only about 5% of all glioblastomas. However, they are a distinct entity, based on their occurrence in younger patients, a higher proportion of females and a genetic pathway characterized by frequent and early TP53 mutations. (v) LOH 10q is the most frequent genetic alteration in both pathways to primary and secondary glioblastomas, and the only one associated with poorer survival of glioblastoma patients. (vi) G:C➔A:T TP53 mutations at CpG sites, particularly in the hotspot codons 248 and 273, constitute an early genetic event associated with malignant transformation in the pathway to secondary glioblastoma. In primary glioblastomas, they are less frequent and may, at least in part, reflect increased genomic instability during tumor progression. Low-grade astrocytomas are genetically characterized by frequent TP53 mutations and show a consistent tendency to progress to glioblastomas, while oligodendrogliomas show frequent and concurrent LOH 1p and 19q, and may progress to anaplastic oligoden-

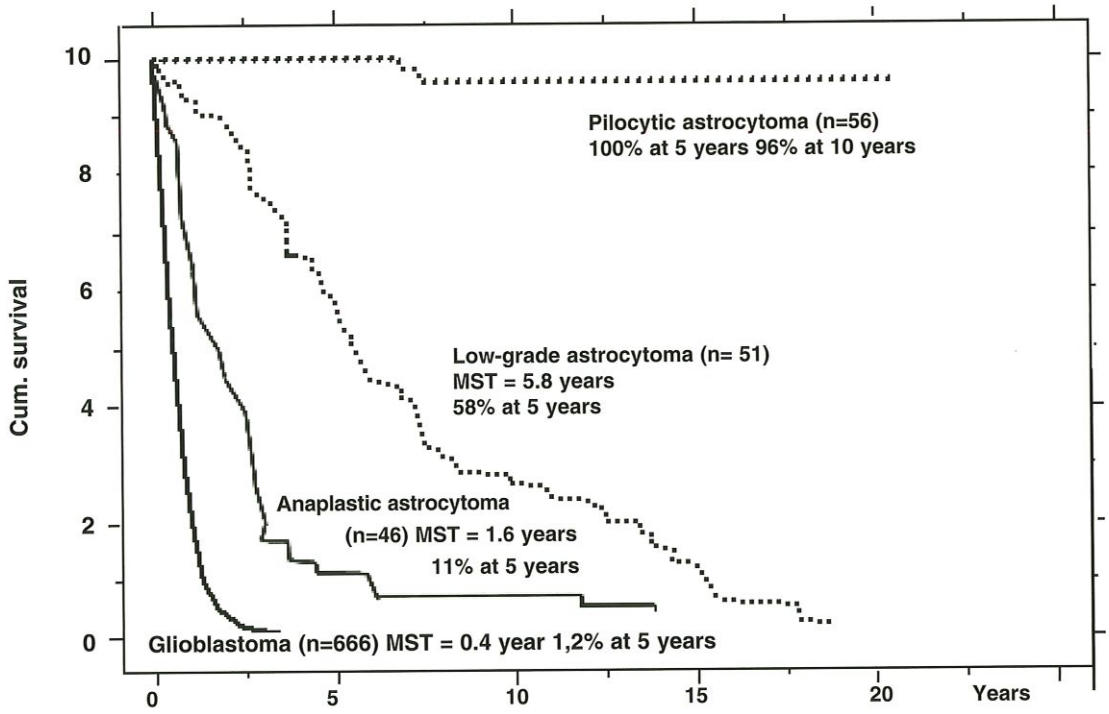


Figure 1. Survival of patients with pilocytic astrocytoma (WHO grade I), low-grade astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), and glioblastoma (WHO grade IV). Except for patients with pilocytic astrocytoma, who have excellent survival, outcome of other diffuse astrocytomas, in particular glioblastomas, is poor

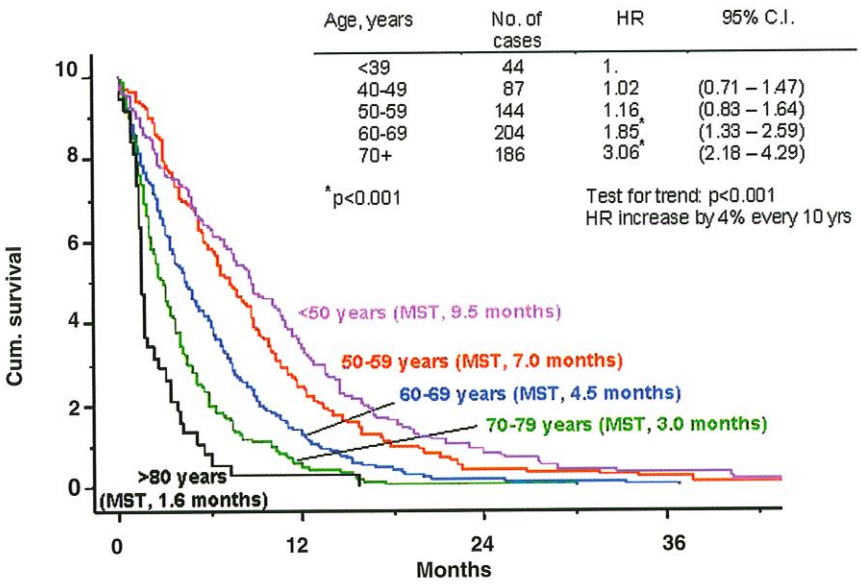


Figure 2. Kaplan-Meier curves showing that younger age of patients with glioblastomas is predictive for longer survival

drogliomas (*Kleihues and Cavenee, 2000). The histological diagnosis of these gliomas may be very difficult, with marked inter-observer variation, particularly in cases that lack the typical patterns of astrocytic and oligodendroglial differentiation. This is at least partly due to the lack of specific and reliable markers for neoplastic oligodendrocytes. cDNA and oligonucleotide microarray techniques have been used to establish gene expression patterns of astrocytic tumors (Fuller *et al*, 1999; Gutmann *et al*, 2002; *Huang *et al*, 2000; Markert *et al*, 2001; Rickman *et al*, 2001; Sallinen *et al*, 2000; Tanwar *et al*, 2002) and oligodendrogliomas (Fuller *et al*, 1999; Mukasa *et al*, 2002; Watson *et al*, 2001) with different histological grades, but direct comparison between oligodendrogliomas and low-grade astrocytomas have never been carried out.

IARC has performed direct comparison of cDNA expression patterns between histologically and genetically typical low-grade oligodendrogliomas and astrocytomas. Cluster analysis and partial least squares analysis of 79 genes that had at least a two-fold difference in expression between oligodendrogliomas and low-grade astrocytomas revealed clear distinctions between oligodendrogliomas, low-grade astrocytomas and normal cerebral white matter. Furthermore, cluster analysis based on the entire gene set divided the 17 subjects with oligoden-

drogliomas into two subgroups with significantly different survival. These results demonstrate that oligodendrogliomas and low-grade astrocytomas differ in their gene expression profiles, and that there are subgroups of oligodendroglioma with distinct expression profiles related to clinical outcome (Fig. 3) (*Huang *et al*, 2004).

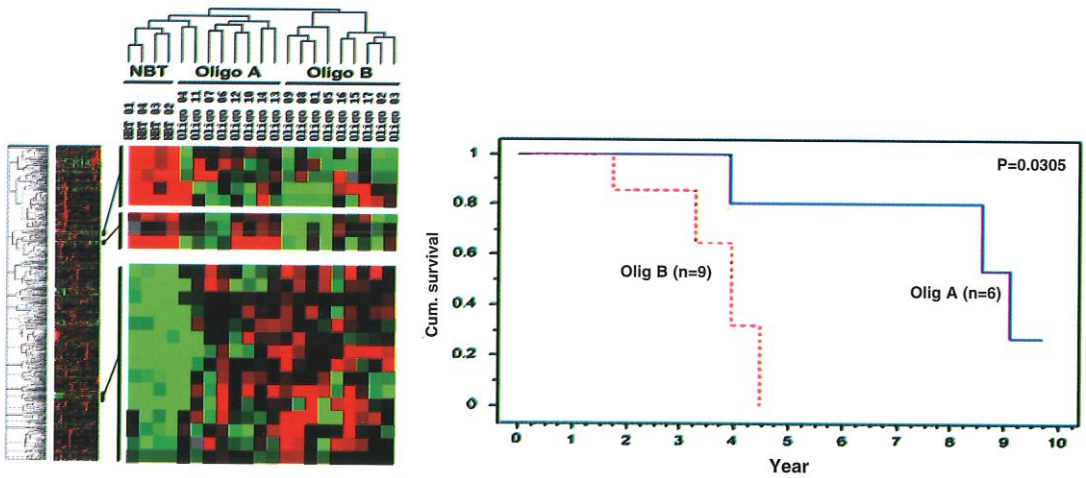


Figure 3. Hierarchical clustering analysis based on the entire set of 1176 genes separated normal brain tissues (NBT) from tumours and divided 17 oligodendrogliomas into two major subgroups A and B (left). Kaplan-Meier analysis showing significantly longer survival for patients in oligodendroglioma subgroup A than those in oligodendroglioma subgroup B (right)

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Breast Cancer Genetics

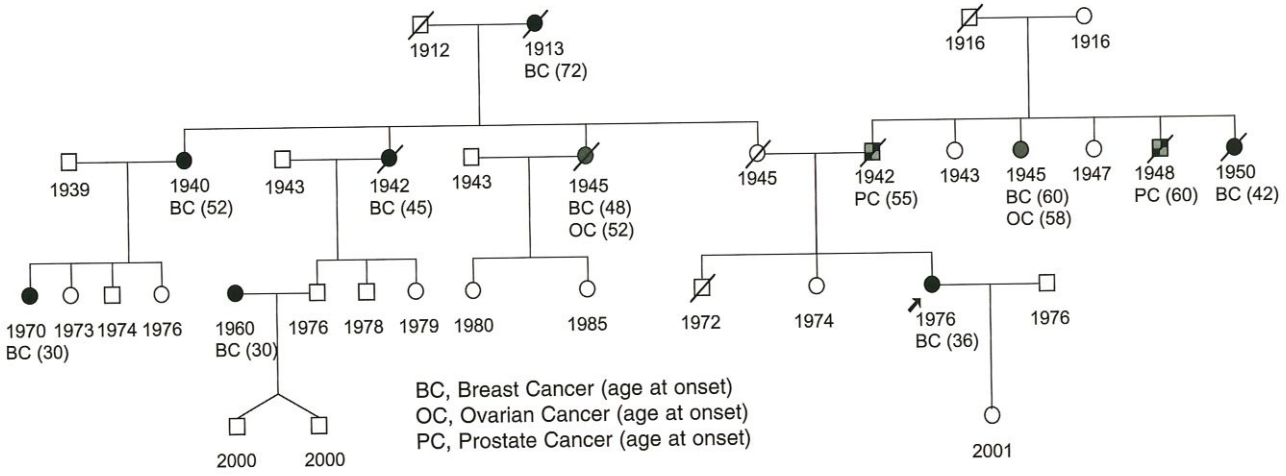
Recent advances in the area of breast cancer genetics have been greatly assisted by work that has refined our ability to define molecular and morphological subgroups of breast cancer.

This refinement has been achieved via skilled interpretation, standardisation and combination of data from expression arrays, immunohistochemistry, array CGH and morphological studies (t'Veer *et al,* 2002; Sorlie *et al*, 2003; West *et al,* 2001). Many of these breast cancer subgroups are now known to represent biologically and genetically distinct diseases.

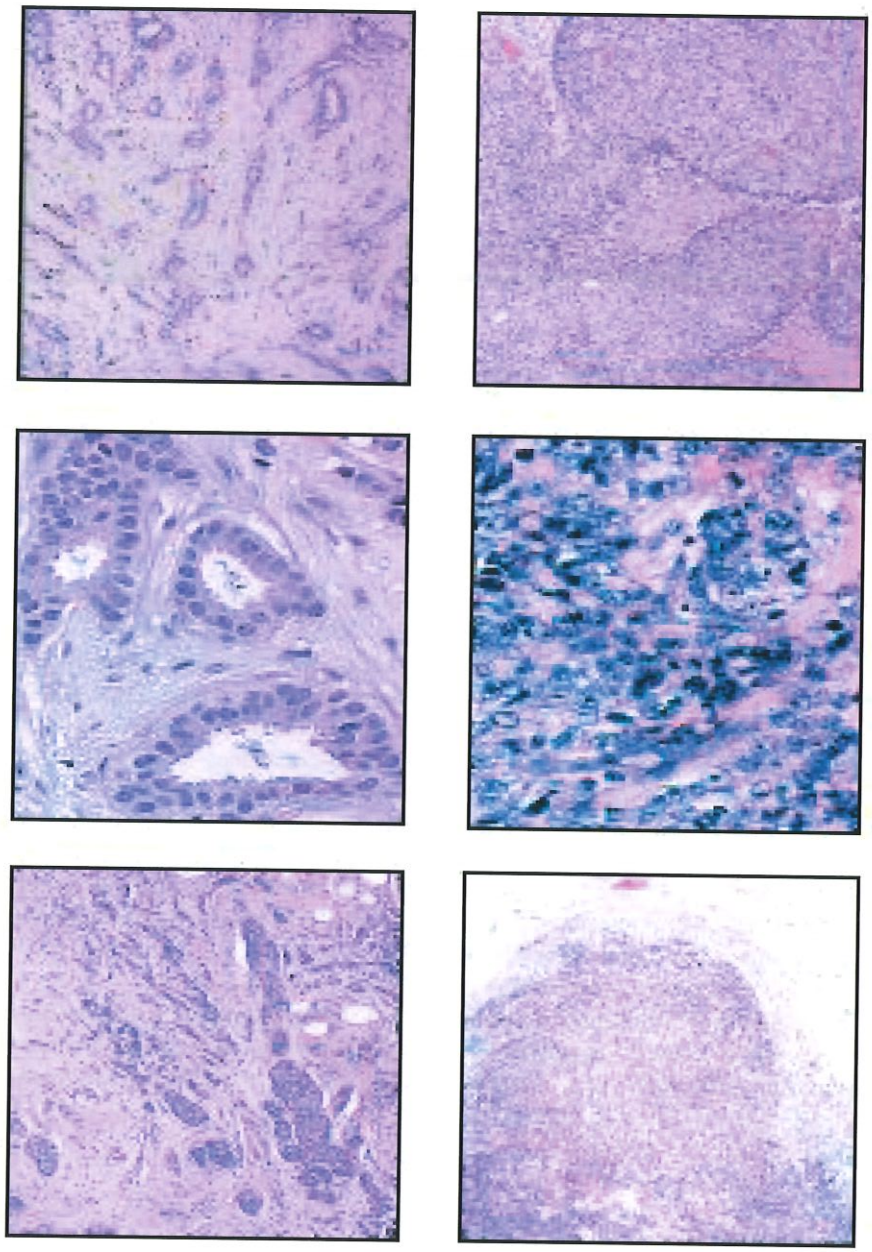
Definition of breast cancer subgroups has been particularly useful to researchers defining the role of *BRCA1* in breast cancer predisposition. Women who carry a germline mutation in *BRCA1* have been found to be predisposed to high grade cancers commonly with medullary or atypical medullary histological features and are ER negative (*Lakhani *et al*, 1998). Further division of ER-negative breast cancers using data from microarray expression studies have placed *BRCA1* mutation-associated breast cancers with the basal epithelial subtype (ER-/HER2/-CK5/6+) (Foulkes *et al*, 2003; Nielsen *et al*, 2004) a cancer subgroup associated with a poor outcome (Foulkes *et al*, 2004).

Refinement of our understanding of the morphological and molecular phenotype of breast cancers associated with *BRCA1* mutations has contributed to ongoing work to classify the cancer predisposition potential of missense sequence variants identified in *BRCA1*. Many studies are now able to combine genetic, functional and histopathological evaluation of individuals and families that carry these unclassified variants that have in many instances provided sufficient data for clinically relevant re-classification (*Goldgar *et al*, 2004; *Lovelock *et al*, 2005; *Southey *et al*, 2003). A detailed summary of work involving the classification of unclassified variants in *BRCA1* and *BRCA2* is provided above in Genetic biomarkers.

Although counselling and genetic testing of at-risk women is now underway in many centres, the information about risk



Multiple-case breast cancer families are valuable resources for breast cancer genetics research.



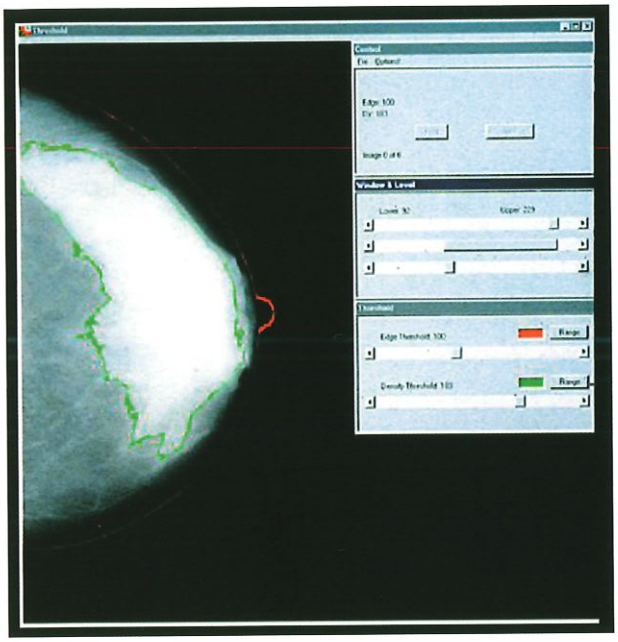
Breast cancer, a heterogeneous disease made up of many molecularly and morphologically definable subgroups

of cancers provided to gene mutation carriers is currently based on limited data obtained from retrospective analyses in families largely selected for high incidence of living affected women. Several large collections of *BRCA1* and *BRCA2* mutation carriers have now been assembled throughout the world to refine these estimates. The International *BRCA1/2* Carriers Cohort Study (IBCCS) is a prospective observational study coordinated from IARC that has now recruited more than 3000 participants (www-gep.iarc.fr). Other studies are progressing our understanding of the possible role of modifier genes (*Hughes *et al*, 2005) and the role of environmental exposures, such as oral contraceptive use (*Milne *et al*, 2005; Narod *et al*, 2002) in carriers of *BRCA1* and *BRCA2* mutations.

Segregation and twin studies support the notion that genetic susceptibility to breast cancer in women is conferred by a large number of genes, of which only a few have been identified. *BRCA1* and *BRCA2* currently explain a proportion of multiple-case breast (and ovarian) cancer families and the screening for mutations in these genes is an important aspect of the clinical management of these families as mutations in these genes confer high lifetime risks of breast and ovarian cancer. A recent meta-analysis of 22 population-based studies estimated that the average cumulative risks in *BRCA1*- and *BRCA2*-mutation carriers by age 70 years were 65% (95% CI 44-78%) and 45% (95% CI 31-56%) respectively (2). However, only 1-2% of all breast cancers are thought to be attributable to *BRCA1* and *BRCA2*.

Mutations in the ATM gene were once thought to account for up to 5% of all breast cancers (Easton, 1994) because the carrier frequency is estimated to be as high as 1% and many studies had found a moderate increased risk of breast cancer in female relatives of AT patients and known heterozygote female carriers (Olsen *et al*, 2001; Swift *et al*, 1990) and many others. Early reports that assessed specific ATM variants estimated the average penetrance to age 70 years to be 55% (95% CI = 26-88%) and 78% (95% CI = 36-99%) for 7271 T>G and c.1066-6T>G respectively but larger international consortia have more recently reported greatly reduced penetrance estimates of only 17.2% (95% CI = 4.7-37.5%) for c.1066-6T>G (*Thompson *et al*, 2005). Further international efforts are underway to clarify which ATM variants convey breast cancer risk and the magnitude of that risk.

The only other genes known to be responsible for a proportion of inherited susceptibility to breast cancer have been identified via the characterisation of Li-Fraumeni and Li-Fraumeni-like kindreds. The proportion and subtype of breast cancer that might be attributable to TP53 mutations is not yet known. CHEK2 (a G2 checkpoint kinase known to phosphorylate p53) was first associated with inherited breast cancer risk with the observation of a protein truncating mutation in a family with Li-Fraumeni syndrome. CHEK2 has become the first example of a relatively common variant (observed in 5% of non-BRCA1/2 breast cancer families in Northern Europe) (Vahteristo *et al*, 2002) that confers a moderate (2-fold, determined after a collaborative analysis of over 10,000



cases and matched controls) risk of breast cancer (Chek2, 2004; *Meijers-Heijboer *et al*, 2002). The contribution of CHEK2 in other ethnic groups, clarification of its cancer spectrum (which may include colorectal cancer, (Meijers-Heijboer *et al*, 2003) and its possible interaction with other breast cancer susceptibility genes is the topic of current investigations.

What and where are the other breast cancer susceptibility genes? Linkage studies have failed to identify further susceptibility loci (*Rahman *et al*, 2002; *Thompson *et al*, 2002). Further searches involving IARC, an international collaboration and several hundreds more multiple-case breast cancer families will need to overcome the challenges associated with possibly searching for lower penetrance genes and the heterogeneity of breast cancer.

Beyond these few high- to moderate-risk genes, an enormous investment has been put into the search for common variants that convey breast cancer risk. Although some associations have been reported, no definitive associations with common polymorphisms have been established in case-control studies (Cox *et al*, 2005; Dunning *et al,* 1999; Thompson and Easton, 2004). The utilization of genome-wide association technology, incorporation of family history and genetic constraints (Thompson and Easton, 2004), and the incorporation of inter-mediate quantitative phenotypes known to be associated with breast cancer risk, such as breast density and hormone levels (*Lurie *et al.*, 2005), may improve the power of current and future searches for breast cancer susceptibility genes.

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Education and Training at the IARC

One of the statutory functions of the Agency in its mission to promote international collaboration and support of all phases of cancer research is the training and education of personnel. The Agency seeks to achieve this aim through its fellowships programme and its courses programme which are designed to assist the development of cancer research and prevention in all countries, with special emphasis on low- and medium-resource countries, as well as those in which such work is not well established, and to train future collaborators in the scientific programme of the Agency.

Research training is one of the key elements of the IARC mission and the Research Training Fellowships Programme has been a major success since its inception. With the passage of time, many of the opportunities offered by the Fellowships Programme which used to be unique have come to be duplicated elsewhere. Whereas 20 years ago the IARC Fellowships Programme was one of the few ways to obtain training in cancer research in a major institute in another country, there are now many possible routes to achieving this.

Rather than compete for students with other programmes with similar offers, IARC endeavours to contribute in a unique manner. The IARC Fellowships Programme is designed to benefit students and junior cancer researchers from parts of the world where training in cancer research is rarely available.

In many instances, students come to IARC to work towards a Ph.D. (Doctorate) or to complete a post-doctoral period of training. This continues to be encouraged and developed although it is essential to focus on training opportunities which do not already exist and to provide some measure of training corresponding to the needs of the student.

Given the widespread possibilities for training in cancer research for students in developed countries, the IARC programme concentrates on unique features including a focus on students from low- and medium-resource countries and a focus on students being trained at the IARC, with a senior IARC scientist designated as a student supervisor.

IARC Post-graduate Training Fellowships

The aim of this programme has been to provide young postdoctoral scientists from any country with training in aspects of cancer research ranging from biostatistics and epidemiology to environmental chemical carcinogenesis and mechanisms of carcinogenesis, so that they can return to their own country to implement and develop programmes in cancer research or cancer control. At the beginning of 2005, given the widespread possibilities for training in cancer research for students in developed countries, the programme was refocused and reorganized in an attempt to make a unique contribution in this area by giving priority to junior scientists from low- or medium-resource countries who are engaged in research in medical or allied sciences, and wish to pursue a career in cancer research. Training is now offered in any of the Agency's Research Groups in Lyon and the duration of the fellowship has been extended to two years.

IARC Post-graduate Training Fellowships are restricted to students from low- and medium-resource countries coming to IARC and a limited number of junior post-doctoral scientists from high-resource countries to work in institutes in low- or medium-resource countries. Five kinds of Fellowships are available: IARC Short-Term Fellowships to learn a precise technique; IARC Senior Visiting Scientist Awards (for one year); IARC Research Training Fellowships – Post-doctoral Fellowships; and IARC Research Training Fellowships – Master's /Ph.D. The additional Fellowship is an Expertise Transfer Fellowship, introduced in 2005 to enable an established and experienced investigator to spend from six to twelve months in an appropriate host institute in a low- to medium-resource country in order to transfer knowledge and expertise in a research area relevant to the host country and related to the Agency's programme.

IARC Short-Term Fellowships provide a structure for supporting short-term students from any country and/or trainees visiting IARC for scientific work experience.

In 2004, the IARC Senior Visiting Scientists was awarded to Dr Christine Friedenreich (Alberta Cancer Board, Calgary, Alberta, Canada), who spent a year in the Hormones Team, Nutrition and Hormones Group, and in 2005 to Dr Gajalakshmi Vendhan (Epidemiological Research Center, Chennai, Tamil Nadu, India), who will spend one year in the Gene-Environment Epidemiology Group.

The IARC Research Training Fellowships will be available for post-doctoral candidates for a period of two years to be spent at the IARC working in a nominated Group. IARC Groups will compete to host awardees. The IARC Master's/Ph.D. Fellowships will follow a new paradigm. Initial awards will be for a period of 18 months to allow the candidate to complete a Master's degree. After nine months, the performance and aptitude of candidates will be reviewed and those who performed to a high level will be offered an additional two years to complete a Ph.D. within the same university programme.

In the 2004-2005 biennial period, post-doctoral Fellowships were awarded to junior scientists from Algeria, Armenia, Australia, Brazil (2), Denmark, Estonia, France (2), India (2), Jordan, Nepal, Nigeria, Pakistan, People's Republic of China, Poland, Republic of Korea, Sweden and the United States of America.

An additional programme of Training Fellowships for laboratory technicians and research engineers is being developed. An award of up to two years will be offered to candidates to study for an advanced technology qualification.

IARC Training Courses

The IARC Training Courses programme has been reviewed and a revised formula has been adopted. Basically, the series of courses which have been staged in various regions of the world has been replaced by a core course in Lyon each summer (IARC Summer School), although the opportunity to hold brief, specialist courses in different regions has been retained.

The IARC Summer School consists of a series of courses offered at IARC during four weeks at the same time each year, starting in 2005. Attendance will be week-specific and participants will be accepted for any combination of weeks and courses. Participants may come back to Lyon to follow different courses in different years.

The IARC Summer School will incorporate and systematize all advanced IARC courses, which are now run sporadically in different locations. It will also incorporate the Summer School of Cancer Registration currently organized by the Descriptive Epidemiology Group. In general, it will focus on the priority areas of IARC activity.

Week 1 of the Summer School includes courses on cancer registration, week 2 courses at a basic level, week 3 will include intermediate courses and week 4 will include advanced-level courses. Lecturers in all courses will be IARC scientists, as well as high-profile guest lecturers. A certificate will be provided at the end of each course; a special certificate will be provided for the completion of a three-week or a four-week cycle. All courses are in English.

Trainees, students, postdocs and senior visiting scientists at IARC

In keeping with the Agency's mission to provide education and training in the field of cancer research, as well as to provide appropriately qualified persons with training and experience in cancer research and related support areas at IARC in positions that will provide some complementary support to the Agency's activities, in addition to the Fellowships programme, IARC welcomes a substantial number of trainees, students, postdocs and visiting scientists each year (between 60 and 70), who come with either outside funds or who are funded in part or in total by the Agency.

As part of the continuing education activities, the IARC Seminar Series was introduced in 2004 to provide a more structured framework for training of junior staff and for communication among scientists. Attendance at the seminars forms part of the on-going training programme.

Of considerable importance is the health and safety of all those working at IARC. The application and admission procedure for these categories of non-staff was reviewed in 2005, taking into account vaccination requirements for those coming to work in the Agency's laboratories, as well as the necessity for all newcomers to follow basic safety training on arrival. This resulted in a new application form and new guidelines being drawn up which enter into effect on 1 January 2006, and should benefit all who are working at IARC.

IARC provides research training at a wide variety of levels which can accommodate the needs of scientists from a broad range of backgrounds and with different levels of skills. IARC funding of these activities is complemented by external resources. The Training and Courses programme gratefully acknowledges the financial support of the Italian Association for Cancer Research for its continuous support of the Fellowships Programme and the International Programme of the National Cancer Institute of the United States.