

International Agency for Research on Cancer



# BIENNIAL REPORT

08/09

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 2008–2009



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## 2008–2009

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

LYON, FRANCE

2009

ISBN 978-92-832-0425-1  
ISSN 0250-8613

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

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



INTERNATIONAL AGENCY FOR RESEARCH ON CANCER  
2008-2009

OMS



WHO

CIRC

Centre International de  
Recherche sur le Cancer

IARC

International Agency for  
Research on Cancer

150, Cours Albert-Thomas 69008 LYON

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# INTRODUCTION



Dr Christopher Wild

THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER WAS ESTABLISHED AS THE SPECIALISED CANCER AGENCY OF THE WORLD HEALTH ORGANIZATION (WHO) BY A RESOLUTION OF THE WORLD HEALTH ASSEMBLY IN 1965. THE FOUNDATION OF ALL THAT THE AGENCY DOES IS ITS EXCELLENT REPUTATION FOR CONDUCTING THE HIGHEST-QUALITY INTERNATIONAL CANCER RESEARCH. OTHER ACTIVITIES, OF UNDOUBTED MAJOR IMPORTANCE, NEVERTHELESS FIND THEIR LEGITIMACY IN BEING PERFORMED IN THE CONTEXT OF AN ORGANISATION AT THE FOREFRONT OF RESEARCH IN ITS AREAS OF EXPERTISE. IN MY FIRST YEAR IN OFFICE I WOULD ALSO EMPHASISE THE TREMENDOUS SUPPORT AND GOODWILL EXPRESSED TOWARDS THE AGENCY BY THE INTERNATIONAL SCIENTIFIC COMMUNITY. SUCH SUPPORT IS MANIFEST IN TOO MANY WAYS TO DETAIL, BUT UNDOUBTEDLY IS A KEY CONTRIBUTOR TO THE SUCCESSES DOCUMENTED IN THIS REPORT.

The Agency's tasks are stated in its Statute, in which the guiding principle is to promote international collaboration in cancer research. Specifically, the Statute of IARC states its role as:

- Planning, promoting and developing research in all phases of the causation, treatment and prevention of cancer;
- Collection and dissemination of information on the epidemiology of cancer, on cancer research and on the causation and prevention of cancer throughout the world;
- Studies on the natural history of cancer; and
- Education and training of personnel for cancer research.

Given that the Statute remains largely unchanged after forty-five years it is remarkably well adapted to the cancer research needs of the future. It is also evident that the contribution to be made

by an international cancer research agency has never been greater. The burden of cancer is rising markedly worldwide, with estimates indicating that by 2050 there will be double the current number of around 12.5 million new cases per year. Strikingly, however, the majority of the increase is expected in low- and middle-income countries, where health services are least able to meet the impending challenge. If left un-addressed this rise in cancer cases will create enormous hardships at the economic, social and personal levels. The emphasis the Agency has placed on identifying the causes of cancer and also evaluating strategies for prevention, both primary and secondary, are a valid response to these challenges, particularly in areas of the world where the opportunities for curative treatment are currently limited.

Therefore the Agency must orientate its activities over the next two decades such that it can best contribute to combating the projected increase in the global cancer burden. It should make its contribution in a way that is consistent with its Statute, plays to its strengths as an international organisation and makes most effective use of its partnerships, nationally and internationally. At the core of its function remains the generation of evidence that, through the conduct of novel research, informs strategies for cancer prevention and control. There are a number of principles underpinning the priorities the Agency makes in addressing its mission.

First, as mentioned above, is the emphasis on research, thus distinguishing the Agency from other international cancer organisations that focus on developing policy and advocating change in order to implement cancer control. This distinction establishes the basis of the complementary relationship with the WHO, where the research conducted by the Agency (e.g. in cancer screening or vaccination) can be translated by WHO into plans for action. A strong working relationship is essential to the success of both organisations. Second is the effort to add value by participating in and promoting collaboration in research. Collaboration is increasingly important not only for scientific reasons—for example, where large multi-centre international studies are required in order to identify risk factors—but also to ensure efficiencies and economies of effort in times of limited resources. Third, since its inception the Agency has promoted interdisciplinary research, pioneering the integration of laboratory sciences and population-based research. This approach has never promised as much as in the current era, where a new understanding of the complexity of carcinogenicity combined with technological advances promises a level of refinement of measurement not previously available to epidemiology. Increased understanding of mechanisms and the associated technologies (for example, “omics”) provide a major opportunity for translational research from the laboratory to the population. Fourth, the Agency has a worldwide mandate including the opportunity to conduct and support research in areas of the world where resources are limited. It remains one of the great values of the Agency that

its now twenty-one Participating States share a common vision in relation to this international mandate. Fifth, the inclusion of education and training as one of the four highlighted aspects of the Agency’s mission is vital, providing as it does the opportunity to build a new generation of cancer researchers worldwide with the motivation and skills to tackle the growing global cancer burden mentioned earlier.

#### CORE ACTIVITIES

Based on these principles drawn from its Statute, the Agency has a number of core areas that are achieved through its scientific and support structures. These comprise the following:

**1. Describing the global cancer burden.** The Agency aims to be the definitive international point of reference for collection, storage and statistical analysis of accurate data on cancer prevalence, incidence, survival and mortality, including for childhood cancer through avenues such as GLOBOCAN and Cancer Incidence in Five Continents.

**2. The IARC Monographs.** The Monographs have an international reputation for evaluation of evidence regarding the causes of cancer through its Working Groups. Identification of risk factors is fundamental to cancer prevention, and the conclusions of the Monographs are used by national health agencies to develop approaches for preventing exposure to known and suspected carcinogens.

**3. Cancer etiology.** This comprises one of the largest areas of activity in the Agency, with contributions across the organisation. The environment (defined in its broadest sense to include lifestyle, nutrition and occupation in addition to physical, chemical and biological factors) plays a role in the overwhelming majority of cancers and consequently, at least in principle, offers opportunities for research to be translated to prevention.

**4. Mechanisms of Carcinogenesis.** An understanding of mechanisms makes a fundamental contribution to cancer prevention in a number of ways, notably through: providing plausibility to exposure-disease associations; providing biomarkers of exposure, susceptibility,

early detection and prognosis; and offering opportunities for evidence-based interventions to interrupt the carcinogenic process. This research provides the essential bridge from basic sciences to population-based research at IARC.

**5. Cancer Prevention.** Research into the effectiveness of intervention strategies is critical, including understanding how these can be best implemented at the population level in particular socio-economic and cultural environments. Increasingly this research requires skills in behavioural epidemiology and health services research.

**6. Education and Training.** The Agency will place more emphasis on developing an integrated and expanded programme of education and training. The activities will include the strengthening of the Fellowships and Courses Programmes with an expanded remit. In addition to supporting scientists from low- and medium-resource countries, the Agency will seek to expand support to young scientists from high-income countries to encourage people with a desire to devote a career to international cancer research.

#### SCIENTIFIC HIGHLIGHTS

The scientific achievements of the Agency are presented by Section in this biennial report. The exciting progress speaks highly of the quality and energy of all working at IARC. There are many highlights that could be selected; those presented below serve to illustrate major findings but also emphasise the validity of working to the principles outlined above in driving the directions of the Agency’s research and related activities.

During the biennium the Agency published the ninth volume of *Cancer Incidence in Five Continents*, with the print version being subject to careful revision before becoming available in 2009, following the web-based release of the volume in 2007. All eight previous volumes are available through the website as part of the *CANCERmondial*, which serves as a point of reference for information on cancer occurrence on an international scale. The Agency was also able to provide CanReg5 software as a support to cancer registries worldwide.

In another of the Agency's flagship projects, the IARC Monographs, the major task was undertaken of reviewing all Group 1 human carcinogens in six parts for Volume 100 of this series. The international Working Groups evaluated evidence that led to new conclusions establishing the links between hepatitis C virus and non-Hodgkin lymphoma, formaldehyde and leukaemia, and asbestos and ovarian cancer, among others.

In terms of how research at the Agency integrates laboratory and population-based research into etiology and prevention, the example of cervical cancer is a model one. There are over half a million new cases of this tumour worldwide each year, most occurring in low- and middle-resource countries. With the advent of HPV vaccines, both vaccination and "screen and treat" approaches can be considered to combat this cancer, and the Agency has made major contributions in both areas. Successful introduction of vaccines as well as screening with HPV-based testing requires knowledge of the infection burden and type-specific distribution of HPV types. The Infections and Cancer Epidemiology Group has provided novel data through its HPV surveys, and through this work has made the important observation that in some populations, high prevalence does not diminish with age. This information is critical in the development of prevention strategies. At the same time, the Infections and Cancer Biology Group has made exciting findings concerning the oncogenicity of different HPV types, both mucosal and cutaneous, particularly in relation to the establishment of chronic infection. A key protein involved in innate immunity, toll-like receptor 9, is down-regulated by HPV oncoproteins and this effect differs among HPV types, thus possibly explaining the heterogeneity in risk associated with the different HPV types.

In parallel to the above studies, Dr Sankaranarayanan and his collaborators in India showed in a cluster randomized trial that a single round of screening using HPV testing resulted in close to a 50% reduction in the numbers of advanced cancers and deaths from cervical cancer (Sankaranarayanan et al., 2009). This collaborative effort has significant public health importance in demonstrating the

value of different screening approaches in cervical cancer prevention in low- and middle-income countries. A new study of around 20 000 girls in eight centres in India has been initiated to compare two doses versus the standard three-dose HPV vaccination schedule in order to guide public health policies for vaccine implementation.

It is evident that a majority of human cancers have an etiology involving environmental risk factors played out on an individual genetic background of varying susceptibility. Consequently, the identification of genetic variants associated with risk is one way to help elucidate how environmental factors exert their effects. These studies require large numbers of subjects which in turn demand multi-centre international collaborations. The Agency has taken leadership in a number of areas and made major advances in identifying susceptibility loci for cancers of the lung, upper aerodigestive tract and kidney. Notable highlights were the reporting of genome-wide association studies that revealed two new susceptibility variants for lung cancer, 15q25, which contains three nicotinic acetylcholine receptor genes, and 5p15.33 (McKay et al., 2008). These observations involved external and internal collaboration with major contributions from the GEP, GCS and LCA Groups. The observations have also stimulated new research within the MOC Group on the functional effects of these variants, notably the 15q25 locus.

Improved methodology to conduct cancer research is also a feature of the Agency's activities. Areas of particular interest here include the progress made in developing the EPIC-Soft® tool as a standardised, computerised 24-hour recall programme applicable across different populations with markedly varying diets (Linseisen et al., 2009). In turn there are exciting initiatives developing biomarkers for epigenetic changes (Vassiere et al., 2009) complementing approaches to measure mutational events (Igetei et al., 2008), both methodologies being applicable to small volumes of blood available from prospective studies such as EPIC.

The Agency played a major role in a number of additional international collaborative studies and consortia, for

example on lymphoma (InterLymph), lung (ILCCO) and head and neck (INHANCE) cancers. The Agency also contributed to important emerging areas of concern, notably the growth in pediatric diagnostic procedures using X-rays and high-dose techniques (e.g. CT scans), through the Child-Med-Rad collaboration. In addition, the Agency took the lead in an important and unique international cooperative project called the Agenda for Research on Chernobyl Health (ARCH) which will set priorities for future investigations of this accident, including understanding the impact of low-dose radiation exposure on cancer risk.

Large-scale prospective studies are far less frequent in low and middle-resource countries than in high-resource countries. However, the Agency has made significant progress with a Russian cohort in Western Siberia and also a prospective study in Golestan province in Northeast Iran, where there are particularly high incidences of cancer of the stomach and oesophagus. In the Russian cohort a remarkable observation was the strong indication that more than half of deaths in males aged 15–54 were due to alcohol (Zaridze et al., 2009).

The Agency balanced its research on etiology with that on prevention. In addition to the work cited above on cervical cancer, there were major efforts in relation to tobacco. Notably this concerned publication of two Handbooks of Cancer Prevention (cited below), an example of the close cooperation developed with WHO and support to the implementation of the WHO FCTC. Agency scientists also provided leadership to development of European guidelines for quality assurance in cervical cancer screening, again an area of strong cooperation with WHO (Arbyn et al., 2008).

## PUBLICATIONS

The Agency published a high volume of peer-reviewed scientific papers in top-quality journals in its fields of expertise as detailed in this report. It is noteworthy how many of the publications involve young scientists training at the Agency and also how many reflect the international collaborations that characterise much of the Agency's work.

The Agency is responsible for the *WHO Classification of Tumours* series, the so-called “Blue Books”, renowned worldwide for their quality. Production of the 4th Edition is currently in progress, and additional resources will be assigned to support future activity in this area. In this biennium the second volume was produced, entitled *Tumours of the Haematopoietic and Lymphoid Tissues*, and has demonstrated quite remarkable sales, with 22 000 copies sold to date in calendar year 2009.

Two Working Group reports came out during the biennium, one on Vitamin D and cancer and the other on the IARC Code of Good Scientific Practice. In

addition, there were two volumes of the *IARC Handbooks on Cancer Prevention* published, both of which were dedicated to different aspects of tobacco control, one entitled *Methods for Evaluating Tobacco Control Policies* (2008) and another on *Evaluating the Effectiveness of Smoke-free Policies* (2009).

#### EDUCATION AND TRAINING

The Agency has for many years awarded post-doctoral fellowships to young scientists to contribute to development of cancer research. In the last five years almost 50 fellowships have been awarded through this programme to scientists from low- and medium-resource

countries. During 2008–09 fellows came from Bulgaria, the People’s Republic of China, India, Indonesia, Mongolia, the Russian Federation and Thailand. The programme was successful in attracting an EU Marie Curie Action grant to increase the number of awards for next year. At the same time, the continued support of the Italian Association for Cancer Research is highly appreciated. It is important to point out that the award of fellowships from the Agency’s own programme comprises only a small fraction of the total contribution to post-doctoral training, with the Agency hosting between 80 and 100 trainees, masters/doctoral students, technical students, posts docs and visiting scientists each year. In 2009 the Agency also awarded two senior Visiting Scientist Awards to Professor Julian Peto (London, UK) and Professor David Richardson (Chapel Hill, North Carolina, USA).

The IARC courses are another route by which support is provided to cancer researchers worldwide. Over the biennium the IARC Summer School attracted 116 participants, many from low- and medium-resource countries, organised two cancer registration training courses in the People’s Republic of China and the Republic of Korea, and delivered six courses in cervical cancer screening and prevention in the People’s Republic of China, India, Tanzania, Gabon and Morocco. A feature of the IARC courses is that they are contiguous with our research programmes, and thus many of the participants are already or become active collaborators with Agency scientists.

#### MAJOR RESEARCH AWARDS

The Agency continues to successfully attract extrabudgetary resources through competitive grants from major funders. The Monograph programme is a case in point, which after a very high scientific score is well positioned to receive a prolongation of the long running, NCI-funded “Evaluation of Carcinogenic Risks to Humans” project, which should be extended for a further 5 years at a budget level of roughly USD 1 000 000 per year. Furthermore, competitive and direct funding was received this year from the American Cancer Society, the US Environmental Protection Agency and the NIEHS, totalling USD 230 000.



Figure 1. Christopher Wild with IARC Medal of Honour Recipients Harald zur Hausen

The groups in the Section of Nutrition and Metabolism continued to successfully receive funding from the World Cancer Research Fund (WCRF). In addition to 3 already active grants, IARC received two further grants as coordinator (together just under USD 500 000) and is currently negotiating a subaward as partner in a third award (USD 50 000). Also, a new funding opportunity was established by joining a consortium through a subcontract to be paid by the European Food Safety Agency (EFSA). The subcontract is currently being negotiated, and should fund our activities at a level of roughly USD 175 000.

Two major awards from the European Commission are currently in negotiation: Cagekid, a large 5-year collaborative project on kidney cancer genomics, which earmarks USD 1 600 000 of a total USD 17 500 000 for IARC's contribution; and CHANCES, a similar, large collaborative 5-year project with a similar overall budget and a share of USD 480 000 for IARC. The following grants were signed with the Commission in the last biennium: IARC Fellows, a project co-funding the IARC postdoctoral fellowships programme with a budget of USD 1 200 000 over 4 years; PPACTE, a small collaborative research project over 3 years that focuses on tax incentives to reduce tobacco consumption, with an IARC budget of USD 480 000; and a direct contract with the EC DG SANCO focussing on several projects, including the European Code Against Cancer and a European Cancer Atlas (budget USD 650 000).

The Agency has also continued to be competitive with French funders, with 5 awards from the INCA (30% success rate) and 8 projects funded from the Ligue Contre Le Cancer (66% success rate).

#### IARC MEDAL OF HONOUR

In 2008 the IARC Medals of Honour were awarded to Maurice Tubiana, member of the French Académie des Sciences and the French Académie de Médecine; Professor Jan Hoeijmakers, Head of the Department of Genetics, Erasmus Medical Centre; and Sir Richard Peto, Professor of Medical Statistics & Epidemiology at the University of Oxford.



Figure 1. ... and Nubia Munoz

In 2009 the Agency awarded the IARC Medal to two distinguished scientists for their truly exceptional achievements in cancer research, namely the identification of human papilloma virus (HPV) as a necessary cause of cervical cancer and the development of a dual strategy to reduce the burden of this cancer by vaccination and by screening. Professor Harald zur Hausen from the German Cancer Research Centre was awarded the Nobel Prize in Medicine in 2008 “for his discovery of human papilloma viruses causing cervical cancer”. Professor Nubia Muñoz made major contributions to the establishment of the etiology of cervical cancer through her pioneering epidemiological studies during her

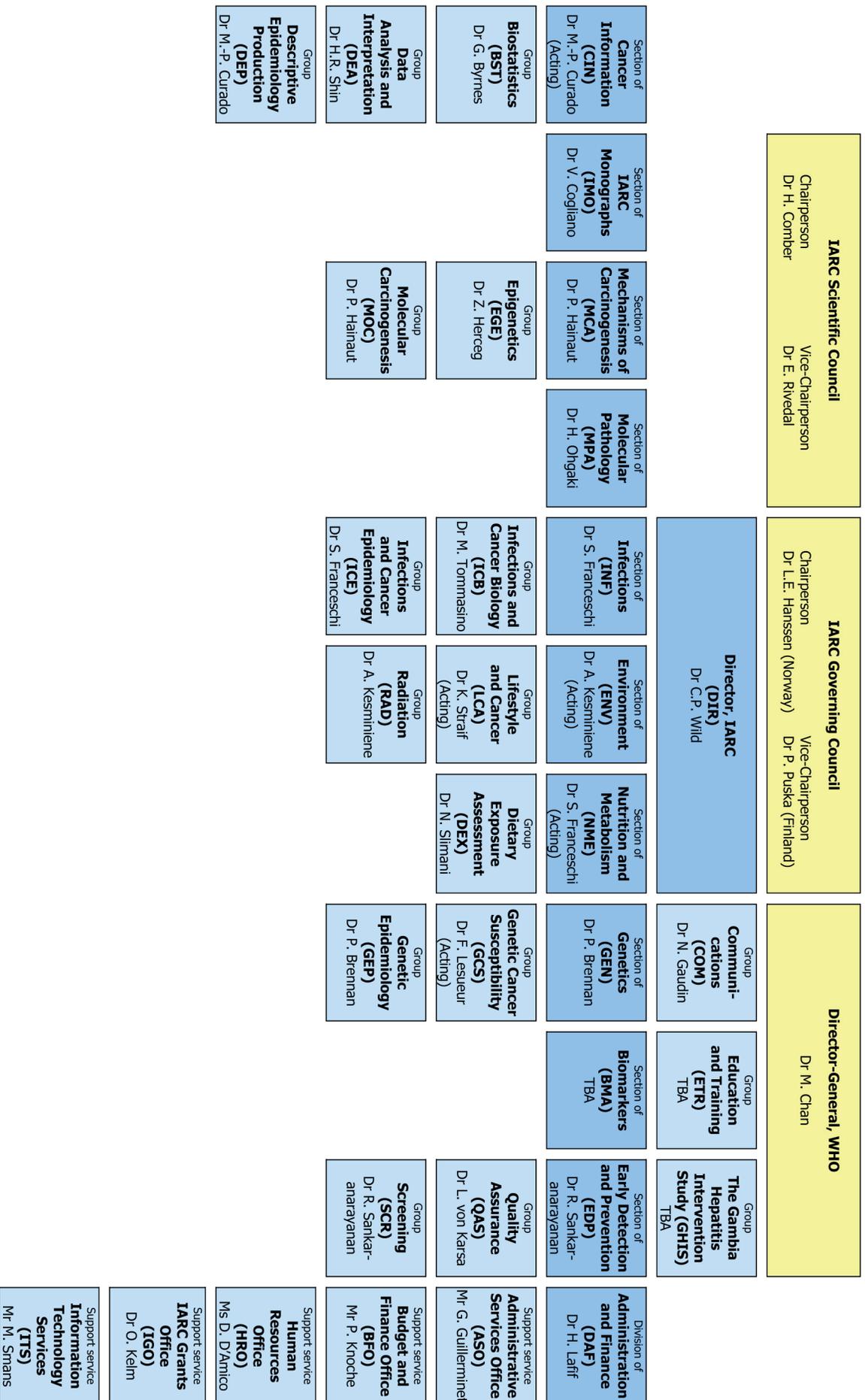
distinguished career as a scientist at IARC. It was a particular pleasure to welcome Nubia back to the Agency to receive this award (Figure 1), and her example of what can be achieved through the Agency is an inspiration to the next generation of young research scientists at IARC.

#### SCIENTIFIC ORGANIZATION

Dr Peter Boyle's term of office as Director of IARC came to an end in December 2008. Dr Boyle had a major impact on the Agency, not just in his time as Director but also previously as a staff scientist from 1986–1991. Aside from his scientific initiatives, Dr Boyle was notably

## International Agency for Research on Cancer World Health Organization

1 December 2009



TBA: to be appointed

Figure 2

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successful in encouraging the admission of several new Participating States to the Agency during his tenure. The publication of the World Cancer Report (2008) edited by Drs Boyle and Levin represented a major effort from many colleagues across the Agency.

The scientific organisation of IARC was changed during 2009 in order to align it with the future strategic directions and to provide clear leadership in key areas. The current structure comprises nine Sections, each with one or more research Groups. The Sections are: Cancer Information, IARC Monographs, Mechanisms of Carcinogenesis, Molecular Pathology, Infections, Environment, Nutrition and Metabolism, Genetics, and Early Detection and Prevention (Figure 2). These changes give increased emphasis to core areas such as cancer information (including cancer registration), the Monographs programme and early detection and prevention as well as providing renewed emphasis on nutrition. New senior appointments to support these initiatives for 2010 include Professor David Forman (formerly at the University of Leeds, UK and National Cancer Intelligence Network, UK) and Professor Isabel Romieu (formerly at the National Institute of Public Health, Mexico).

In order to support the scientific activity, two leadership committees were created. The first is the Senior Leadership Team (SLT), comprising the Director, all Heads of Sections, the Director of Administration and Finance (DAF) and the Head of Communications. The primary role of the SLT is to provide strategic leadership to the Agency through its advice to the Director. The second leadership committee is the IARC Operational Team (IOT), comprising the Director of Administration and Finance, the Heads of the Support Services (Finance, Human Resources, Buildings, Information Technology, Grants, Communication), and one Section Head. The primary role of the IOT is to ensure the support services enhance the scientific activity of the Agency.

#### PARTICIPATING STATES

During the biennium a further participating State, Austria, was admitted to the

Agency, bringing the total number to twenty-one. In October 2009 the Agency held a one-day workshop in Vienna in cooperation with the Austrian Federal Ministry of Science and Research which was attended by around 100 participants from across the country together with six staff from the Agency.

#### DIDIER COLIN

It was with great sadness that Agency staff learned of the untimely death of our colleague Didier Colin in November 2009 at the age of 43 years. Didier worked at the Agency since 1992, beginning in the Environmental Cancer Epidemiology Unit and since 2003 working in Infections and Epidemiology Group. Didier was a committed, professional staff member, discreet and determined. He was also a warm friend to many and will be sadly missed by all. The Agency extends its condolences to the family and friends of Didier.



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# IARC 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, Netherlands) – DNA repair: maintaining nature's perfection
- 1997 Luca Cavalli-Sforza (Stanford University, CA, 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
- 2006 Georg Klein (Karolinska Institute, Sweden) – Viral contributions to tumorigenesis
- 2007 Mariano Barbacid (Centro Nacional de Investigaciones Oncológicas, Spain) – Ras genes, Ras oncogenes and cancer
- 2008 Jan Hoeijmakers (Rotterdam, The Netherlands) – Genome maintenance and the link with cancer and ageing
- 2009 Harald zur Hausen (German Cancer Research Centre, Heidelberg) – The search for infectious agents in human cancers

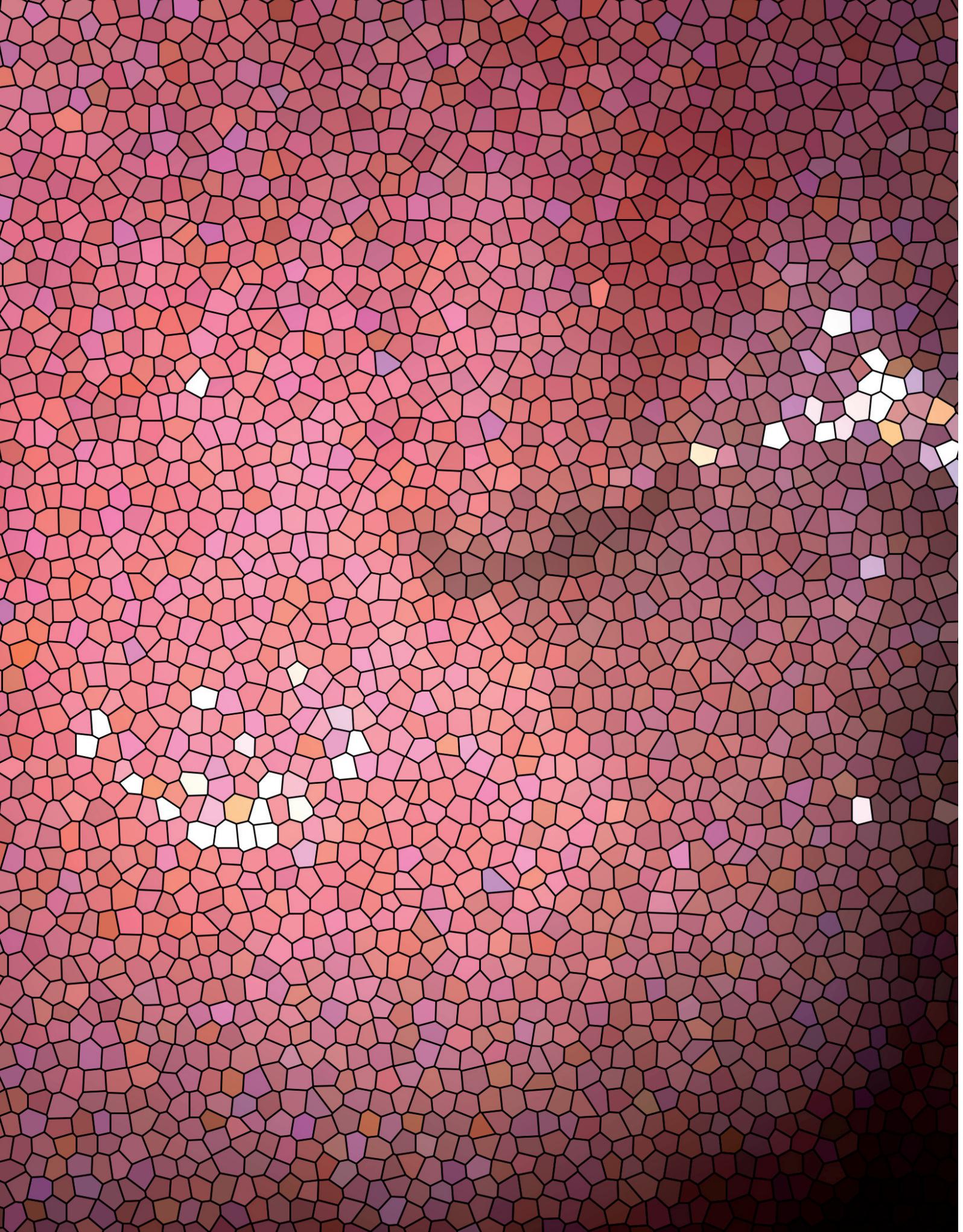
#### RICHARD DOLL LECTURE

- 2004 Richard Doll (London, UK) – Fifty years follow-up of British doctors
- 2005 Brian MacMahon (Needham, MA, USA) – Epidemiology and the causes of breast cancer
- 2006 Joseph Fraumeni Jr (National Institutes of Health, USA) – Genes and the Environment in Cancer Causation: An Epidemiologic Perspective
- 2007 Dimitrios Trichopoulos (Harvard School of Public Health, USA) – Breast cancer: Epidemiology and etiology
- 2008 Sir Richard Peto (Oxford, United Kingdom) – Halving premature death
- 2009 Nubia Muñoz (National Cancer Institute of Colombia) – From aetiology to prevention: The case of cervical cancer



#### IARC LECTURE

- 2005 Tadao Kakizoe (National Cancer Centre, Tokyo, Japan) – Bladder cancer: A model of human cancer determined by environmental factors and genetics
- 2006 Ketayun Dinshaw (Tata Memorial Hospital, India) – Cancer Treatment and Control
- 2007 LaSalle D. Leffall on behalf of Ambassador Nancy G. Brinker (Komen Foundation, USA)
- 2008 Maurice Tubiana (Paris, France) – La prévention des cancers, de l'analyse scientifique des données à la prise en compte des facteurs psychosociologiques



# CANCER INFORMATION SECTION (CIN)

**Acting Section Head:**  
Dr Maria-Paula Curado

THE CANCER INFORMATION SECTION IS COMPOSED OF THREE GROUPS: THE NEWLY-CREATED BIostatISTICS GROUP (HEADED BY DR GRAHAM BYRNES), THE DESCRIPTIVE EPIDEMIOLOGY PRODUCTION GROUP (HEADED BY DR MARIA-PAULA CURADO) AND THE DATA ANALYSIS AND INTERPRETATION GROUP (HEADED BY DR HAI-RIM SHIN).

The overall objective of the Section is to provide scientists, epidemiologists and public health professionals with comparable data on cancer incidence from as wide a range of geographical locations worldwide as possible. Cancer incidence data allow the identification of high-risk incidence and mortality by gender, age groups and race in different parts of the world, underlining the need to establish research groups in those high-risk areas.

The Section manages a database covering some 11% of the world population, with most of its contents coming from developed countries. There is therefore a crucial need to collect more data from low- and middle-income countries, which represent more than 75% of the world population. The limited quality of the data coming from these countries underlines the importance of establishing some specific methodologies to analyse the information in such a way that it can be used for cancer research and control.

The main research issues of the Section are:

- (a) To enhance geographical coverage of cancer incidence worldwide to better understand the heterogeneity of the cancer burden;
- (b) To provide population-based cancer registries in low- and middle-income countries with adequate statistical means to enable them to analyse their results correctly and thus provide good quality data;
- (c) To measure the impact of cancer incidence and mortality in developed countries and to use this information as a basis for cancer research and control.



# BIOSTATISTICS GROUP

## Head

Dr Graham Byrnes

## Secretary

Ms Katuska Veselinovic

THE BIOSTATISTICS GROUP (BST) WAS CREATED WITHIN THE CANCER INFORMATION SECTION IN APRIL 2009, WITH A SINGLE PROFESSIONAL STAFF MEMBER, GRAHAM BYRNES, WHO MOVED FROM THE PREVIOUS BIO GROUP. THE ROLE OF THE GROUP IS BROADLY COLLABORATIVE:

- TO ASSIST OTHER GROUPS IN DESIGNING EFFICIENT STUDIES;
- TO ASSIST THEM IN THE ANALYSIS OF COLLECTED DATA;
- TO DEVELOP NEW METHODOLOGY WHERE EXISTING METHODS ARE NOT ADEQUATE FOR THE TYPE OF DATA AVAILABLE.

A NUMBER OF COLLABORATIONS ARE PROGRESSING WELL, WITH SOME HAVING COMMENCED WHILE DR BYRNES WAS IN THE BIO GROUP. A FEW OF THE MORE IMPORTANT ONES ARE DETAILED BELOW.

## IN-SILICO CLASSIFICATION OF VARIANTS IN GENES ASSOCIATED WITH CANCER RISK

### *Collaboration with the Genetic Cancer Susceptibility Group (GCS).*

A number of genes are known to harbour variants that greatly increase the risk of certain types of cancer, notably BRCA1 and BRCA2 for breast cancer and the group of mismatch repair genes for colo-rectal cancer. However these genes are observed to present many different variants, hundreds in the case of BRCA1. Not all of these will have the same effect on gene function and hence on cancer risk, while most are seen so rarely that it is not possible to investigate each using epidemiological methods. For each, differing amounts of different types of data are available, so one task is to agree on an appropriate method of combining information from family histories, biochemistry and genetic sequence data. A second is to develop a method to recognize which changes are likely to alter gene function, based on the evolutionary history of the gene. Finally, it is necessary to find a method of communicating conclusions in a way that is clear and useful to people seeking to understand their personal risk and to clinicians who advise them.

The first and third of these issues were addressed in international meetings convened at IARC in 2008 (Breast cancer) and 2009 (Colo-rectal cancer). The second is the subject of a method developed in GCS with collaboration from BST, called GVGD. Several publications on the development and application of this method have now appeared.

## RADIATION DOSE-RESPONSE AND THYROID CANCER

### *Collaboration with the Radiation Group (RAD).*

It is known that exposure to ionizing radiation increases the risk of cancer of the thyroid, but it is not well understood how the risk depends on the magnitude of the dose received. Often a linear response is assumed, but this has a different meaning in the two different models that are commonly used. Another problem is that the exposure is inferred rather than directly measured. This makes it more difficult to evaluate the precision of estimates, and therefore to know if different estimates of dose response can really be said to be different.

These problems were addressed by using spline regression, which allows

the same response to be represented in each of the standard models, while the error was accounted for using multiple random draws. This highlighted theoretical and practical limitations of the existing software, so new programs were written. Efforts to account for all the complexities of the data continue.

#### POPULATION LINKAGE AND LONG HAPLOTYPES

*Collaboration with the Genetic Epidemiology Group (GEP).*

Standard methods of analysing genetic data are efficient for finding rare mutations that greatly increase the risk of cancer (linkage analysis) or for common variants that yield a modest increase in risk (association studies). At present there is no standard way of detecting the intermediate case: less common variants with intermediate effect. One approach is to look among cases for unexpectedly long lengths of shared DNA. Together with James McKay in GEP, we have been developing computer programs able to recognise such features. This work is still in its infancy.

#### ANALYSIS OF DIETARY PATTERNS

*Collaboration with the Dietary Exposure Assessment Group (DEX).*

The search for a link between the consumption of individual food items and cancer has a long history. However it is complicated by the fact that different foods and nutrients are often consumed together, making it difficult to separate their effects. To address this, we are seeking to study patterns of consumption, rather than individual items. The methodological interest is in recognising which are the pertinent patterns.

Also, imperfect recall of foods consumed can lead to both random noise and systematic bias in the dietary measurement. This can be partly addressed by calibrating the data against more precise measurement carried out on a subset of the cohort. However, these two techniques interact, and it is not obvious how standard methods for pattern recognition should be applied when the data needs to be calibrated.

These problems are being investigated experimentally using data from the European Prospective Investigation into Cancer and Nutrition.

#### BREAST CANCER RISK AND MAMMOGRAPHIC DENSITY

*Collaboration with the University of Melbourne, Australia.*

It is known that a woman whose breasts appear more dense on a mammogram will be at higher risk of breast cancer than another woman of same age, height and weight, assuming other important

risk factors are the same. This raises the possibility that important mechanisms for the development of breast cancer may depend on genes associated with mammographic density. A particularly useful resource for such studies is the Australian Twisters study, a cohort of female twins and their sisters. Comparing genetic and mammographic density information within these families has given rise to a number of methodological difficulties which have now been resolved, resulting in several publications submitted and published.

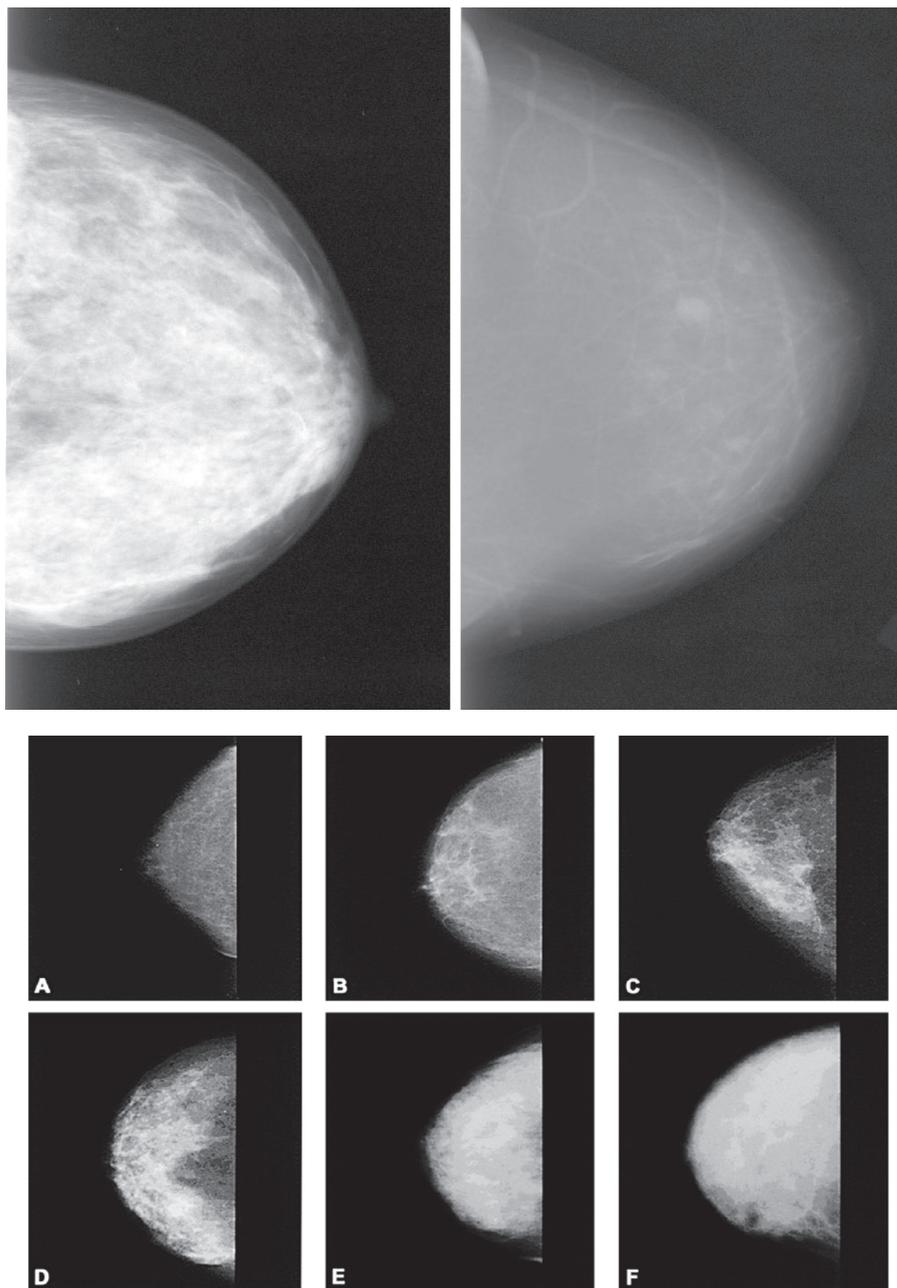


Figure 1: Examples of a dense breast (left) and a non-dense breast (right).

## TRAINING COURSES

IARC Summer School in Cancer Epidemiology 2008 (IARC, 2–27 June 2008 and 15 June–3 July 2009).

## MEETINGS ATTENDANCE

Unclassified variants/clinical interpretation workshop (IARC, 4–5 Feb. 2008);  
Unclassified Variants in Mismatch Repair Genes Working Group (IARC, 19–20 Feb. 2009).

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

**Australia:** Lyle Gurrin, Carolyn Nickson, John Hopper, Jennifer Stone;

**Germany:** Heiner Boeing, Brian Buijsse;

**USA:** David Goldgar

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# DATA ANALYSIS AND INTERPRETATION GROUP

## Head

Dr Hai-Rim Shin

## Scientists

Dr Jari Haukka (April 2008-April 2009)

Dr Eva Steliarova-Foucher

## Informatics Officer

Mr Jacques Ferlay

## Assistants (statistics)

Mr Eric Masuyer

Mrs Aurélie Millerat (until Dec. 2008)

## Visiting collaborator

Mr Mark O'Callaghan (from July 2009)

## Visiting Scientists and Postdoctoral fellows

Dr Jiansong Ren (from Sept. 2009)

Dr Kumiko Saika (July-Dec. 2009)

## Secretary

Ms Katuska Veselinovic (since May 2008)

## Students

Mr Pierre Boniol (July-August 2008)

Ms Clarisse Hery

Mr Ryan Shin (July-August 2009)

THE OBJECTIVE OF THE DEA GROUP IS TO MAKE THE BEST USE OF ALL EXISTING DESCRIPTIVE EPIDEMIOLOGY DATA TO DEVELOP BETTER HYPOTHESES ON THE ETIOLOGY OF CANCER AND REPORT ON THE DEVELOPMENT OF PREVENTION AND SCREENING ACTIVITIES.

The overall objective of the Group is to develop a comprehensive program of activities on the creation of appropriate statistical methodology for the analysis of descriptive epidemiology data; to apply statistical methods to the analysis of available incidence and mortality data; to provide assistance in data analysis to Cancer Registries and Vital Statistics Offices worldwide; to provide interpretation of the available data and the data analyses for the development of priority hypotheses, and finally to work with appropriate Groups within IARC and external bodies to develop and undertake appropriate etiological studies.

The estimation of the burden of cancer is an important core project of the Group. In order to improve accessibility to and comprehension of this information by the general public, the results are presented in a clear format to the layperson on the *CANCERmondial* website through different databases: GLOBOCAN, the WHO mortality database, NORDCAN, and Cancer Incidence in Five Continents (CI-5) volumes I-IX.

## GLOBOCAN

The GLOBOCAN estimates, one of IARC's major projects, are currently being updated for the year 2008 and should be available at the beginning of 2010. To this end, a collaborative working group has been set up between WHO (Global Burden of Disease) and IARC to allow a deeper exchange of data and methods (Figures 1 and 2).

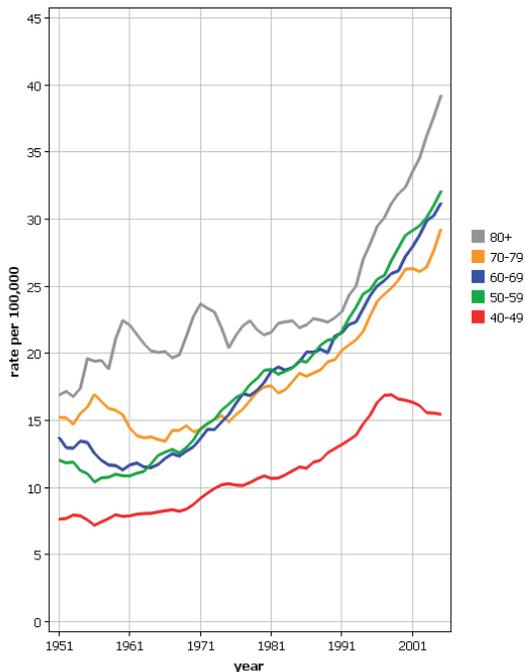
## NORDCAN

In collaboration with the Association of Nordic Cancer Registries (ANCR), the NORDCAN web application has been implemented and has been available since 2007 (<http://www-dep.iarc.fr/NORDCAN.htm>) (Figure 3). It provides access to the most up-to-date information on the incidence, mortality and prevalence of cancer in the five Nordic countries. The facilities created within the NORDCAN web application are then integrated into the other IARC web sites (WHO and CI5 I-IX) and have been extensively used for the development of the ECO web site (see European Cancer Observatory).

Another aim of the Group is to analyse temporal trends and gather additional descriptive information about these trends to allow a better interpretation of the reasons for temporal changes in incidence and mortality. Thus breast cancer incidence and mortality in Asia, epidemiology of cholangiocarcinoma (incidence rate and risk factors in East Asian countries), epidemiology of liver fluke infection in East Asia, brain cancer in Nordic countries, prostate cancer incidence and mortality have been studied and articles published or in the process of publication.

The relative importance of major risk factors in the global burden of cancer is currently estimated in the Attributable Causes of Cancer project, led in collaboration with scientists of two other groups (Prevention Group and Lifestyle

Japan  
Mortality from Breast Cancer



International Agency for Research on Cancer (IARC) - 14.9.2009

Figure 1

and Cancer Group). One specific aspect in which DEA is involved is Attributable Causes of Cancer in Korea, in collaboration with the Korean National Cancer Center.

ACCIS

The Automated Childhood Cancer Information System (ACCIS) (<http://www-dep.iarc.fr/accis.htm>) is an international project funded by the European Commission, La Ligue contre le cancer - Comité du Rhône, CLARA (Canceropôle Lyon, Auvergne, Rhône-Alpes) and the Ministry of Health of the Federal Government of Germany, jointly with IARC.

The need for substantial population coverage for studies of childhood cancer has led to this collaborative project involving some 80 population-based cancer registries in 35 European countries. The aim of this project is to use automated procedures to collect, analyse, interpret and disseminate data on incidence and survival of children and adolescents with cancer in Europe.

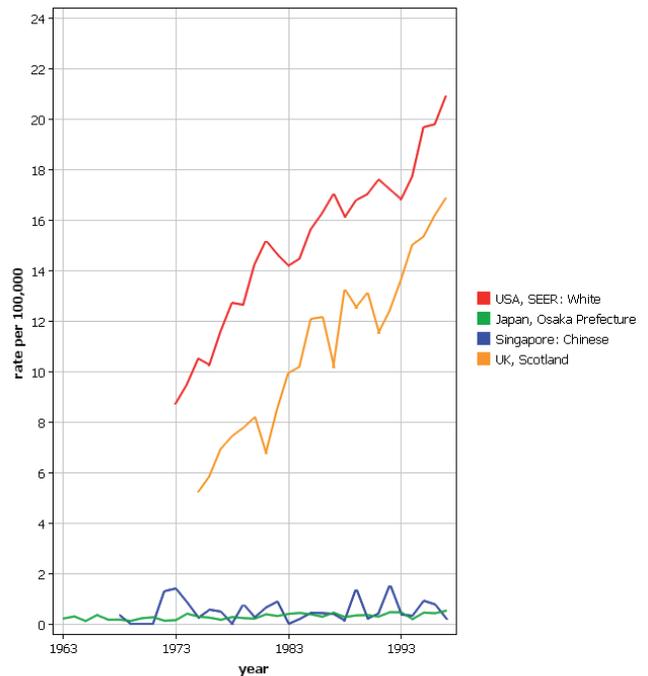
To date, data have been accumulated for some 160 000 tumours in children and adolescents (age 0–19), arising from 1300 million person-years over the 1970s, 1980s and 1990s, and became thus the world's largest childhood cancer database.

The collected data are being explored, and two versions of a data presentation software package, ACCIS pass, are being developed for different audiences. Meanwhile, the database is being extended in time and geographic coverage. These activities are overseen by the ACCIS Scientific Committee.

INTERNATIONAL INCIDENCE OF CHILDHOOD CANCER, VOL. 3 (IICC-3)

A core project of DEA, the next volume of International Incidence of Childhood Cancer aims to address the lack of data on cancer incidence in children and adolescents through a worldwide collaboration with cancer registries (<http://www.iacr.com.fr/childhood/iicc3.htm>). A check program to facilitate data quality control and evaluation has been developed, and a modern system of data submission and processing has been

Melanoma of skin  
Age Standardised Incidence Rate (World), Female age [20-74]



International Agency for Research on Cancer (IARC) - 14.9.2009

Figure 2

implemented, including website upload of the files, on-line questionnaires and partial automation of data processing. The publication of the monograph is planned for 2010 (Figure 4).

UICC "MY CHILD MATTERS" PROGRAMME

The Group's expertise in the descriptive epidemiology of childhood cancer has also contributed to the international programme My Child Matters, organised by the UICC and Sanofi-Aventis. It is devoted to improve the conditions and management of childhood cancer in selected low-resource countries. Eva Steliarova-Foucher, as a member of the UICC Childhood Cancer Task Force, mentors two projects involving registration and follow-up of childhood cancer patients, awarded in 2008 to Cali, Colombia and Karachi, Pakistan.

EUROPEAN NETWORK OF CANCER REGISTRIES (ENCR)

Since December 2008, when Eva Steliarova-Foucher became the ENCR Scientific Coordinator, DEA has contributed substantially to the activities



and (c) Scenarios, meaning modelling of cancer burden in population, using available data on incidence, mortality, survival and prevalence.

Jacques Ferlay has contributed significantly to the design and content of the ECO website (Figure 5).

**SUPPORT TO CANCER REGISTRIES IN LOW- AND MIDDLE-RESOURCE COUNTRIES: TRAINING COURSES**

As cancer registry data is seen as an aid to the evaluation of the local cancer burden and as a tool for cancer control, it is important to continue supporting cancer registration in the world through training courses. Therefore, several international training courses on cancer registration were organised during this biennial period. The aim is to provide an intensive introduction to the methodology of cancer registration and to the use of cancer registry data. The target participants are individuals who are working in cancer registration on aspects of data collection, analysis and presentation of data, or ideally, both.

Our Group actively participated in the cancer registration modules of the 2008–09 IARC Summer Schools, providing faculty members and training in cancer control and cancer registration basic principles.

Other courses attended were:

(a) IARC/National Cancer Center, Korea – International Course on Introduction to Cancer Registration and its Application to Cancer Epidemiology, Seoul, Korea, Sept. 08; (Figure 6)

(b) IARC/National Cancer Institute, Bangkok (Thailand) with the Thai Association of Cancer Registries – International Course on Introduction to Cancer Registration, Pattaya, Thailand, Feb. 09;

(c) IARC/Jigme Dorji Wangchuck National Referral Hospital, Thimphu (Bhutan) – Course on Cancer Registry and Management of Cancer Prevention Programme, Thimphu, Bhutan, May 09. Bhutan is the only country in the world not allowing tobacco sales, and for this reason cancer statistics are of great importance for cancer research and control. As this country has no comprehensive incidence

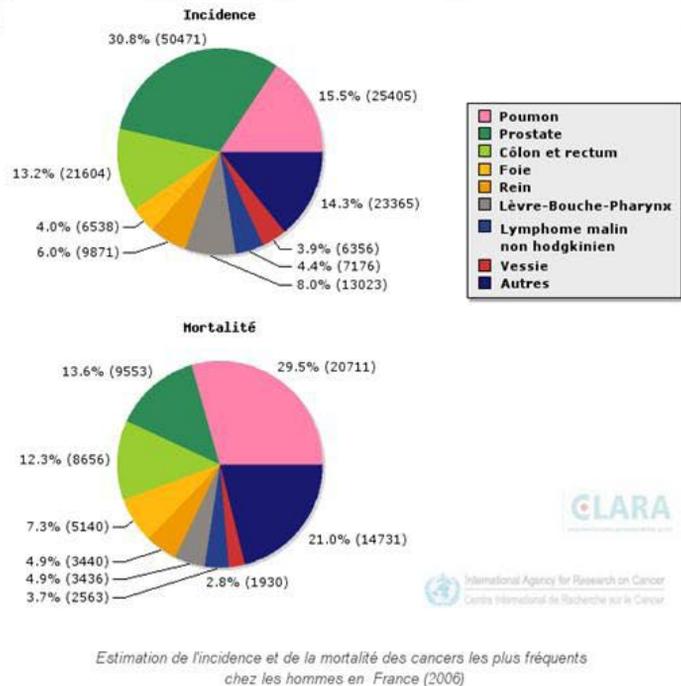
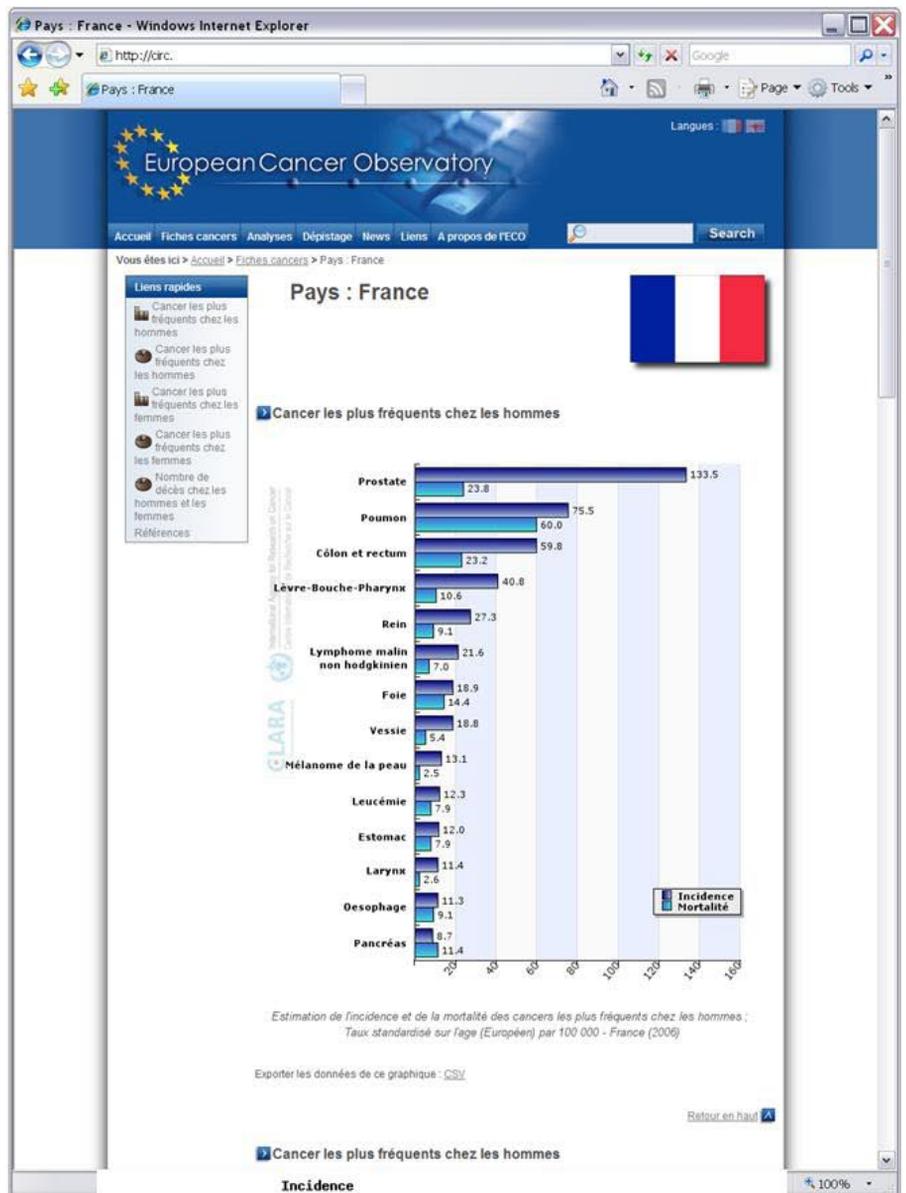


Figure 5. European Cancer Observatory website. <http://eu-cancer.iarc.fr>

statistics on cancer, the training course was an opportunity for the participants to have an overview on cancer registration and cancer prevention;

(d) IARC/Cancer Institute & Hospital Chinese Academy Medical Sciences (CIHCAMS), Beijing – International Course on Introduction to Cancer Registration and its Application to Cancer Epidemiology, Beijing, People's Republic of China – Sept. 2009.

## MEETINGS

Group members have also organised or attended the following meetings: Methodology for Estimating the Global Cancer Burden (IARC, 21 January 2008); Attributable causes of cancer in Korea (11-12 Feb. 2008 and 9-11 Sept 2009 at National Cancer Center, Korea, and 9-13 July 2009 at IARC); ACCIS Scientific Committee (IARC, 30 June - 1 July 2008); Editorial Board Meeting for Vol. 3 of the International Incidence of Childhood Cancer (IARC, 1 - 2 July 2008); Satellite meeting to discuss the creation of an Asian Cancer Registry Network (National Cancer Center, Korea, 29 Sept. 2008); ENCR/ECO/ EUROCOURSE (IARC, 13 Jan. 2009); GLOBOCAN (IARC, 14 Jan. 2009); Establishment of an Asian Cancer Registry Network (Thailand, 12 Feb. 2009); 41st and 42nd ENCR Steering Committee Meetings (IARC, 6 - 7 April 2009 and Turin, 6 Nov. 2009); 1st meetings of the EUROCOURSE Steering and Executive Boards (IARC, 7 and 8 April 2009).

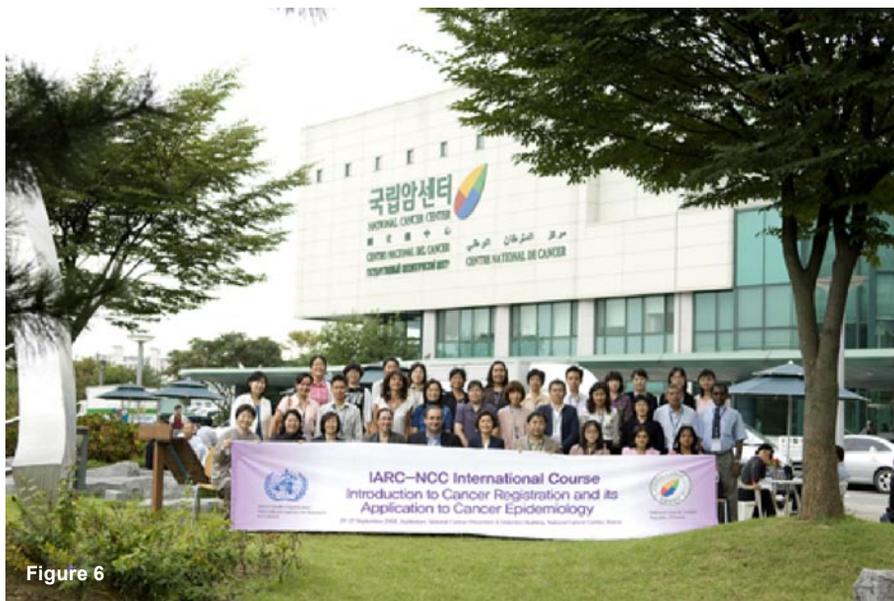


Figure 6

**Financial support from the following bodies is gratefully acknowledged:**  
 Cancéropôle Lyon, Auvergne, Rhône-Alpes/CLARA, France (ECO, ACCIS)  
 Federal Ministry of Health for the German Federal Government (ACCIS)  
 International Union Against Cancer (ICRETT Training Workshop in Bhutan)  
 National Cancer Center, Japan (contribution to the International Courses in the Republic of Korea and People's Republic of China)

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

Argentina: Florencia Moreno; Austria: Paola Di Giulio, Nadine Zielonke;

Belgium: Carole Equeter, Ian Magrath

Denmark: Dorte Hansen Thrige, Hans Storm; Estonia: Mati Rahu; Germany: Peter Kaatsch, Marc Luy;

Finland: Ahti Antilla, Risto Sankila; France: Frédéric Bennaïm, Murielle Colombet, Pascale Grosclaude, Brigitte Lacour, Jean Lemerle, Isabelle Tabah-Fisch; Iceland: Laufey Tryggvadóttir; Ireland: Harry Comber;

Italy: Emmanuele Crocetti, Stefano Rosso, Roberto Zanetti;

Korea: Kyung-Ja Cho, Jim Kyuoung Oh, Sohee Park, Aesun Shin, Hee Young Shin, Hyun Woong Shin Young Seok Shin, Seok-Jun Yoon;

Netherlands: Jan Willem Coeberg, Maarten Egeler, Sabine Siesling, Corina Van Der Hurk;

Norway: Freddie Bray; Romania: Daniela Coza; South Africa: Glynn Wessels;

Spain: Isabel Izarzugaza; Sweden: Joakim Dillner, Mats Lambe;

Switzerland: Franco Cavalli, Jean-Michel Lutz, Colin Mathers;

Tanzania: Twalib Ngoma; Turkey: Tezer Kutluk; United Kingdom: Anna Gavin, Henrik Møller, Max Parkin, Charles Stiller; USA: Greta Bunin, Majid Ezzati, Ruth Hoffman, Paul Ribeiro

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# DESCRIPTIVE EPIDEMIOLOGY PRODUCTION GROUP

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Mr Morten Ervik

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Mr Adrien Bouhot

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Ms Marianna de Camargo Cancelli

Ms Karima Chaabna

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Ms Thais Pontes

(March-October 2009)

THE CORE ACTIVITY OF THE DEP GROUP IS TO SUPPORT CANCER REGISTRATION ALL OVER THE WORLD AND TO MONITOR AND PROVIDE CANCER INCIDENCE DATA AS A BASIS FOR ETIOLOGICAL RESEARCH AND CANCER CONTROL POLICIES, WHETHER LOCAL OR INTERNATIONAL. THE INFORMATION ON CANCER INCIDENCE, MORTALITY AND TRENDS QUANTIFIES THE SIZE OF THE BURDEN OF CANCER INCIDENCE, ALLOWING ASSESSMENTS OF CANCER CONTROL ACTIONS TAKEN IN THAT POPULATION. TO DATE, OUR DATABASE COVERS 11% OF THE WORLD POPULATION, I.E. 705 MILLION PEOPLE. RECENTLY, THE NEED TO IMPROVE CANCER INFORMATION DATA IN LOW- AND MEDIUM-RESOURCE COUNTRIES HAS BEEN EMPHASISED, IN ORDER TO PROVIDE RELIABLE CANCER FIGURES TO GOVERNMENTS AND ENABLE THEM TO PROMOTE RESEARCH AND CANCER CONTROL PROGRAMMES IN THEIR COUNTRIES. A CRUCIAL ISSUE IN THESE REGIONS IS THE LACK OF MORTALITY DATA, SO CANCER REGISTRIES ARE OFTEN THE BEST SOURCE FOR CANCER OCCURRENCE DATA. SINCE THE 1970s, IARC HAS SYSTEMATICALLY RECEIVED DATA FROM POPULATION-BASED CANCER REGISTRIES WORLDWIDE, WHICH IS THEN REFINED BASED ON DATA QUALITY INDICATORS FOR EACH CANCER REGISTRY. THE CANREG5 SOFTWARE HAS BEEN ONE OF THE STRATEGIES TO HELP REGISTRIES PRODUCE CONSISTENT QUALITY DATA, ALONG WITH TRAINING COURSES HELD IN LYON AND LOCALLY. THE DATA RECEIVED ARE SCREENED TO MATCH IARC STANDARDS AND SUBSEQUENTLY ADAPTED TO ENABLE COMPARISONS BETWEEN THE POPULATIONS DISTRIBUTED OVER THE FIVE CONTINENTS.

## CANCER INCIDENCE IN FIVE CONTINENTS

### (1) Volume IX

The series on *Cancer Incidence in Five Continents* is one of the most important databases in the world. It has a long history (since the 1960s) of compiling population-based cancer registries from the five continents and providing comparability data to evaluate the worldwide cancer burden. Its information is used by scientists and health policies to promote research and cancer control. The latest volume is available in two versions, the first web-based ([www.dep.iarc.fr](http://www.dep.iarc.fr)) with chapters describing the methodologies applied to evaluate the data from the cancer registries and their practices. Online analysis was also made available so that users can perform specific analyses as needed via a user-friendly site that also provides links to other related databases. An Editorial Board composed of representatives from around the world (Drs Maria-Paula

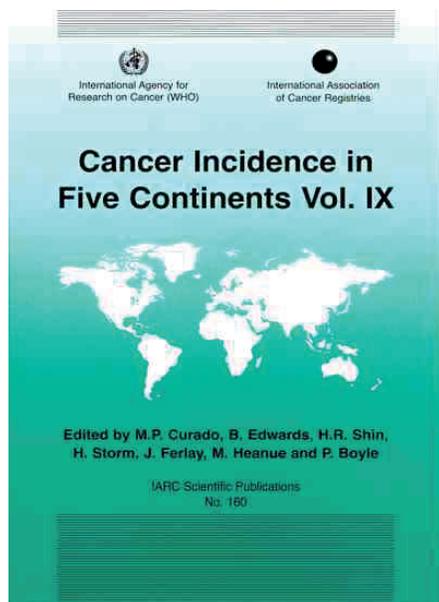
Curado, Brazil; Brenda Edwards, USA; Hans Storm, Denmark; Hai Rim Shin, Republic of Korea; as well as DEP/DEA IARC staff) reviewed the data produced by the population-based cancer registries for Volume IX which was then converted into standardized data and disseminated to the scientific community.

This publication is produced on an aggregated 5-year basis; in this case the time of reference was from 1998 to 2002. In order to allow the editors to verify local situations in the areas covered by the cancer registries, a questionnaire about the registry activities was submitted to the contributors to better understand quality, comparability and completeness issues. Contributors were also asked to send data for the years preceding the reference period.

Volume IX has been divided into 7 chapters: introduction, techniques of registration; classification and coding;

histological groups; comparability and quality of data; processing data; age standardisation, and denominators, with narratives and maps. The evaluation criteria used to analyse the data submitted by the cancer registries were based on cancer registration data quality indicators outlined in *Cancer Registration, Principles and Methods* (IARC Scientific Publication No. 95) and the Manual for Cancer Registry Personnel, IARC Technical Report No.10 (Chapter 5).

We received data from 406 populations and published cancer incidence data from 300 populations, 225 cancer registries and 60 countries. The number of populations included represents a 38% increase over Volume VIII. The incidence rates and numbers as originally published can be accessed from the electronic version available on the IARC website.



## (2) Volumes I-IX

This database is a compilation of the nine already published volumes in the series, containing updated data from cancer registries whose results have been published in at least 3 consecutive volumes in the series. Whenever possible, the years have been re-grouped to correspond to standard consecutive five-year periods, and denominators (person-years at risk) and number of cancer cases have also been updated; as a result some data included in this database may not correspond to those published in the original one. The cancer sites dictionary is identical to that used in the original

database. More options are available to analyse the data (by histological groups and by year of incidence). An Editorial Board (Dr Brenda Edwards, NIH, USA; Dr Max Parkin, Univ. of Oxford, UK; Dr Hai-Rim Shin, Dr Maria-Paula Curado and Mr Jacques Ferlay from IARC) was convened on 29-30 Oct. 2009 to establish the contents and layout of the volume.

## EUROPEAN CANCER ATLAS

A meeting of European experts took place at IARC in October 2008 to review the 1993–1997 European Cancer Atlas prior to publication and to submit data for the 1998–2002 atlas. Mortality data was collected at sub-national level (NUTS III) from 34 countries, and world age-adjusted rates for 25 of the most common cancers (Figure 1) calculated for presentation in maps in order to examine the geographic pattern of cancer in Europe. In examining the recently published atlas, distinct geographical groupings are evident; map production at sub national level removes international borders to highlight the international problem cancer is. Processing is underway thanks to DG Sanco Direct funding, and publication is expected in 2010.

## FUND FOR CANCER REGISTRATION

Following two Working Group meetings on (1) Data production in Low- and Medium-Resource Countries and (2) Cancer Registration in Africa, Asia and Latin America, Improving Data Quality, held at IARC in July and December 2007 respectively, the Agency was advised to set up a Fund for Cancer Registration to support seven African cancer registries in the Republic of Guinea (Conakry), Mali (Bamako), Mozambique (Beira), Nigeria (Ibadan and Maiduguri) and Zimbabwe (Harare). The sum of US\$10 000 was attributed to each of them, payable in four instalments of US\$2500 respectively (one in 2008, two in 2009 and a last one in 2010).

## INTERNATIONAL CLASSIFICATION OF DISEASES (ICD)

The 11<sup>th</sup> revision of ICD was officially launched at the WHO Collaborating Centres meeting in Trieste, in April 2008. IARC has agreed to review ICD-10 and make recommendations for the

neoplasms chapter of the latest revision of ICD in order to bring it into line with ICDO, the IARC “Blue Book” series, TNM and SNOMED under the chair of Dr Maxwell Parkin in collaboration with the IACR.

The ICD (International Statistical Classification of Diseases and Related Health Problems) provides codes to classify diseases and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or disease. ICD is used worldwide for morbidity and mortality statistics, reimbursement systems and automated decision support in medicine. This system is designed to promote international comparability in the collection, processing, classification and presentation of these statistics. The ICD is a core classification of the WHO Family of International Classifications (WHO-FIC).

## CANREG SOFTWARE

During the biennium, new or modified versions of the CanReg4 software have been developed and installed in Africa (Algeria, Botswana, Mozambique, Nigeria, Yemen), Latin America (Argentina, Grenada, Nicaragua), Asia (Iraq, Syria), Europe (Cyprus, France) and Oceania (Australia, New Caledonia). Staff were trained during the IARC Annual Summer School in Cancer Epidemiology held in Lyon, as well as in regional courses in Colombia, Australia, Syria, Nigeria, Peru, Turkey and China.

## CanReg5

A 5<sup>th</sup> version of the software is currently under preparation as open-source software. The program was designed based on the outcome of a survey held among all members of IACR. The biggest changes from previous versions are that it has stronger multi-user network support, it can run under all major operating systems, and it has a more powerful database engine and a more modern graphical user interface. Implementation started at IARC in March 2008 (Morten Ervik). The first closed beta version was released in January 2009 with cancer registries from Cyprus, Turkey, Jordan, Egypt, France and Italy participating in the testing.

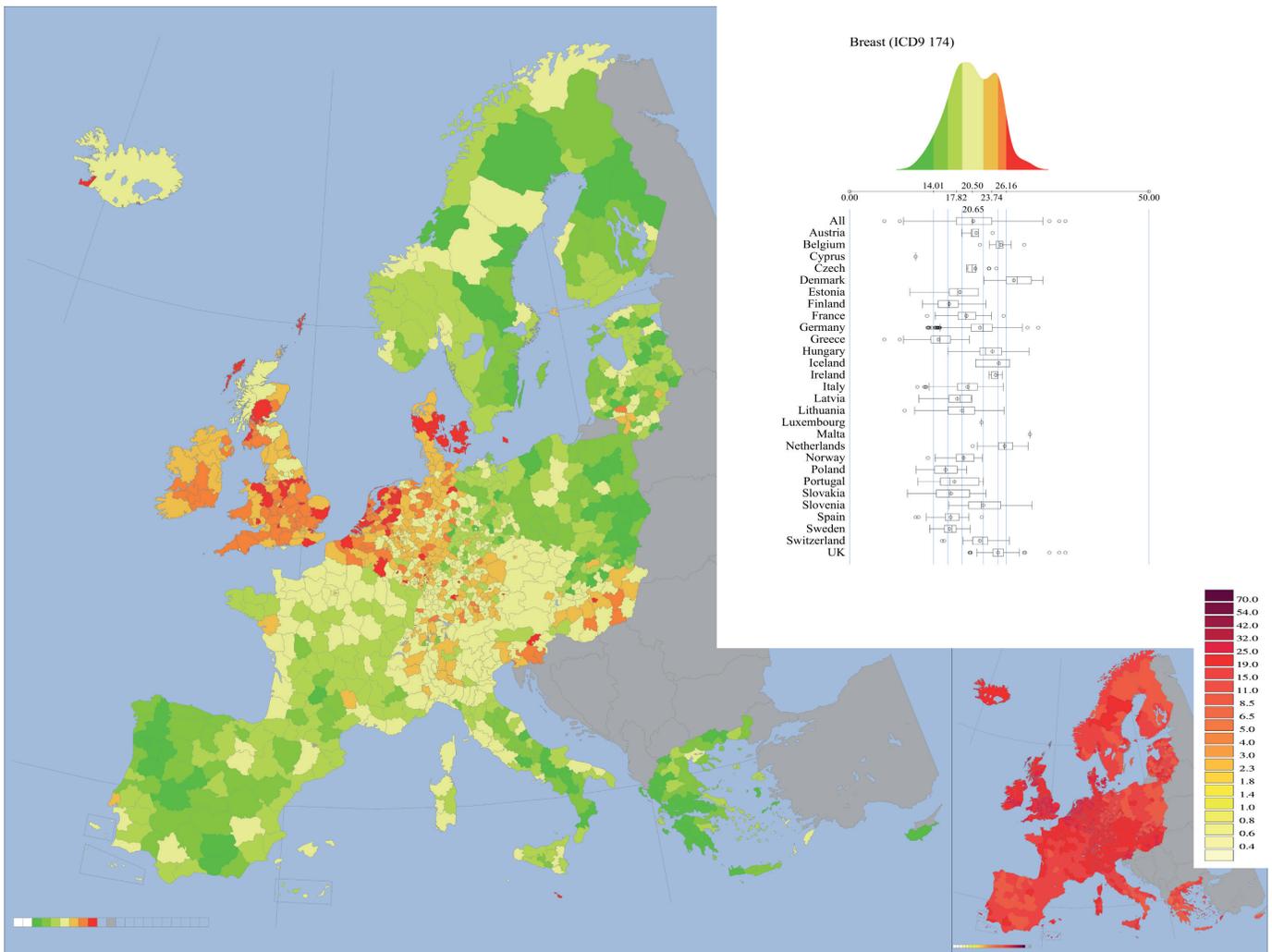


Figure 1. Sample page from European Cancer Atlas showing Female Breast Cancer



Sample screen from CanReg5

A workshop on CanReg5 was held in Istanbul in June 2009, with participants from the MECC countries, and another one in Beijing in September 2009.

### IACR/ENCR

The Group provides the facilities for the administration and secretariat of the International Association of Cancer Registries (IACR) and the European Network of Cancer Registries (ENCR).

*IACR (International Association of Cancer Registries)*

Since 1973, IACR has supported the activities of the non-governmental International Association of Cancer Registries (IACR) by hosting its secretariat. During 2008–09, the role of IACR Executive Secretary has been assumed by Maria-Paula Curado, with technical assistance provided by Isabelle Savage. This team is responsible

for coordinating the activities of the Association and for promoting exchange of information between over 600 members all over the world. During the biennium, the IACR Secretariat helped to raise funds and organised two Annual Scientific Meetings—in Sydney (18–20 November 2008) and in New Orleans (3–5 June 2009)—and the Executive Board Meetings held on 16–17 November 2008 and 1 June 2009. Other activities included maintenance of the IACR website at <http://www.iacr.com.fr/>, the publication of the IACR Newsletter, communication with associated journals, management of membership (applications, fees and data-base) and IACR fellowships, and grant applications. IACR collaborated with IARC in several projects, namely Volume IX of Cancer Incidence in Five Continents, and the development of CanReg..

*ENCR (European Network of Cancer Registries)*

ENCR was established in 1989 to improve quality, comparability and availability of cancer incidence data across Europe. It was originally funded by the European Commission until 2003; its activities were partially supported by the French Cancéropôle (CLARA) until 2008.

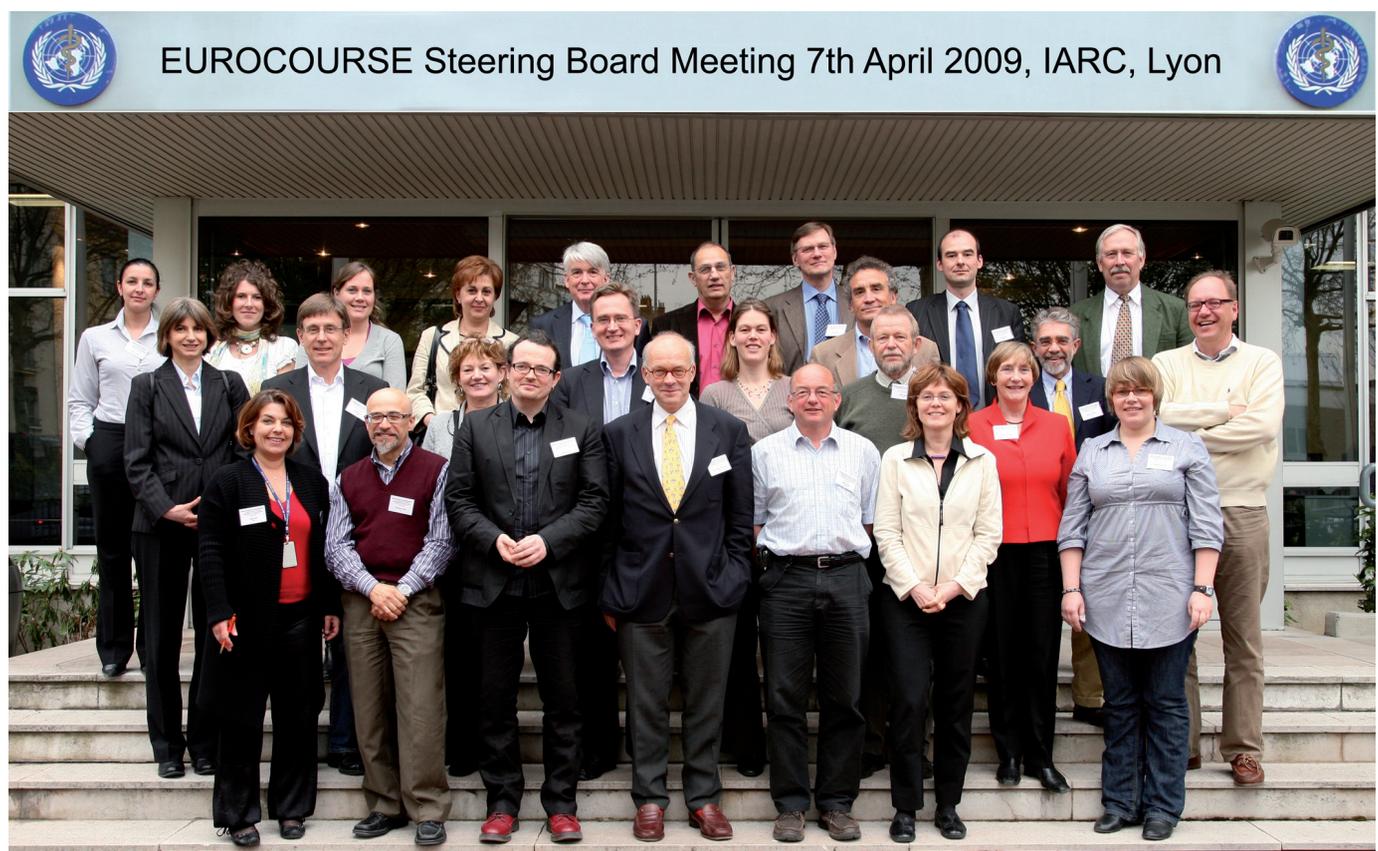
Further funds are being identified to allow continuous support to the Network, which is the provider of cancer incidence data in Europe.

IARC hosts the Secretariat of ENCR, which is the executive body of the Network. The Scientific Coordinator was Lydia Voti (until December 2008) and Eva Steliarova-Foucher (since then). The decisions are being made by the ENCR Steering Committee (SC), currently composed of Freddie Bray (Cancer Registry of Norway, Oslo), Anna Gavin (Dept of Epidemiology and Public Health, Northern Ireland), Jean-Michel Lutz (National Institute for Cancer Epidemiology and Registration - NICER, Zurich, Switzerland), Stefano Rosso (Piedmont Cancer Registry, Turin, Italy), Sabine Siesling (Comprehensive Cancer Centre North East – IKNO, Groningen, The Netherlands), Emanuele Crocetti (Tuscany Tumour Registry and GRELL representative), Risto Sankila (Finnish Cancer Registry and representative from the Nordic Cancer Registries Association), Max Parkin (Chairman and representative of IACR) and Maria-Paula Curado (IARC representative). The SC usually meets twice a year.

Over the period 2008–09, much effort has been devoted to identifying new funding sources, and partial success has been achieved with the IARC-coordinated application for the EURO COURSE project (see below). Further funds to finance ENCR core activities are being sought.

Other activities included collection of cancer data to update the EURO CIM European database after the year 1997; development of DEP edits software for verification of cancer registries data and at IARC, organisation of a structured review of the Munster Cancer Registry, reviewing several research proposals using EURO CIM data and other output from ENCR. Further details may be found on the dedicated ENCR website <http://www.enccr.com.fr/ENCCr.htm>.

Steering Committee meetings were held at IARC on 5 March 2008, 12–13 May 2008, 2–3 Sept. 2008, 6–7 April 2009, and in Turin (Italy) on 6 Nov. 2009. A joint ENCR/ECO/EURO COURSE meeting was also held in Lyon on 13 January 2009, as well as the first meetings of the EURO COURSE Steering and Executive Boards (7-8 April 2009)





## IARC SUMMER SCHOOL Cancer Registration, Lyon, 15 to 19 June 2009



### EUROCOURSE

A grant application (EUROCOURSE) was submitted by the ENCR to the European Commission through its FP7/ERA-net Programme (Work Package on Cancer Incidence and Trends in Europe). The EUROCOURSE project, driven by cancer registries and their supporting bodies, will tackle fragmentation in the funding and usage of cancer registries in Europe. It will do so by exploring ways to link and integrate national/regional programmes aimed at supporting cancer registries and research carried out using registry data. At the same time, EUROCOURSE is seeking to optimise the use of cancer registration data to improve cancer control and the strengthening of population-based cancer research in Europe. This 3-year project started in April 2009 (<http://www.eurocourse.org/>).

Intended to be the coordinator of the project, IARC has eventually become an important sub-contractor of the two partners in the key work packages. This change of the role reflected the specific conditions of participation in ERAnet.

Within EUROCOURSE, IARC assumes the strategic role of collection, processing, quality control and dissemination of European cancer data. Other support to EUROCOURSE involves survey of registries status and practices, establishment of a teaching course,

organisation of large-scale meeting and management of the project. Some of the above activities are supported by other sources.

#### TRAINING COURSES

##### (1) *IARC Summer School in Cancer Epidemiology*

As in previous years, our Group actively participated in the cancer registration modules of the 2008 and 2009 IARC Summer Schools, providing the course coordinator (Mary Heanue), faculty members and training in cancer registration basic principles, methods in data collection, quality control measures, CanReg software data entry, checks and practical exercises (See the section on IARC Education and Training).

##### (2) *IARC courses on introduction to cancer registration and its application to cancer epidemiology*

Courses were held in Goyang, Korea on 22–25 September 2008, in collaboration with the National Cancer Center, and on 14–18 September 2009 in Beijing, People's Republic of China, in collaboration with the Cancer Institute Hospital and the Chinese Academy of Medical Sciences (CIHCAMS). The localised nature of these courses allows for more in-depth training and a focus on methods.

##### (3) *Other courses*

Presentations were also given by Group staff at the following courses: University of Goiania (Brazil) Summer Course on Cancer Epidemiology (7–15 March and 11–22 Aug. 2008); Workshop on Cancer Registration and Epidemiology (6–10 April 2009 in Abuja, Nigeria); Workshop to enhance collaboration with PAHO in the field of cancer registration in Latin America (23–24 April 2009 in Quito, Ecuador); University of Michigan at Ann Arbor Summer Course (22–24 July 2008); MECC Cancer Registries Meetings (3–4 Nov. 2008 in Larnaca, Cyprus and 8–13 June 2009 in Istanbul, Turkey) and at the IARC/PAHO/MOH Regional Meeting of Cancer Registries and Cancer Managers on Improving Cancer Information in Latin America and the Caribbean (13–16 Oct. 2009, in Brasilia).

#### MEETING ATTENDANCE

The following international events were attended by DEP staff: Michigan Symposium on Cancer in Africa (8–11 Jan. 2008, Ann Arbor, MI, USA); ICD Topical Advisory Group and Revision Steering Committee Meeting (WHO, Geneva, 10–11 April 2008); GRELL Annual Meetings (30 April–2 May 2008 in Parma, Italy and 19–21 May 2009 in Lugano, Switzerland); IACR Annual

Conferences (Sydney, 14–17 Nov. 2008 and New Orleans, LA, USA on 1–7 June 2009); Meeting on National Cancer Control Programmes (Geneva, 2–4 July 2008); Editorial Board Meeting for the revision of the IARC Scientific Publication “Cancer Registration, Principles and Methods” (Oxford, UK, 20–21 Oct. 2008); 5th National Arab-American Health Conference and Symposium on Cancer in Africa (Ann Arbor, MI, USA, 8–10 Nov. 2008); International Congress on Head and Neck Cancer (Fortaleza, Brazil, 2–9 Sept. 2009) and the 3rd International Cancer Control Congress (Cernobbio, Italy, 8–11 Nov. 2009).

## REVIEW OF CANCER REGISTRATION IN THE WORLD

The activities of the following cancer registries were reviewed by the Group Head: Antigua (31 March–1 April 2008); Grenada (2–3 April 2008); Barbados (3–4 April 2008); Banjul, The Gambia (16–21 June 2008); Gezira and Khartoum, Sudan (5–10 July 2009) and Tirana, Albania (17–19 Nov. 2009). Meetings of the Italian/Libyan registries (31 Oct.–2 Nov. 2008, Benghazi, Libya), Oncological Registries (4 July, Porto), “Organizing a Local Cancer Registry” (5 April 2008, Chania, Crete) and the MOH/INCA Working Group on Population-Based Cancer Registries (6–9 Oct. 2008, Brasilia) were also attended.

## COLLABORATIONS

### (1) IAEA/PACT

As a follow-up to its collaboration with the International Atomic Energy Agency PACT Programme in developing countries to introduce, expand and improve their cancer care capacity by integrating radiotherapy into comprehensive cancer control programmes, IARC participated in imPACT missions to Sri Lanka (Kandy, Galle and Colombo, 14–18 Jan. 2008), Chisinau, Moldova (8–10 April 2008), Sana'a, Yemen (23–26 June 2008), and Mongolia (12–15 Oct. 2009), and in the development of national cancer control plans in these countries.

### (2) PATH

The Program for Appropriate Technology in Health (Seattle, WA, USA) has launched screening and vaccination programmes

in various low-resource countries, and in order to assess the effectiveness of their on-going cervical cancer vaccination programmes in Uganda, Peru and Vietnam, they decided to devote funds to cancer registration in these countries. The DEP Group was asked to submit a grant proposal along these lines, and the related funds were received for site visits in the three countries to evaluate cancer registry capacity for cervical cancer as a first step (4–8 Feb. 2008 in Kampala, Uganda; 24–28 March 2008 in Lima and Trujillo, Peru and 20–22 May 2008 in Hanoi, Vietnam). Then, workshops on cancer registration and HPV vaccine were organized on 10–11 Feb. (Kampala), 19–21 May (Lima) and

26–27 May 2009 (Hanoi).

### (2) Low- and Medium-Resource Countries in Latin America

DEP has begun a collaboration with the Pan-American Health Organization (PAHO; Washington, DC, USA) to enhance cancer registration in low- and medium-resource countries in Latin America. A preliminary meeting was held in Quito on 23–24 April 2009, and a Regional Meeting on “Improving Cancer Information in Latin America and the Caribbean” took place in Brasilia, 13–16 Oct. 2009.

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

Albania: Nuriye Çausi; Austria: Barbara Leitner; Argentina: Eduardo Laura; Austria: Dan Malin, Eduardo Rosenblatt, Massoud Samiei, Nadine Zielonke; Belgium: Marc Arbyn, Leila Bellamammer, Carole Equeter, Anne Kongs; Bulgaria: Finka Denkova; Croatia: T Coric; Cyprus: Eleni Kyriacou; Czech Republic: Magdalena Poppova; Denmark: Dorte Hansen Thrige, Jesper Munk Marcussen, Hans Storm; Estonia: Gleb Dennisov, Matti Rahu; Finland: Ahti Anttila, Timo Hakulinen, Helena Korpi, Nea Malila, Eero Pukkala, Risto Sankila; France: Pascale Grosclaude, Eric Jouglu, Gerard Pavillon, Gregoire Rey; Germany: Hermann Brenner, Thomas Graf; Greece: Kostas Voulgaris; Guinea: Ibrahim Kabba, Moussa Koulibaly; Hungary: Ferenc Kamaras; Iceland: Olof Gardarsdottir, Omar Hardarson, Laufey Tryggvadottir; Ireland: Harry Comber, Joseph Keating, Sandra Tobin; Italy: Silvia Bruzzone, Emanuele Crocetti, Alberto d'Onofrio, Sara Gandini, Carlo La Vecchia, Antonio Ponti, Stefano Rosso, Roberto Zanetti; Latvia: Janis Misins, Sniedze Karlson; Lithuania: Liuda Kasparaviciene; Luxembourg: Elodie Cayotte, Sabine Gagel, Guy Weber; Macedonia: Biljana Stefanovska; Mali: Siné Bayo; Malta: Kathleen England; Mozambique: Josefo Ferro; Helder Rassolo; Netherlands: Jan-Willem Coebergh, Esther de Vries, Peter Harteloh, Jan Kardaun; Sabine Siesling, Corina van der Hurk; Niger: Hassan Nouhou; Nigeria: M.I.A. Khalil, Olufemi Ogunbiyi; Norway: Freddie Bray, Grethe Westby; Poland: Lucyna Nowak, Witold Zatonski; Portugal: Jaime Bothelo; Romania: Anca Coricovac, Ioana Pertache; Russia: David Zaridze; Serbia: Snezana Zivkovic; Slovakia: Monika Dudova, Ivan Plesko; Slovenia: Maja Primic-Zakelj, Jozica Selb; Spain: Luis de Andrés Ramos, Isabel Izarzugaza; Sweden: Shiva Ayoubi, C Bjorkenstam, Joakim Dillner, Lars Egevad, Lars Age Johansson, Mats Lambe, Nils Wilking; Switzerland: Christoph Junker, Jean-Michel Lutz, Doris MaFat, Pierre Pury, Robert Jakob; United Kingdom: Frank Dixon, Gillian Fegan, Anna Gavin, Myer Glickman, Henrik Møller, Naomi O'Neill, Max Parkin, Mike Quinn, Chris Robertson, Claire Watson; USA: Brenda Edwards, April Fritz, Branka Legetic, Joe Harford, Christina Smith, Vivien Tsu, Tongzhang Zheng; Zimbabwe: Margaret Borok, Eric Chokunonga

### Financial support from the following bodies is gratefully acknowledged:

Canceropôle Lyon, Auvergne, Rhône-Alpes (CLARA)  
Centers for Disease Control and Prevention, USA (CDC)  
European Commission (DG-SANCO)  
International Atomic Energy Agency (PACT)  
Programme for Appropriate Technology in Health (PATH)  
National Cancer Institute, USA (NCI)

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# IARC MONOGRAPHS

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THE FIRST STEP IN CANCER PREVENTION IS TO IDENTIFY THE CAUSES OF HUMAN CANCER. THE *IARC MONOGRAPHS* ARE A SERIES OF SCIENTIFIC REVIEWS THAT IDENTIFY ENVIRONMENTAL FACTORS THAT CAN INCREASE THE RISK OF CANCER IN HUMANS.

Each *Monograph* includes a critical review of the pertinent scientific studies on a known or suspected carcinogen, followed by an evaluation of the overall weight of the evidence that the agent can alter the risk of cancer in humans. It is written by an international, interdisciplinary Working Group of expert scientists. Since 1971, *Monographs* have been developed for more than 900 agents, 400 of which have been identified as carcinogenic, probably *carcinogenic*, or *possibly carcinogenic* to humans. These include chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and personal habits and household exposures.

The *IARC Monographs* are a worldwide endeavour that has involved more than 1200 scientists from 53 countries. The *Monographs* are unique in that the critical reviews and evaluations are developed by experts who conducted the original research.

National and international health agencies use the *Monographs* as a source of scientific information on known or suspected carcinogens and as scientific support for their actions to prevent exposure to these agents. Individuals, too, use the information and conclusions from the *Monographs* to make better choices that reduce their exposure to potential carcinogens and their risk of developing cancer. In this way, the *IARC Monographs* contribute to cancer prevention and the improvement of public health. The 2008–2009 biennium saw the publication of Volume 97 of the

*Monographs*, *1,3-Butadiene*, *Ethylene Oxide*, and *Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide)*.

## UPDATING THE ASSESSMENTS OF HUMAN CARCINOGENS

The programme's principal activity during the 2008–2009 biennium has been a special review of known human carcinogens, which will be published as Volume 100 of the *IARC Monographs*. This volume is updating IARC's assessments of the more than 100 agents that had been classified as *carcinogenic to humans* (Group 1) in Volumes 1–99. This volume is being developed in six parts that span the diversity of carcinogenic agents:

- A. *Pharmaceuticals* (Oct 2008)
- B. *Biological Agents* (Feb 2009)
- C. *Metals, Arsenic, Dusts and Fibres* (Mar 2009)
- D. *Radiation* (June 2009)
- E. *Personal Habits and Household Exposures* (Sept 2009)
- F. *Chemical Agents and Related Occupations* (Oct 2009)

Volume 100 has shown that there is stronger evidence of carcinogenicity for most of these agents, identified some new human carcinogens (Table 1) and extended earlier findings to include additional target sites. For example, estrogen-only menopausal therapy is now causally associated with ovarian cancer, asbestos is also causally associated with ovarian cancer, hepatitis C virus with non-Hodgkin lymphoma, formaldehyde with leukaemia, ultraviolet-emitting tanning devices with ocular melanoma,

**Table 1. Human carcinogens that were newly identified in Volume 100**

<i>Pharmaceuticals</i>
- Aristolochic acid
- Etoposide
- Phenacetin
<i>Biological Agents</i>
- Kaposi sarcoma herpes virus
- <i>Clonorchis sinensis</i>
<i>Dusts</i>
- Leather dust
<i>Radiation</i>
- Ultraviolet radiation (including UVA, UVB, UVC)
- Ultraviolet-emitting tanning devices
<i>Personal Habits and Household Exposures</i>
- Acetaldehyde associated with alcohol consumption
<i>Chemical Agents</i>
- 3,3',4,4',5-Pentachlorobiphenyl (PCB-126)
- 2,3,4,7,8-Pentachlorodibenzofuran

welding with ocular melanoma, and parental smoking with hepatoblastoma in the smokers' children, among many other similar findings.

Volume 100 is highlighting the contribution of mechanistic information to the identification of carcinogenic agents. Some examples:

**Aristolochic acid:** within 6 years after plants of the genus *Aristolochia* were classified as carcinogenic, mechanistic studies were able to attribute this risk to aristolochic acid, which could lead to a practical means of testing herbal preparations for this cancer hazard.

**Formaldehyde:** Within 5 years after the previous *Monograph* on formaldehyde, mechanistic studies have replaced previous assertions of biological implausibility with new evidence that formaldehyde can cause blood-cell abnormalities that are consistent with leukaemia development.

**Alcohol consumption:** Genetic epidemiology studies provided evidence that alcohol consumption poses particularly high risks of oesophageal and other cancers based on a genetic polymorphism of metabolic activity that occurs in a large proportion of people of eastern

Asian origin.

In addition, epidemiological studies recently confirmed the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin, which was classified in 1997 as *carcinogenic to humans* based on mechanistic information. This shows that mechanistic studies can provide robust evidence of carcinogenicity without waiting for the observation of tumours in exposed humans.

Volume 100 continues the international character of the *Monographs*. The experts who participated in its development numbered 160 scientists from 28 countries (Table 2). More importantly, these *Monographs* addressed several carcinogenic hazards that disproportionately affect developing countries. Some examples:

**Hepatitis B and C viruses:** these infect a half-billion people, mostly in Asia and Africa, and lead to high rates of liver cancer in these areas.

**Aflatoxins:** these fungal toxins are prevalent in humid tropical areas and cause liver cancer, particularly in people infected with hepatitis B virus.

**Parasitic infections:** *Schistosoma*

*haematobium*, endemic in Africa and the eastern Mediterranean region, causes urinary bladder cancer; some liver flukes endemic in southeastern Asia cause cholangiocarcinoma.

**Areca nut:** chewed by 600 million people in southeastern Asia, especially India, and responsible for high incidences of cancers of the oral cavity and oesophagus in those areas.

**Smokeless tobacco:** used by hundreds of millions of people in southeastern Asia and responsible for cancers of the oral cavity, oesophagus, and pancreas.

**Household use of coal:** use of solid fuels for cooking and heating is highly prevalent in many developing countries and causes high rates of lung cancer, including in nonsmokers.

**Table 2. Country of affiliation of the experts for Volume 100**

Australia	5
Belgium	1
Brazil	1
Canada	7
China	2
Costa Rica	1
Czech Republic	1
Denmark	4
Finland	7
France	7
Germany	10
India	3
Iran	1
Italy	5
Japan	5
Mexico	1
Netherlands	1
New Zealand	1
Norway	2
Portugal	1
Republic of Korea	2
Russian Federation	1
South Africa	1
Spain	3
Sweden	2
Thailand	1
United Kingdom	13
USA	71
<i>Total</i>	<i>160</i>

In the future, cancer assessments will increasingly rely on molecular epidemiology and on information about mechanisms of carcinogenesis. To this end, Volume 100 is summarising currently available information on the multiple mechanisms of carcinogenesis for the agents known to cause cancer in humans. This will provide insight into how other agents might cause cancer in humans and will be particularly useful in future assessments of new and untested chemicals, for which 2-year bioassays and epidemiological studies of cancer are unlikely to be available. The *Monographs* developed for Volume 100 will provide information that will be synthesised in two future IARC Scientific Publications: *Tumour Concordance between Animals and Humans* and *Mechanisms Involved in Human Carcinogenesis*. These scientific publications will be initiated during the 2010–2011 biennium, after the results of Volume 100 have been published.

#### PRIORITIES FOR FUTURE IARC MONOGRAPHS

In June 2008 IARC convened an Advisory Group to identify high priorities for new *IARC Monographs* during the next 5 years. Before the Advisory Group met, IARC solicited nominations from the scientific community and the general public via the Internet. Seeking such input is meant to ensure that new *Monographs* reflect current research and public health priorities. Most of the Advisory Group's recommendations (Table 3) are new topics that have never before been reviewed by IARC or by other public health agencies. This indicates a high level of interest in the continued work of the *IARC Monographs* to provide authoritative evaluations of new or previously established cancer hazards.

In addition, other topics will be scheduled as significant new scientific information becomes available or as national health agencies identify an urgent public health need. Some additional topics (Table 3) have already arisen from discussions during the expert meetings for Volume 100.

**Table 3. High priorities for future *IARC Monographs***

<p><i>Most pressing priorities from the Advisory Group</i></p> <ul style="list-style-type: none"> <li>*Radiofrequency electromagnetic fields and radar (includes mobile telephones)</li> <li>Motor vehicle emissions (includes diesel, gasoline, biofuel exhausts)</li> <li>*Polyomaviruses (SV40, BK, JC, Merkel cell virus)</li> <li>Asphalt/bitumen</li> <li>Acrylamide, furan</li> </ul> <p><i>Other high priorities from the Advisory Group</i></p> <ul style="list-style-type: none"> <li>Acetaldehyde</li> <li>*Carbon-based nanoparticles</li> <li>*Crystalline fibres other than asbestos</li> <li>*Growth hormone</li> <li>*Iron and iron oxides</li> <li>*Malaria</li> <li>Nucleoside-analogue antiviral drugs</li> <li>*Outdoor air pollution (includes sulfur oxides, nitrogen oxides, ozone, dusts)</li> <li>*Perfluorooctanoic acid (PFOA) and other perfluorinated compounds</li> <li>*Sedentary work</li> <li>*Statins</li> <li>*Stress</li> <li>Testosterone and other androgenic steroids</li> <li>*Ultrafine particles</li> <li>Welding</li> <li>Some agents recently tested in experimental animals</li> </ul> <p><i>Additional high priorities arising from Volume 100</i></p> <ul style="list-style-type: none"> <li>Benzene</li> <li>Nickel metal</li> <li>Polyhalogenated dibenzo-para-dioxins, dibenzofurans, and biphenyls</li> </ul>
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\*Never before reviewed by IARC



## PUBLICATIONS

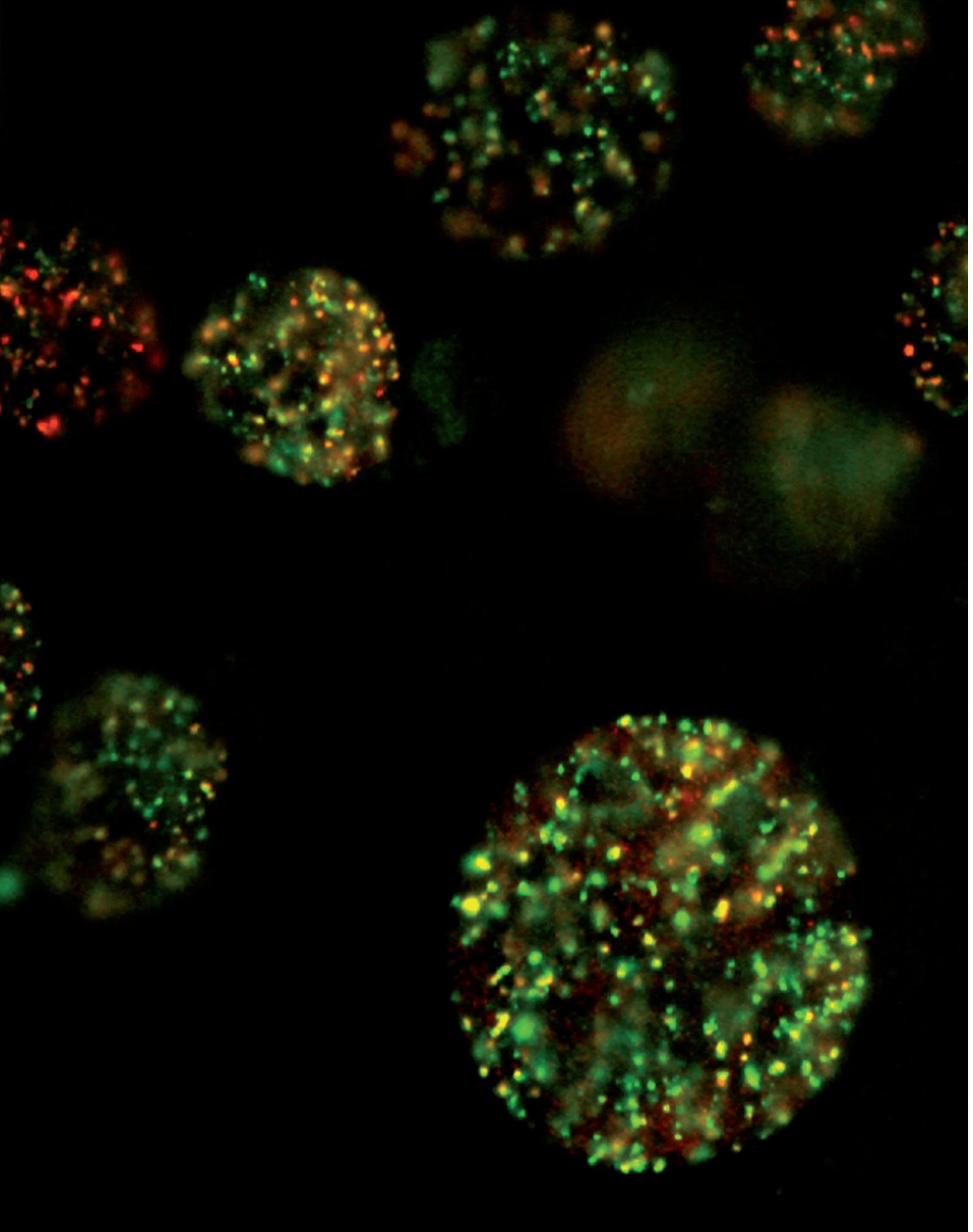
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# SECTION OF MECHANISMS OF CARCINOGENESIS (MCA)

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THE OVERALL AIM OF THE SECTION IS TO CONTRIBUTE TO CANCER PREVENTION AND CONTROL THROUGH A BETTER UNDERSTANDING OF MECHANISMS OF CARCINOGENESIS. THIS INCLUDES INVESTIGATING INTERACTIONS BETWEEN THE ENVIRONMENT, THE GENOME AND THE EPIGENOME. MOST OF THE SECTION'S WORK INVOLVES TRANSLATIONAL STUDIES ON BIOMARKERS OF EFFECTS OF ENVIRONMENTAL EXPOSURES AND BIOMARKERS OF EARLY CANCER, FOCUSING ON CANCERS COMMON IN LOW-RESOURCE COUNTRIES, SUCH AS HEPATOCELLULAR CARCINOMA (HCC), SQUAMOUS CELL CARCINOMA OF THE AERO-DIGESTIVE TRACT (SCC) AND BREAST CANCER.

Highlights of the Section's work during this biennium include (1) the development of techniques and processes that allow the application of multi-loci mutation and epigenetic studies to large, molecular pathology and molecular epidemiology studies; (2) novel lines of mechanistic research on the contribution of TP53 mutations to specific cancers (lung, breast, liver) and on the molecular basis of epigenetic regulation of stem cells, based on the use of elaborated *in vitro* cell culture systems; (3) the development and coordination of an international consortium on liver cancer (International Liver Cancer Study, <http://ilcs.iarc.fr/>); and (4) further studies on the coordination of molecular databases, including further development of the IARC TP53 database (<http://www-p53.iarc.fr>) and establishment of a pilot for an international cancer epigenetics database. The Section has also carried out the development and management of a large biobanking infrastructure at IARC that has gained international recognition, in particular through the publication of Guidelines and Standard Protocols now recognised as a worldwide standard for biobanks.



# EPIGENETICS GROUP (EGE)

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## EPIGENETICS: AN EMERGING FIELD IN MOLECULAR CARCINOGENESIS

The field of cancer epigenetics has become increasingly "mainstream", as it promises to further advance our understanding of the etiology of human cancer and mechanisms of carcinogenesis, and to facilitate the development of novel strategies for cancer detection, treatment and prevention. The intrinsic reversibility and ubiquity of epigenetic changes in virtually all types of human cancer make them attractive subjects for biomarker discovery and strategies for cancer prevention. The Epigenetics Group (EGE) conducts both mechanistic studies and epigenetic profiling, aiming to gain a better mechanistic understanding of tumourigenesis and to discover and validate new epigenetic biomarkers. This programme exploits new concepts in cancer epigenetics and recent technological advances in epigenetics and epigenomics, and is carried out in close collaboration with IARC laboratory scientists and epidemiologists as well as external groups. EGE activities can be divided broadly into three major areas: (1) studies aiming to elucidate the role of epigenetic changes induced by major risk factors in specific human cancers, (2) studies aiming to investigate epigenetic changes for the mechanistic understanding of cancer development and progression, and (3) studies aiming to discover and validate new epigenetic biomarkers.

## DNA METHYLATION CHANGES IN LUNG CANCER AND THEIR ASSOCIATION WITH ENVIRONMENTAL RISK FACTORS

We have applied quantitative profiling of DNA methylation in a large panel of cancer-associated genes in a case-control study of lung cancer. Our analyses revealed a high frequency of aberrant hypermethylation of MTHFR, RASSF1A and CDKN2A in lung tumours as compared to control blood samples, whereas no significant increase in methylation levels of GSTP1 and CDH1 was observed, consistent with the notion that aberrant DNA methylation occurs in a tumour-specific and gene-specific manner (Vaissière *et al.*, 2009a). Importantly, tobacco smoking, sex, and alcohol intake had a strong influence on the methylation levels of distinct genes (RASSF1A and MTHFR), whereas folate intake, age and histological subtype had no significant effect. We observed a strong association between MTHFR hypermethylation in lung cancer and tobacco smoking, whereas methylation levels of CDH1, CDKN2A, GSTP1 and RASSF1A were not associated with smoking, indicating that tobacco smoke targets specific genes for hypermethylation. We also found that methylation levels in RASSF1A, but not the other genes under study, were influenced by sex, with males showing higher levels of methylation. This study identifies aberrant DNA methylation patterns in lung cancer and thus exemplifies the mechanism by which environmental factors may interact with key genes involved in tumour suppression and contribute to lung cancer (Vaissière *et al.*, 2009a).

## METHYLOME ANALYSIS REVEALS DEREGLATION OF SPECIFIC PATHWAYS IN PUTATIVE BREAST CANCER STEM CELLS AND HUMAN SPORADIC BREAST TUMOURS

Growing evidence supports the existence of a subpopulation of cancer cells with stem cell characteristics within breast tumours. We used the mammosphere model combined with DNA methylation bead arrays to characterise the epigenetic mechanisms involved in the regulation of developmental pathways in putative breast cancer stem cells. Our results revealed that these cells exhibit distinct CpG promoter methylation

profiles in a specific set of genes, including those involved in Jak-STAT and T-cell receptor signalling pathways. Remarkably, aberrant methylation of Jak-STAT pathway gene promoters was also observed in human breast cancer samples relative to its matching surrounding tissue, and hypermethylation in tumours was consistently correlated with reduced gene expression of Jak-STAT-related transcripts. These results favour the concept that the expression of cancer stem-like pathways and the establishment and maintenance of the defining properties of cancer stem cells are orchestrated by epigenetic mechanisms (Hernandez *et al.*, submitted).

## DNA METHYLATION PROFILES AS POTENTIAL BIOMARKERS IN HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is a malignancy characterised by late detection and fast progression, and epigenetic disruption may be the cause of molecular and clinicopathological distinction of subsets of HCC tumours. To further investigate this possibility, we characterised the changes in promoter methylation in a series of HCC tumours and their respective surrounding tissue. A wide panel of cancer-related gene promoters (1505 CpG sites in 807 gene promoters) was analysed using bead array technology (in collaboration with Florence Le Calvez-Kelm [GEN/GCS] and Sean Tavtigian [GEN/GCS]), and CpG sites were selected according to their ability to classify clinicopathological parameters. An independent series of HCC tumours and matched surrounding tissue was used for validation of the signatures. We identified a signature that distinguished HCC from surrounding tissue and from other tumour types. Differentially methylated promoters were significantly enriched in the Wnt, TGF- $\beta$ , Hedgehog and Notch signalling pathways. The results also revealed a set of genes aberrantly methylated in HCC, including imprinted genes. In addition, methylation of an independent panel of gene promoters was strongly correlated with survival after cancer therapy (Hernandez Vargas *et al.*, 2009b, submitted).

## EPIGENETIC MECHANISMS IN CONTROL OF CRITICAL CELLULAR PROCESSES AND TUMOURIGENESIS

While it is well established that aberrant epigenetic events can cause incorrect gene activation and improper gene silencing, recent evidence argues that deregulated epigenetic states may contribute to cancer development by compromising other critical cellular processes such as DNA repair, replication, cell cycle, and stem cell features ("stemness"). We have discovered a novel mechanism for ubiquitination of b-Catenin, the central player in the canonical Wnt pathway that is frequently deregulated in human cancers (Finkbeiner *et al.*, 2008). The Wnt pathway is a key regulator of embryonic development and stem cell self-renewal, and hyperactivation of Wnt/b-Catenin signalling is associated with many human cancers. We found a new mechanism of b-Catenin ubiquitination acting in the context of chromatin, which is mediated by the histone acetyltransferase (HAT) complex component TRRAP and Skp1, an invariable component of the Skp-Cullin-F-box (SCF) ubiquitin ligase complex. Our results demonstrate that there is a distinct regulatory mechanism for b-Catenin ubiquitination/destruction acting in the nucleus that functionally complements cytoplasmic destruction of b-Catenin and prevents oncogenic stabilisation of b-Catenin and chronic activation of the canonical Wnt pathway (Finkbeiner *et al.*, 2008).

In another study, we have identified a role for HATs in the mechanism that balances self-renewal and differentiation of embryonic stem cells (ESC) and adult stem cells (hematopoietic stem cells, HSC). Conditional deletion of TRRAP in mice resulted in unscheduled differentiation of these cells as judged by morphological, biochemical and gene markers. TRRAP-deficient mouse stem cells showed a loss of histone acetylation to be associated with condensation of chromatin into distinct foci (heterochromatization), loss of hyperdynamic properties of chromatin, and uncoupling of H3K4-dimethylation and H3K27-trimethylation, markers believed to be important in the establishment of the bivalent chromatin domains in stem cells. These findings establish histone acetylation and HATs

as a part of common mechanisms that restrict differentiation and promote the maintenance of embryonic and adult stem identity (self-renewal and pluripotency), and underscore the importance of histone modifications and chromatin signature in the control of “stemness” and differentiation fates (Loizou *et al.*, Journal of Immunology, 2009, in press).

#### DEVELOPMENT OF EPIGENETIC METHODS APPLICABLE TO LARGE-SCALE EPIDEMIOLOGY STUDIES

Cell-free circulating DNA isolated from the plasma of individuals with cancer has been shown to harbour cancer-associated changes in DNA methylation, and thus represents an attractive target for biomarker discovery. We have developed a novel combination of methods that allows quantitative and sensitive detection of DNA methylation in minute amounts of DNA present in body fluids (**quantitative Methylation Analysis of Minute DNA amounts after whole Bisulfite Amplification, qMAMBA**) (Vaissière *et al.*, 2009b). This method involves genome-wide amplification of bisulphite-modified DNA template followed by quantitative methylation detection using pyrosequencing, and allows analysis of multiple genes from a small amount of starting DNA. qMAMBA offered high efficacy in the analysis of methylation levels and patterns in plasma samples with extremely small amounts of DNA and low concentrations of methylated alleles. Therefore, qMAMBA will facilitate methylation studies aiming to discover epigenetic biomarkers, and should prove particularly valuable in profiling a large sample series of body fluids from molecular epidemiology studies as well as in tracking disease in early diagnostics (Vaissière *et al.*, 2009b).

#### The EGE Group is grateful to the following persons for their collaboration in its projects:

Carlo Croce, Columbus, USA; Bruno Amati, Milan, Italy; Laszlo Tora, Strasbourg, France; Zhao-Qi Wang, Jenna, Germany; Thomas Jenuwein, Vienna, Austria; Saadi Khochbin, Grenoble, France; Claire Vourc'h, Grenoble, France; Eric Gilson, Lyon, France; Claude Sardet, Montpellier, France; Eric Julien, Montpellier, France; Christian Trepo, Lyon, France; Isabelle Chemin, Lyon, France; Jorg Tost, Paris, France; Jean-Pierre Issa, Houston, USA; Paolo Vineis, London, UK; Carlos Gonzalez, Barcelona, Spain; Vivek Shukla, Bethesda, USA; Ahmed Amine Khamlichi, Toulouse, France; Jean-Yves Scoazec, Lyon, France; Mark Billaud, Lyon, France; Alain Puisieux, Lyon, France; Qing Wang, Lyon France; Caroline Moyret-Lalle, Lyon, France; Caroline Relton, Newcastle, UK; Felipe Pinto, Rio de Janeiro, Brazil; Chantal Matar, Monton, Canada; Andreas Trumpp, Heidelberg, Germany; Gabriella Oser, Basel, Switzerland; Floriana Bulic-Jakus, Zagreb, Croatia; Maja Vlahovic, Zagreb, Croatia; Rafael Casellas, Bethesda, USA

#### Financial support from the following bodies is gratefully acknowledged:

National Institutes of Health/National Cancer Institute (NIH/NCI), USA  
Institut National du Cancer, France  
Agence nationale de recherches sur le sida et les hépatites virales, France  
Association pour la Recherche sur le Cancer (ARC), France  
Ligue Nationale (Française) Contre le Cancer, France  
European Commission  
Ligue Nationale Contre le Cancer, Comité du Rhône, France  
Ligue Nationale Contre le Cancer, Comité de Saône-et-Loire, France  
Ligue Nationale Contre le Cancer, Comité de la Loire, France  
European Molecular Biology Organisation (EMBO)  
Swiss Bridge Award

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MUTATIONS IN CANCER-RELATED GENES ARE THE CORNERSTONE OF CARCINOGENESIS. WHILE MANY MUTATIONS ACCUMULATE DURING TUMOUR PROGRESSION, SOME OF THEM MAY OCCUR IN NORMAL CELLS AS THE RESULT OF IMPROPER DNA REPAIR PROCESSES OR EXPOSURE TO ENVIRONMENTAL MUTAGENS. THE MOST FREQUENTLY AND MOST DIVERSELY MUTATED GENE IN HUMAN CANCER IS TP53, ENCODING AN ALL-ROUND TUMOUR SUPPRESSOR THAT CONTROLS CELL PROLIFERATION, APOPTOSIS, DNA REPAIR AND SENESCENCE (HAINAUT AND WIMAN, 2009). STUDIES IN THE MOC GROUP ADDRESS THE ROLE OF TP53 MUTATIONS AS MARKERS OF EXPOSURE TO MUTAGENS AND AS BIOMARKERS FOR TUMOUR PROGRESSION, PROGNOSIS AND RESPONSE TO THERAPY. MOST OF THE WORK FOCUSES ON COMMON CANCERS (BREAST, LUNG) AND IN PARTICULAR ON CANCERS THAT SHOW WIDE GEOGRAPHIC VARIATIONS IN INCIDENCE AND ETIOLOGICAL MECHANISMS (LIVER, OESOPHAGUS). EXPERIMENTAL LABORATORY STUDIES ARE CARRIED OUT TO UNDERSTAND THE MECHANISTIC BASIS OF MUTANT P53 CONTRIBUTION TO CARCINOGENESIS AND TO ELUCIDATE NEW POTENTIAL MECHANISMS THAT REGULATE P53 FUNCTION.

#### SOMATIC TP53 MUTATIONS AND ROLE OF P53 IN MECHANISMS OF CARCINOGENESIS

Studies on TP53 mutations have focused on cancers of the breast, lung, oesophagus and liver. In breast cancer, we further assessed the value of TP53 mutations as independent prognostic markers (Zalcman et al., 2008). Using cultured breast cancer cells, we have shown that cells with mutant TP53 have altered responses to estrogens and anti-estrogenic drugs, providing a biological basis for the previously reported observation of an interaction between TP53 and hormone receptor status (Fernandez et al., submitted). In lung cancers, following our previous studies on the correlations between EGFR or HER2 mutations and TP53 mutations in never-smokers, we further characterised the specific pathological and molecular profiles of cancers in never-smokers (Aranda et al., 2007; Clement-Duchene et al., 2009; Paris et al., 2009). The prognosis/predictive value of TP53 mutations was investigated in 783 patients of the International Adjuvant Lung Cancer Trial (IALT). TP53 mutations predicted response to therapy, with a significant trend toward benefit in patients with wild-type TP53 and toward worse prognosis in patients with mutant TP53 (P for interaction: 0.05) (Ma et al., submitted;

Stacher et al., submitted). In oesophageal cancer, we have investigated patterns of TP53 mutations in relation to expression of inducible nitric oxide synthase (NOS2) and accumulation of nitrotyrosine in patients with gastroesophageal reflux disease (GERD), Barrett's oesophagus or primary ADC. Our results show a correlation between elevated levels of inflammation markers and TP53 mutations at CpG dinucleotides (83% vs. 11%;  $P=0.008$ ), providing further evidence for a link between chronic inflammation and oesophageal malignancy (Vaninetti et al., 2008). Additional studies identified an association between p53 functional status and expression of a novel, interferon-inducible gene, GBP2, in squamous cell carcinomas (Duarte et al., 2009; Guimaraes et al., 2009). We also investigated the effect of bile acids on the expression of differentiation markers in normal oesophageal mucosa. We found that this treatment induces rapid proteasome-dependent degradation of p63, a protein required for the formation of squamous epithelium. Additional studies using RNA interference demonstrated that loss of p63 induces a major change in cell adhesion patterns, providing a molecular mechanism for initial steps in the formation of intestinal metaplasia in response to GERD (Thépot et al., submitted).

In liver cancer, in collaboration with Gerd Pfeifer (Duarte, CA) we further assessed the mechanisms of TP53 mutagenesis by aflatoxin (Besaratnia et al., 2009) and analysed the significance of p.R249S TP53 mutation in the plasma of chronic HBV carriers from Egypt, Nigeria, Gambia and China (Hosny et al., 2008; Igetei et al., 2008; Kuniholm et al., 2008; Szymanska et al., 2009). In a cohort from China, we found that the mutation was detectable ahead of cancer diagnosis in a subset of subjects (Szymanska et al., 2009). Using cell line model systems, we showed that the candidate therapeutic drug PRIMA1 could at least partially reactivate the suppressive function of p.R249S, suggesting a possible mechanism for intervention in patients carrying this mutation (Gouas et al., 2009; Shi et al., 2008). In collaboration with Klas Wiman (Stockholm, Sweden), we demonstrated that PRIMA1 operates through a redox-dependent mechanism of action (Bykov et al., 2009; Lambert et al., 2009). Overall, our work on liver cancer contributed to a better understanding of the interplay between risk factors and viral infections, and may have useful application in preventive interventions (Pujol et al., 2009; Viviani et al., 2008; Hainaut and Boyle, 2008; Pujol et al., 2009).

#### GERMLINE TP53 MUTATIONS AND LI-FRAUMENI SYNDROME

Li-Fraumeni Syndrome is a complex familial predisposition to multiple early cancers. We found that this syndrome was more common than previously recognised (Palmero et al., in press). In collaboration with Maria Isabel Waddington Achatz (Sao Paulo) and Patricia Ashton Prolla (Porto Alegre, Brazil), we developed studies of specific inherited (germline) TP53 mutations in

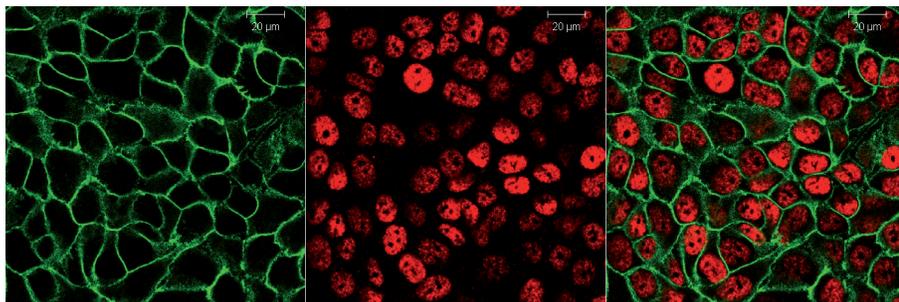


Figure 1. Immunofluorescent staining for the cell adhesion molecule p-Cadherin (green, left), for the differentiation protein p63 (red, center) and for both (right) in cultured human oesophageal cancer cells



**Figure 2. A gathering of subjects from cancer prone families, proudly showing their familial tree spanning 8 generations**



**Figure 3. TP53 R337H mutation and Newborn screening**

Presence of a common TP53 mutation in 0.3% of the population of South Brazil has led to questions about whether it was appropriate to screen newborns for this mutation in order to better detect subjects at high risk of cancer. Studies by IARC and collaborators have argued against this approach, considering that there is not enough evidence to predict the risk of cancer over lifetime. Childhood predictive genetic testing for R337H should not be carried out in mass screening programs, although it may represent a suitable approach in some families, on a case-by-case basis and within counseling and follow-up strategies that take into account the wide diversity of tumour patterns in mutation carriers

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Southern Brazil (Palmero et al., 2008). Together with Sean Tavtigian (GCS) and Stephano Landi and Raphaela Gemignani (Pisa, Italy), we generated a fine haplotype map of TP53 and used it to demonstrate a frequent founder mutation, p.R337H (Garritano et al., in press). This mutant carries a lifetime risk of cancer of 70% at age 60 and is predicted to cause up to 2000–3000

annual cancers currently not identified as familial in Brazil, potentially identifying an opportunity for cancer risk detection via genetic screening of newborns in this area (Achatz et al., 2009). Two genetic modifiers were identified, including an already known polymorphism in MDM2 promoter (SNP309), and an intragenic TP53 polymorphism in intron 3. The latter modulates the age of cancer onset

by, on average, 20 years (Marcel et al., 2009). *In vitro* studies demonstrated that this polymorphism modifies the structure of a secondary motif in p53 mRNA and regulates p53 alternative splicing, thus generating different levels of p53 isoforms. These isoforms appear to act as potential inhibitors of p53 function, suggesting a novel genetic mechanism of regulation of p53 activity (Hall et al., 2009; Marcel and Hainaut, 2009).

#### TP53 MUTATION DATABASE

The IARC TP53 Database (<http://www-p53.iarc.fr/>) is a popular web resource that has been maintained at IARC since 1994. It is both a research and educational tool that contains information and data related to TP53 gene variations in human cancers. The aim of the database is to provide data and tools that may be used to characterise the impact and phenotypes of TP53 mutations in human cancers. Available data and annotations include TP53 mutation frequency, spectrum, phenotype and biological activities of mutant proteins. Data are compiled from the peer-reviewed literature and other online databases. Over the last two years, several developments have been made, including the addition of new annotations on the predicted effect of mutations on splicing and on the production of altered p53 isoforms. We have also been actively promoting the use of standards for database annotations by publishing guidelines for improving mutation data collection, distribution and integration (Olivier et al., 2009b). Within a FP6 European network project on mutant p53 (<http://www.mutp53.com/>) that has supported the database for the last 5 years, we have organized a series of International workshops on mutant p53, the most recent one being held in Israel (4<sup>th</sup> International workshop on mutant p53, <http://www-p53.iarc.fr/P53meeting2009/P53meeting2009.html>). A review on 'Recent advances in p53 research' based on new findings presented at the 3<sup>rd</sup> workshop was published in 2008 (Olivier et al., 2009a).

## The MOC Group is grateful to the following persons for their collaboration in its projects:

Gerd Pfeifer, Duarte, CA, USA; Isabelle Chemin, Lyon, France; Laura Beretta, Seattle, WA, USA; Gerard Zalzman, Caen, France; Jean Charles Soria, Villejuif, France; Christophe Paris, Nancy, France; Elisabeth and Christian Brambilla, Grenoble, France; Philippe Merle, Lyon, France; Moshe Oren, Rehovot, Israel; Varda Rotter, Rehovot, Israel; Claude Caron de Fromentel, Lyon, France; Maria Isabel Achatz, Sao Paulo, Brazil; Patricia Ashton Prolla, Porte Alegre, Brazil; Klas Wiman, Stockholm, Sweden; Alan Casson, Saskatoon, SK, Canada; Mark Lathrop, Paris, France; Hany Ariffin, Kuala Lumpur, Malaysia; Gihan Hosny, Alexandria, Egypt; Flor Pujol, Caracas, Venezuela; Maria Christina Navas, Medellin, Colombia; Reza Malekzadeh, Tehran, Iran; Sandy Dawsey, Bethesda, MD, USA; Richard Cotton, Victoria, Australia

## Financial support from the following bodies is gratefully acknowledged:

Association for International Cancer Research, UK  
Agence nationale de recherches sur le sida et les hépatites virales, France  
Cancéropôle-CLARA, France  
European Commission  
ECOS-Nord, France  
INCA, France  
Ligue Nationale Contre le Cancer, Comité de Saône-et-Loire, France  
Ligue Nationale Contre le Cancer, Comité de Savoie, France  
Ligue Nationale Contre le Cancer, Comité du Rhône, France  
Ligue Nationale Contre le Cancer, Comité de la Drôme, France  
National Cancer Institute, USA

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# SECTION OF MOLECULAR PATHOLOGY (MPA)

**Section Head**  
Dr Hiroko Ohgaki

THE SECTION OF MOLECULAR PATHOLOGY STUDIES THE MOLECULAR BASIS OF HUMAN NEOPLASMS, IN PARTICULAR BRAIN TUMOURS, USING TUMOUR SAMPLES FROM PATIENTS WITH EXCELLENT CLINICAL DATA AND FOLLOW-UP. WE CORRELATE HISTOLOGICALLY RECOGNISED PHENOTYPES WITH GENOTYPES AND EXPRESSION PROFILES, WITH THE OBJECTIVES OF ELUCIDATING THE MOLECULAR BASIS AND GENETIC PATHWAYS THAT ARE OPERATIVE IN HUMAN NEOPLASMS; IDENTIFYING MOLECULAR MARKERS FOR IMPROVEMENT OF TUMOUR DIAGNOSES AND CLASSIFICATION; IDENTIFYING GENETIC FACTORS THAT PREDICT SENSITIVITY TO TREATMENT, TUMOUR PROGRESSION AND PATIENT OUTCOME; AND USING GENETIC DATA TO IDENTIFY THE ETIOLOGY OF HUMAN CANCERS. SINCE 2006, THE SECTION OF MOLECULAR PATHOLOGY HAS ALSO BEEN RESPONSIBLE FOR THE 4<sup>TH</sup> EDITION OF THE WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF TUMOURS SERIES (WHO BLUE BOOKS). THE SECOND VOLUME, WHO CLASSIFICATION OF TUMOURS OF THE HAEMATOPOIETIC AND LYMPHOID TISSUES, WAS PUBLISHED IN 2008, AND THE THIRD VOLUME (WHO CLASSIFICATION OF TUMOURS OF THE DIGESTIVE SYSTEM) IS IN THE EDITING STAGES.

In its current configuration the Section consists of a single Group, the Molecular Pathology Group (MPA), with the objectives stated above. A few of its more important projects over the Biennium are detailed below.



# MOLECULAR PATHOLOGY GROUP

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## *IDH1* MUTATIONS AS MOLECULAR SIGNATURE AND PREDICTIVE FACTOR OF SECONDARY GLIOBLASTOMAS AND AS EARLY EVENTS IN THE DEVELOPMENT OF ASTROCYTOMAS AND OLIGODENDROGLIOMAS

*IDH1* encodes isocitrate dehydrogenase 1, which participates in the citric acid cycle and was first reported to be mutated in a study of sequencing >20 000 protein coding genes (Parsons *et al.* Science. 321:1807-1812 2008). We assessed *IDH1* mutations in 321 gliomas of various histological types and biological behavior. A total of 130 *IDH1* mutations were detected, all located at codon 132; 91% of these were G->A mutations (R132H). *IDH1* mutations were frequent in low-grade diffuse astrocytomas (88%) and in secondary glioblastomas that developed through progression from low-grade diffuse or anaplastic astrocytoma (82%). Similarly high frequencies of *IDH1* mutations were found in oligodendrogliomas (79%) and oligoastrocytomas (94%). Analysis of multiple biopsies from the same patient (51 cases) showed that there was no case in which an *IDH1* mutation occurred after acquisition of a *TP53* mutation or loss of 1p/19q, suggesting that *IDH1* mutations are very early events in gliomagenesis and may affect a common glial precursor cell population. *IDH1* mutations were co-present with *TP53* mutations in 63% of low-grade diffuse astrocytomas, and with LOH 1p/19q in 64% of oligodendrogliomas. They were rare in pilocytic astrocytomas (10%) and primary glioblastomas (5%), and absent in ependymomas.

Our analyses of *IDH1* mutations in glioblastomas from a population-based study (407 cases) showed that approx. 9% of all glioblastomas in a population contain *IDH1* mutations, and

that glioblastoma patients with *IDH1* mutations are significantly younger (mean 47.9 years) and show longer survival than those without *IDH1* mutations. *IDH1* mutations were frequent in glioblastomas diagnosed as secondary (22/30; 73%), but rare in primary glioblastomas (14/377; 3.7%;  $P < 0.0001$ ). *IDH1* mutations as genetic marker of secondary glioblastoma corresponded to the respective clinical diagnosis in 95% of cases. *IDH1* mutations are the therefore most reliable molecular marker of secondary glioblastomas available and should be used to complement clinical criteria to distinguish them from primary glioblastoma. The frequent presence of *IDH1* mutations in secondary glioblastomas and their almost complete absence in primary glioblastomas reinforces the concept that despite their histological similarity, these subtypes are genetically and clinically distinct entities.

We assessed *IDH1* mutations in brain tumors diagnosed in patients from 3 families with Li-Fraumeni syndrome. We identified *IDH1* mutations in 5 astrocytomas that developed in carriers of a *TP53* germline mutation. Without exception, all were R132C, which in sporadic astrocytomas accounts for <5% of *IDH1* mutations. This remarkably selective occurrence of R132C mutations may reflect differences in the sequence of genetic events, with a preference for R132C mutations in astrocytes or precursor cells that already carry a germline *TP53* mutation.

## ROLE OF MUTATIONS IN THE NIJMEGEN BREAKAGE SYNDROME GENE (*NBS1*) IN BRAIN TUMOURS

Nijmegen breakage syndrome, caused by *NBS1* germline mutations, is a rare autosomal recessive disease with clinical features that include microcephaly, increased radiosensitivity and predisposition to cancer. *NBS1* plays a key role in DNA double-strand break repair and the maintenance of genomic stability. There may be functional interactions between *NBS1* and the *TP53* pathways.

We assessed whether *NBS1* mutations play a role in the pathogenesis of sporadic medulloblastomas. Screening for mutations in the *NBS1* gene (all 16 exons) and the *TP53* gene (exons 5-8) revealed that 7 of 42 (17%) medulloblastomas carried a total of 15 *NBS1* mutations (10 missense point mutations and 5 intronic splicing mutations). Of five medulloblastomas with *TP53* mutations, four (80%) contained *NBS1* mutations, and there was a significant association between *TP53* mutations and *NBS1* mutations ( $P=0.001$ ), suggesting that medulloblastomas characterised by *NBS1* mutations typically associated with mutational inactivation of the *TP53* gene.

We also screened 87 glioblastomas for *NBS1* mutations, and showed 12 *NBS1* mutations (8 missense and 4 intronic mutations) in 9 of 28 (32%) primary (de novo) glioblastomas carrying two or more *TP53* mutations. In contrast, *NBS1* mutations were not detected in 19 primary glioblastomas with one *TP53* mutation, nor in 21 primary glioblastomas without *TP53* mutations. These results suggest that multiple *TP53* mutations in some glioblastomas are due to deficient repair of DNA double-strand breaks caused by mutational inactivation of the *NBS1* gene.

## PROMOTER METHYLATION AND POLYMORPHISMS OF THE *MGMT* GENE IN GLIOBLASTOMAS: A POPULATION-BASED STUDY

O<sup>6</sup>-Methylguanine-DNA methyltransferase (*MGMT*) is a repair enzyme that removes promutagenic

O<sup>6</sup>-methylguanine adducts in DNA in order to protect cells from acquisition of G:C→A:T mutations. *MGMT* promoter methylation and polymorphisms may affect *MGMT* expression and activity. We assessed *MGMT* promoter methylation and polymorphisms (Leu84Phe, Ile143Val, c.-56C>T) in 371 glioblastomas diagnosed at the population level. *MGMT* methylation was observed in 165 (44%) glioblastomas, with a higher frequency in females than males (53% vs. 39%;  $P=0.0106$ ), and in secondary than primary glioblastomas (73% vs. 43%,  $P=0.0074$ ). The frequency of *TP53* G:C→A:T mutations in glioblastomas with *MGMT* methylation was 25%, which was significantly higher than that in glioblastomas without *MGMT* methylation (16%;  $P=0.0385$ ). The *MGMT* 143 Val allele was significantly less frequent in glioblastomas than in a healthy European Caucasian population, and was associated with longer survival than those with the *MGMT* 143 Ile allele (hazard ratio 0.70; 95% CI=0.48-1.01). These results suggest that *MGMT* methylation may be associated with susceptibility to acquire *TP53* G:C→A:T mutations, and that *MGMT* polymorphisms may affect the risk and prognosis of glioblastomas.

## COMMON POLYMORPHISMS IN THE *MDM2* AND *TP53* GENES AND THE RELATIONSHIP BETWEEN *TP53* MUTATIONS AND PATIENT OUTCOMES IN GLIOBLASTOMAS

*MDM2* SNP309 is associated with a younger age of tumour onset in patients with Li-Fraumeni syndrome, and *TP53* codon 72 polymorphism decreases its apoptotic potential. Glioblastomas frequently show genetic alterations in the *TP53* pathway. We assessed *MDM2* SNP309 in 360 glioblastomas, and correlated these with patient age and survival, as well as other alterations in the *TP53* pathway. Frequencies of the *MDM2* SNP309 T/T, T/G and G/G genotypes in glioblastomas were 40%, 46% and 14%, respectively. Multivariate analysis showed that the *MDM2* SNP309 G/G allele was significantly associated with favourable outcome in female glioblastoma patients (hazard ratio 0.54; 95% CI=0.32–0.92). There was a significant association between *MDM2* SNP309 G alleles and *TP53* codon 72

Pro/Pro in glioblastomas. Glioblastoma patients with *TP53* codon 72 Pro/Pro genotype were significantly younger than Arg/Arg carriers (mean 50.2 vs. 56.1 years;  $P=0.018$ ). Multivariate analysis showed that those with *TP53* codon 72 Arg/Pro allele had significantly shorter survival than those with the Arg/Arg allele (hazard ratio 1.35; 95% CI=1.07–1.71). Detailed analyses revealed that the *TP53* codon 72 Pro allele was significantly associated with shorter survival among patients with glioblastomas carrying a *TP53* mutation, and among those treated with surgery plus radiotherapy.

## WHOLE GENOME AMPLIFICATION FOR ARRAY CGH USING DNA EXTRACTED FROM FORMALIN-FIXED PARAFFIN-EMBEDDED HISTOLOGICAL SECTIONS

Array comparative genomic hybridization (CGH) is useful to assess genome-wide chromosomal imbalance, but the requirement for relatively large amounts of DNA can be a limitation, in particular for samples extracted from small tumour areas on paraffin sections. Whole genome amplification (WGA) can be carried out before array CGH to obtain sufficient DNA, but the possibility of artefacts due to biased amplification cannot be excluded. We optimized the WGA protocol to generate sufficient DNA with minimum amplification bias. Using formalin-fixed paraffin-embedded histological sections of tumours carrying known *TP53* mutations, LOH 1p, LOH 10q, LOH 19q, and *EGFR* amplification, we first optimised the protocol so that these genetic alterations are detected after WGA. We found that a ligation step before WGA is important, as it allows a short reaction time with Phi29 to generate WGA-DNA with greatly decreased amplification bias. Using template >150 ng of DNA, a ligation step before WGA, and a short reaction time with Phi29 DNA polymerase (<1.5 h), we obtained WGA-DNA (>4  $\mu$ g) with minimum amplification bias (<3-fold). Using this protocol, we carried out array CGH (Agilent 105K) before and after WGA. Pearson correlation analysis indicated a significant positive correlation in array CGH results between DNA before and after WGA ( $P<0.0001$ ). These results suggest that genetic analyses are possible using WGA-DNA extracted from

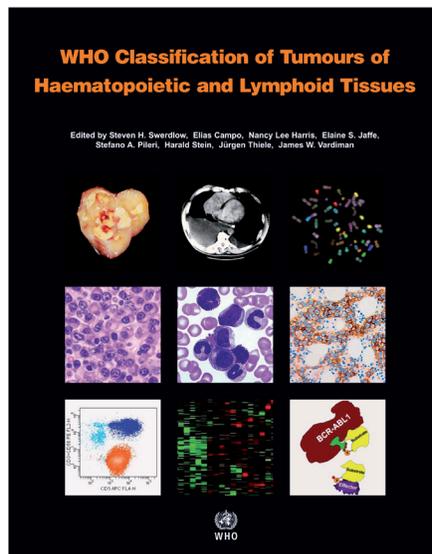
paraffin sections, but that they should be carried out with a carefully optimised and controlled protocol.

## WHO CLASSIFICATION OF TUMOURS SERIES (WHO BLUE BOOKS)

The objective of this project is to establish a pathological and genetic classification and grading of human tumours that is accepted and used worldwide. Without clearly defined clinical and histopathological diagnostic criteria and, more recently, genetic and expression profiles, epidemiological studies and clinical trials are difficult to conduct. This project therefore has a substantial impact in not only pathology communities, but also cancer registration, epidemiology studies, clinical trials, and cancer research in general.

IARC has been responsible for this book project since the 3<sup>rd</sup> edition (2000–2005), which covered all organ sites in 10 volumes. Diagnostic criteria, pathological features and associated genetic alterations were described in a strictly disease-oriented manner. For each volume, 10 000–35 000 copies were printed and distributed worldwide.

The current edition (4<sup>th</sup> edition) was initiated in 2006, with four new series editors (Dr Fred Bosman, University of Lausanne, Switzerland; Dr Elaine Jaffe, National Institutes of Health, Bethesda, USA; Dr Sunil Lakhani, University of Queensland, Brisbane, Australia; and Dr Hiroko Ohgaki, IARC). The first volume of the 4<sup>th</sup> edition, *Tumours of the Nervous System*, was published in June 2007. The second volume, *Tumours of the Haematopoietic and Lymphoid Tissues*, was published in September 2008, and over 30 000 copies have already been printed and distributed worldwide. We are currently preparing the 3<sup>rd</sup> volume, *Tumours of the Digestive System*, with 4 volume editors (Dr F. Bosman, Lausanne, Switzerland; Dr F. Carneiro, Porto, Portugal; Dr R.H. Hruban, Baltimore, USA; and Dr N.D. Theise, New York, USA) and with >110 contributors. The consensus and editorial conference is scheduled for December 2009, and the book is scheduled to be published in 2010.



### The Section of Molecular Pathology is grateful to the following scientists for their collaboration in its projects:

Dr F. Berger, Grenoble, France	Dr Y. Nakazato, Gunma, Japan
Dr F. Bosman, Geneva, Switzerland	Dr H.-K. Ng, Hong Kong, China
Dr D.J. Brat, Atlanta, USA	Dr J. Pang, Hong Kong, China
Dr E. Campo, Barcelona, Spain	Dr T. Pietsch, Bonn, Germany
Dr F. Carneiro, Porto, Portugal	Dr S. Pileri, Bologna, Italy
Dr W.K. Cavenee, La Jolla, USA	Dr N. Probst, Zurich, Switzerland
Dr I. Ciernik, Zurich, Switzerland	Dr S. Rutkowski, Wurzburg, Germany
Dr M.A. Grotzer MA, Zurich, Switzerland	Dr G. Schafer, Innsbruck, Austria
Dr N.L. Harris, Boston, USA	Dr H. Stein, Berlin, Germany
Dr F. Heppner, Zurich, Switzerland	Dr S.H. Swardlow, Pittsburgh, USA
Dr E. Hewer, Zurich, Switzerland	Dr N.D. Theise, New York, USA
Dr R.H. Hruban, Baltimore, USA	Dr J. Thiele, Cologne, Germany
Dr J.P. Issartel, Grenoble, France	Dr J.W. Vardiman, Chicago, USA
Dr E.S. Jaffe, Bethesda, USA	Dr A. Vital, Bordeaux, France
Dr P. Kleihues, Zurich, Switzerland	Dr W.A. Weiss, San Francisco, USA
Dr H. Klocker, Innsbruck, Austria	Dr S. Wellek, Mannheim, Germany
Dr S.R. Lakhani, Herston, Australia	Dr M. Weller, Zurich, Switzerland
Dr UM Lutolf, Zurich, Switzerland	Dr H. Yokoo, Gunma, Japan
Dr M. Mittelbronn, Frankfurt, Germany	

### The financial support from the following bodies is gratefully acknowledged:

Foundation for Promotion of Cancer Research, Japan  
MEDIC Foundation

## PUBLICATIONS

### ORIGINAL ARTICLES

Huang J, Grotzer MA, Watanabe T, Hewer E, Pietsch T, Rutkowski S, Ohgaki H. Mutations in the Nijmegen breakage syndrome gene in medulloblastomas. *Clin Cancer Res*. 14: 4053-4058 (2008)

Yokoo H, Tanaka Y, Nobusawa S, Nakazato Y, Ohgaki H. Immunohistochemical and ultrastructural characterization of brain tumors in S100beta-v-erbB transgenic rats. *Neuropathology*, 28: 591-598 (2008)

Zawlik I, Vaccarella S, Kita D, Mittelbronn M, Franceschi S, Ohgaki H. Promoter methylation and polymorphisms of the MGMT gene in glioblastomas: a population-based study. *Neuroepidemiology* 32: 21-29 (2009)

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Watanabe T, Nobusawa S, Kleihues P, Ohgaki H. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. *Am J Pathology* 174: 1149-1153 (2009)

Huang J, Pang J, Watanabe T, Ng H-K, Ohgaki H. Whole genome amplification for array comparative genomic hybridization using DNA extracted from formalin-fixed paraffin-embedded histological sections. *Journal of Molecular Diagnostics* 11: 109-116 (2009)

Kita D, Ciernik I, Vaccarella S, Franceschi S, Kleihues P, Lutoff UM, Ohgaki H. Age as predictive factor in glioblastomas: population-based study. *Neuroepidemiology* 33: 17-22 (2009)

Sun X, Huang J, Homma T, Kita D, Klocker H, Schafer G, Boyle P, Ohgaki H. Genetic alterations in the PI3K pathway in prostate cancer. *Anticancer Res* 29: 1739-1743 (2009)

Watanabe T, Vital A, Nobusawa S, Kleihues P, Ohgaki H. Selective acquisition of IDH1 R132C mutations in astrocytomas associated with Li-Fraumeni syndrome. *Acta Neuropathol* 117: 653-656 (2009)

Nobusawa S, Watanabe T, Kleihues P, Ohgaki H. IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. *Clinical Cancer Res* in press

## BOOK CHAPTERS AND REVIEWS

Ohgaki H. Brain Cancer. In: *Prognosis in Advanced Cancer*. Glare P, Christakis NA (eds.) Oxford University Press pp. 201-213 (2008)

Ohgaki H. Epidemiology of brain tumors. *Methods Mol. Biol.* 472: 323-342 (2009)

Ohgaki H. and Kleihues P. Genetic alterations and signaling pathways in the evolution of gliomas. *Cancer Science*, submitted.

**Section Head**  
Dr Silvia Franceschi

## SECTION OF INFECTIONS (INF)

THE NEW SECTION OF INFECTIONS (INF) COMPRISES TWO GROUPS: THE INFECTIONS AND CANCER EPIDEMIOLOGY GROUP (ICE) AND THE INFECTIONS AND CANCER BIOLOGY GROUP (ICB). THE REORGANISATION OF THE SCIENTIFIC STRUCTURE OF IARC HAS THEREFORE LEFT THE SITUATION OF ICE AND ICB UNCHANGED, AS THEY WERE TOGETHER IN THE EPIDEMIOLOGY AND BIOLOGY CLUSTER BEFORE 2009.

Persistent infection with viruses, bacteria and parasites account for approximately 20% of the cancer burden worldwide, with less developed countries being the hardest hit. Infections also represent, or might represent in the future, some of the most preventable cancer causes through immunisation or early detection. Table 1 summarises the infectious agents and the different aspects of the infection/cancer relationship currently under study in INF.

Not all of the topics listed in Table 1 are covered by both Groups. ICB, for instance, is focused on HPV to an even greater extent than is ICE, although it also works on EBV and Merkel cell polyomavirus. Although ICE has never performed large epidemiological studies of non-melanomatous skin cancer, it has collaborated very closely with ICB on the association between cutaneous HPV and squamous cell carcinoma of the conjunctiva.

ICE is more active than ICB in the study of other cancer-associated infections that have either been present in the IARC portfolio for years (*Helicobacter*), or were brought to IARC by the present ICE Group Head (e.g., HIV and HCV). In particular, ICE is a world leader in the study of cancer excess among HIV-positive people. For consistency, some of the long-duration population-based studies previously established in ICE continued with the same extra-mural laboratories they started with. Similarly, the attractiveness of the ICB laboratory has successfully led to extra-

mural collaborations with distinguished epidemiologists and clinicians.

With respect to aspects under study, some are exclusive to ICB (e.g., transformation mechanisms) or ICE (worldwide distribution and trends of cancer-associated infections). Collaborations on other relevant aspects (the role of innate and acquired immunity, the impact of different HPV variants) are becoming possible along with the increasing availability at ICB of tests suitable for large-scale application.

Regardless of the infectious agent or the aspect under study, one of the great assets of INF is the collaboration on methodological issues. It has become routine for ICB to provide advice to ICE regarding decisions on biological protocol

aspects, and for ICE to provide statistical assistance to ICB in its protocols and publications.

Additional collaborations are ongoing with other Sections, notably the Sections of Early Detection and Prevention (EDP), Nutrition and Metabolism (NME), Genetics (GEN), Environment (ENV), Molecular Pathology (MPA) and Mechanisms of Carcinogenesis (MCA).

The over 100 publications produced by INF in 2008–2009 provide good evidence of the high productivity and width of topics and international collaborations entailed in projects coordinated by INF.

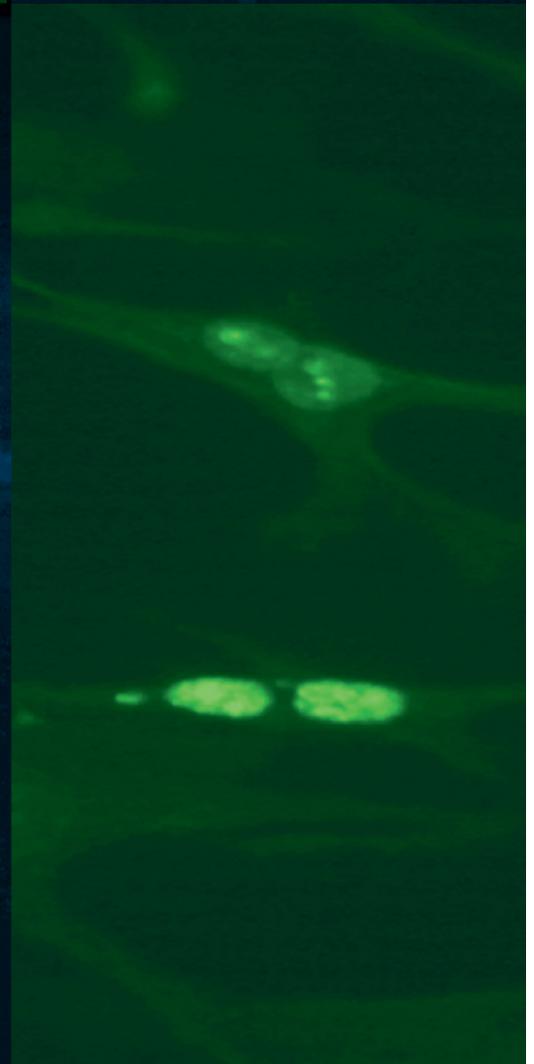
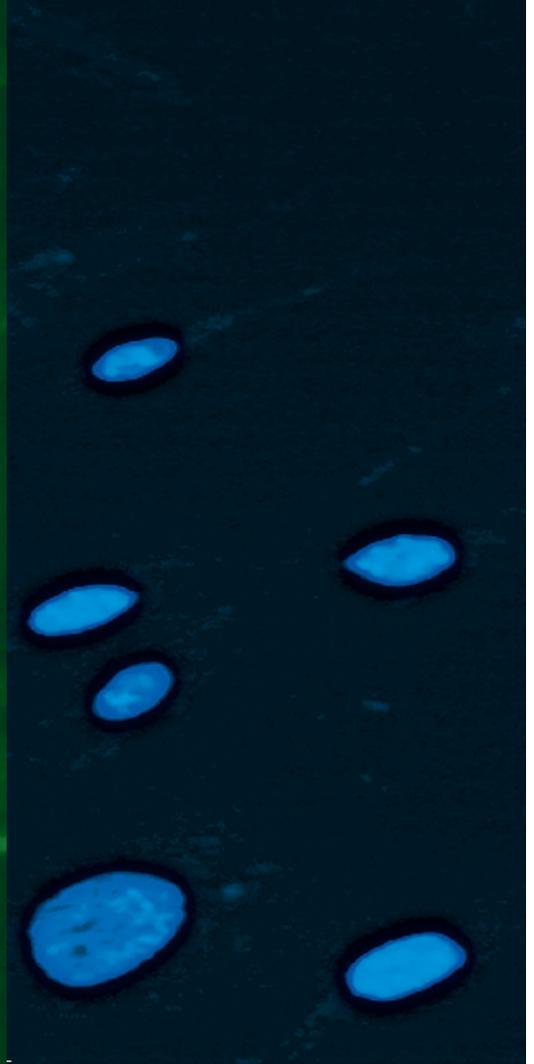
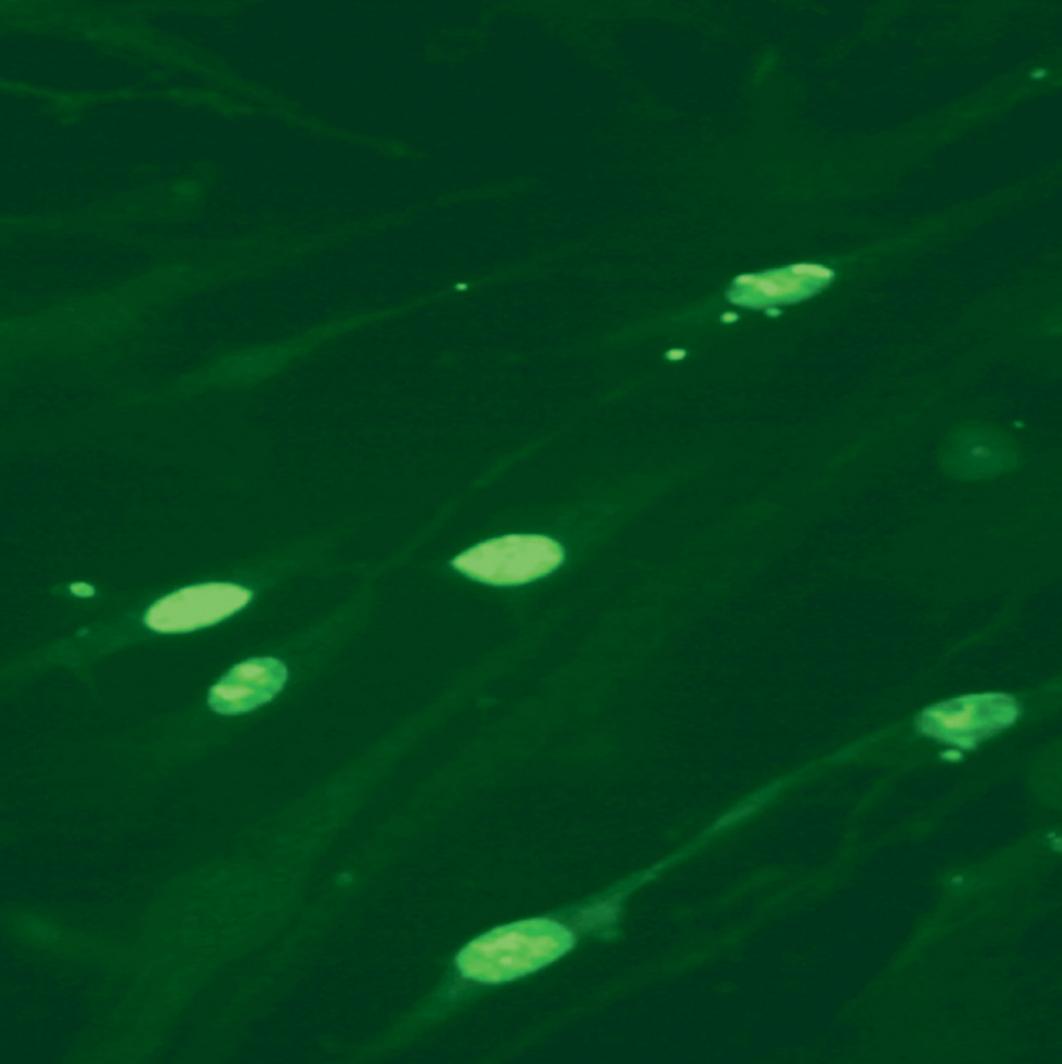
**Table 1. Section of Infections Studies**

*Aspects under study*

- Worldwide distribution and trends over time of infections associated with cancer
- Range of tumours associated with infection and strength of the association
- Transformation mechanisms
- Meaning of viral variants
- Role of innate and acquired immunity
- New virological and bacteriological tests for epidemiological studies

*Agents included*

- Mucosal and cutaneous human papillomavirus (HPV) types
- HIV, in combination with other viruses associated with cancer
- *Helicobacter* species
- Hepatitis B and C virus (HBV/HCV)
- Epstein Barr virus (EBV)
- Merkel cell polyomavirus



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Mr Djamel Saidj (January 2009-March 2009 & August 2009-July 2010)

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IT IS WELL ESTABLISHED THAT APPROXIMATELY 20% OF HUMAN CANCERS WORLDWIDE ARE ASSOCIATED WITH INFECTIOUS AGENTS. IN ADDITION, NEW EVIDENCE SUPPORTS THE INVOLVEMENT OF ADDITIONAL INFECTIOUS AGENTS IN HUMAN CARCINOGENESIS, WHICH MAY ADD TO THIS TOTAL. A SUB-GROUP OF HPV TYPES THAT INFECT THE SKIN ARE SUSPECTED TO BE INVOLVED, TOGETHER WITH ULTRAVIOLET RADIATION, IN THE DEVELOPMENT OF NON-MELANOMA SKIN CANCER (NMSC). IN ADDITION, A RECENTLY-DISCOVERED HUMAN POLYOMAVIRUS, MERKEL CELL POLYOMAVIRUS (MCPyV), IS ASSOCIATED WITH A RARE TUMOUR, MERKEL CELL SARCOMA.

The main goal of our Group is to establish a causal role of specific infectious agents in human cancer. Two complementary strategies are currently followed: (i) Functional studies to characterise the biological properties of specific infectious agents using *in vitro* and *in vivo* model systems; and (ii) Epidemiological studies to determine the presence of specific infectious agents in benign and malignant human lesions.

The rationale of our functional studies is based on the fact that viruses directly associated with human cancers have developed several mechanisms to efficiently evade immune surveillance and promote cellular transformation. Therefore, studies in the Group aim to characterise the ability of viruses to de-regulate cellular pathways involved in the immune response and cellular transformation in order to predict their oncogenic potential.

Regarding the epidemiological studies, we have generated novel human papillomavirus (HPV) detection assays with high throughput, sensitivity and specificity. Validation studies have shown that our assays significantly increased the HPV DNA detection rate, especially in multiple infections, in comparison to other well-validated and widely-used HPV detection methods. The development of these novel detection assays allowed us to initiate and complete several epidemiological studies.

Future plans of the Group include (i) extension of the functional studies to emerging oncogenic viruses, e.g. human Merkel cell polyomavirus and related viruses; (ii) developing novel detection assays for additional infectious agents; and (iii) expanding the epidemiological studies in collaboration with other groups from IARC and other institutes, including institutes from low-resource countries.

### CUTANEOUS HPV TYPES

The skin-tropic HPV types from the genus beta of the HPV phylogenetic tree, also known as Epidermodysplasia verruciformis (EV) HPV types, are strongly suspected to be involved in NMSC. However, their direct role in human carcinogenesis is not yet fully proven. In addition, it is not yet known whether, as has been observed with mucosal HPV types, beta HPVs may be sub-grouped into low- and high-risk HPV types. To address these questions, we have initiated the characterisation of the biological properties of the main oncoproteins, E6 and E7, from several beta HPV types. Several experimental models have been used, ranging from primary keratinocytes to transgenic mice.

Our data show that certain beta HPV types (i.e. HPV24, 38 and 49) display transforming activities in comparison to other beta HPV types (i.e. HPV14, 22, 23 and 36), supporting the existence of low- and high-risk HPV types (\*Gabet *et al.*, 2008; \*Bouvard *et al.*, ongoing study). Studies on HPV38 have resulted in the identification of a novel viral mechanism of inactivation of p53. Unlike HPV16, HPV38 does not induce p53 degradation but rather promotes accumulation of a potent inhibitor of p53 transcriptional functions, *\_Np73\_* (\*Accardi *et al.*, 2006). HPV38 E6 and E7 expression in the skin of transgenic mice using K10 promoter induced *\_Np73\_* accumulation, cellular proliferation, hyperplasia and dysplasia in the epidermis (\*Dong *et al.*, 2005; \*Accardi *et al.*, 2006; \*Dong *et al.*, 2008). In conclusion, our functional studies support the role of certain beta HPV types in human carcinogenesis.

### MUCOSAL HPV TYPES AND TOLL-LIKE RECEPTOR SIGNALLING

Establishment of a chronic infection is a key event for virus-induced carcinogenesis. Several prospective studies, in which

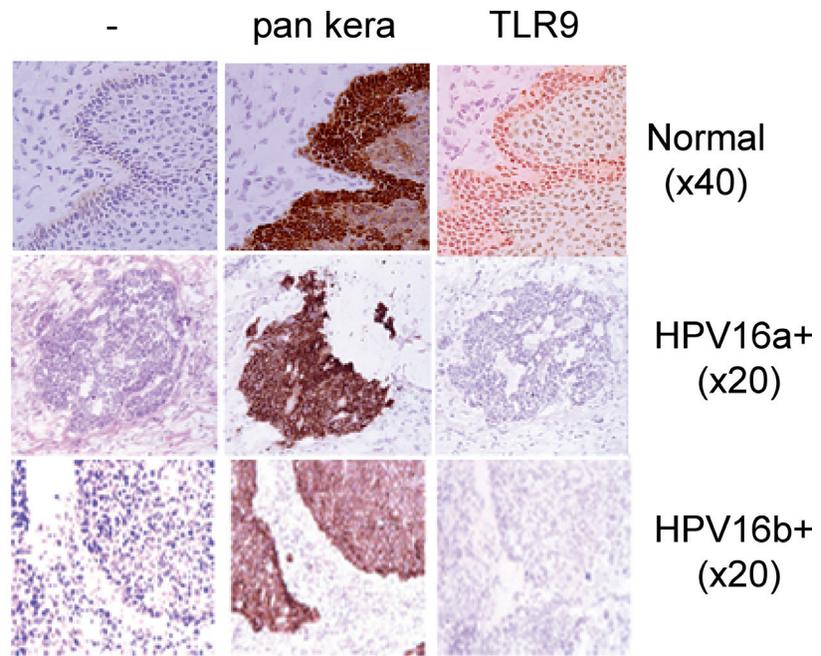
HPV-positive women have been followed-up for many years, have shown that HPV16 is able to persist much longer in the host than the other mucosal high-risk HPV types. Thus, the high carcinogenicity of HPV16 may be explained by its greater efficiency than the other mucosal high-risk HPV types in evading the immune system. We observed that the expression of a key player in innate immunity, Toll-like receptor 9 (TLR9), which senses the double-stranded viral DNA, is strongly down-regulated by HPV16 E6 and E7 oncoproteins in several *in vitro* experimental models (\*Hasan *et al.*, 2007). Accordingly, immunohistochemical analyses revealed weak TLR9 expression in HPV-positive malignant cervical lesions, while strong TLR9 staining was detected in normal cervical tissues (\*Hasan *et al.*, 2007; ongoing studies). E6 and E7 from other mucosal high-risk HPV types, including HPV18, are less efficient than E6 and E7 from HPV16 in down-regulating TLR9 expression, while the mucosal low-risk HPV6 E6 and E7 do not interfere at all with TLR9 transcription. Thus, the ability of the different HPV types to down-regulate TLR9 expression appears to correlate with their ability to persist.

Based on these data, we have extended our studies to cutaneous beta HPV types and other cancer-associated viruses to target the TLR9 signalling pathway.

### PREVALENCE OF HPV INFECTIONS FROM DIFFERENT ANATOMICAL SITES IN HUMAN SPECIMENS

We have developed a novel assay for the detection of three different groups of HPV, namely (i) mucosal high-risk HPV types (n=19), (ii) mucosal low-risk HPV types (n=18) and (iii) beta and gamma cutaneous HPV types (n=31) (\*Gheit *et al.*, 2006; Gheit *et al.*, 2007; Gheit *et al.*, ongoing study). Due to the high sensitivity and versatility of our HPV detection assay, we were able to perform several epidemiological studies to evaluate the ability of HPV types (i)

to infect a specific anatomical site and/or (ii) to promote carcinogenesis (\*Dai *et al.*, 2007; \*Cazzaniga *et al.*, 2008; \*Rollison *et al.*, 2008). Our data did not provide evidence for the role of the high-risk mucosal HPV types in breast carcinogenesis, but they do suggest a possible involvement of these viruses in a small percentage of oesophageal cancers. In addition, some of the cancer case studies aimed at determining the prevalence of specific mucosal high-risk HPV types in populations that have not yet been analysed (\*Gheit *et al.*, 2009; \*Sideri *et al.*, 2009).



**Figure 1. TLR9 is downregulated in HPV16-positive cervical cancers.**

Sections of normal and tumoral cervical tissues were stained by immuno-histochemistry for pan keratin or TLR9. No TLR9 expression was detected in cervical cancer of two different donors (HPV16a+ and HPV16b+).

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

- Christophe Caux, Centre Léon-Bérard, Lyon, France
- Massimiliano Cazzaniga, Fausto Chiesa, Mario Sideri and Umberto Veronesi, European Institute of Oncology, Milan, Italy
- Christine Clavel and Philippe Birembaut, Hôpital de la Maison Blanche, Reims, France
- Charles Dumontet, Hôpital Edouard Herriot, Lyon, France
- Lutz Gissmann, DKFZ, Heidelberg, Germany
- Thomas Iftner, University of Tübingen, Germany
- Susanne Krüger Kjær, Institute of Cancer Epidemiology, Copenhagen, Denmark
- Evelyne Manet, Ecole Normale Supérieure, Lyon, France
- Jacqueline Marvel, Immunité, INSERM U851 Lyon, France
- Michael Pawlita, DKFZ, Heidelberg, Germany
- Dana Rollison, Lee Moffitt Cancer Center, Tampa, FL, USA
- Levana Sherman, Sackler School of Medicine, Tel Aviv, Israel
- Ingeborg Zehbe, Regional Cancer Care, Thunder Bay, Canada
- Fabien Zoulim, INSERM U871, Lyon, France

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# INFECTIONS AND CANCER EPIDEMIOLOGY GROUP (ICE)

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## HUMAN PAPILLOMAVIRUS (HPV)

The study of HPV, the necessary cause of cervical cancer, has been the main focus of the Infections and Cancer Epidemiology Group (ICE) in the last two years and has led to 25 published articles, as well as several in press, on related topics.

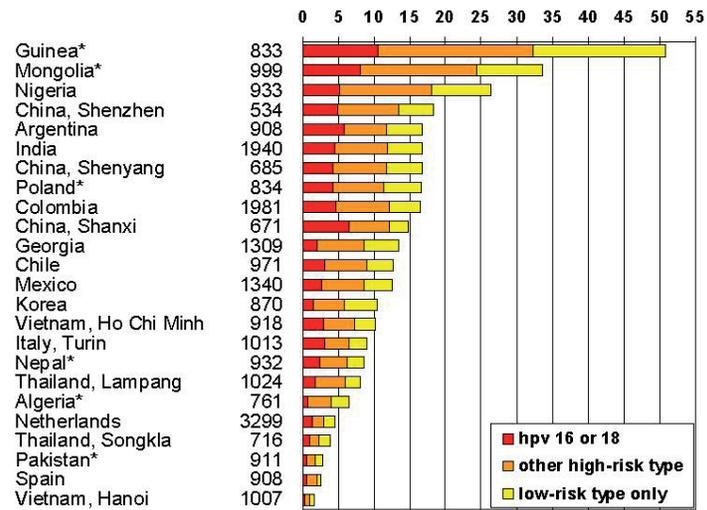
The successful introduction of vaccines against HPV, as well as HPV-based testing, presupposes accurate knowledge of the infection burden and type-specific distribution of HPV types in different parts of the world. In order to address this issue and fill knowledge gaps on this subject, ICE has carried out in the last two years new population-based HPV prevalence surveys among women with and without cervical cancer in six world areas (\*Bardin *et al.*, 2008; \*Dondog *et al.*, 2008; \*Keita *et al.*, 2009; \*Sherpa *et al.*, 2009) (Figure 1). HPV testing is also in progress for an additional study site in Iran.

The existence of populations in which HPV prevalence does not diminish in middle-aged women is one of the most important discoveries of the IARC HPV Prevalence Surveys (Figure 2).

Meta-analyses of women with and without cervical cancer, as well as cancers of the anogenital tract, have also been carried out or updated. This has resulted in publications showing that worldwide HPV16/18 prevalence in cervical cancer is indeed more similar than initially expected, lending further credence to the universal efficacy of the HPV vaccines currently available (\*Schiffman *et al.*, 2009). A meta-analysis on anogenital cancers further suggested that approximately 40% of vulvar, 70% of vaginal and 84% of anal carcinoma may be prevented by current HPV vaccines against HPV16/18 (\*De Vuyst *et al.*, 2009).

### INTERNATIONAL COLLABORATION ON CERVICAL CANCER

During this period, we have brought to fruition two collaborative manuscripts on the role of sexual behaviour in cervical cancer risk (\*International Collaboration of Epidemiological Studies of Cervical



\* Carried out in the last 2 years

Figure 1. Prevalence of cervical HPV DNA in sexually active women. IARC HPV Prevalence Surveys, 1995-2009.

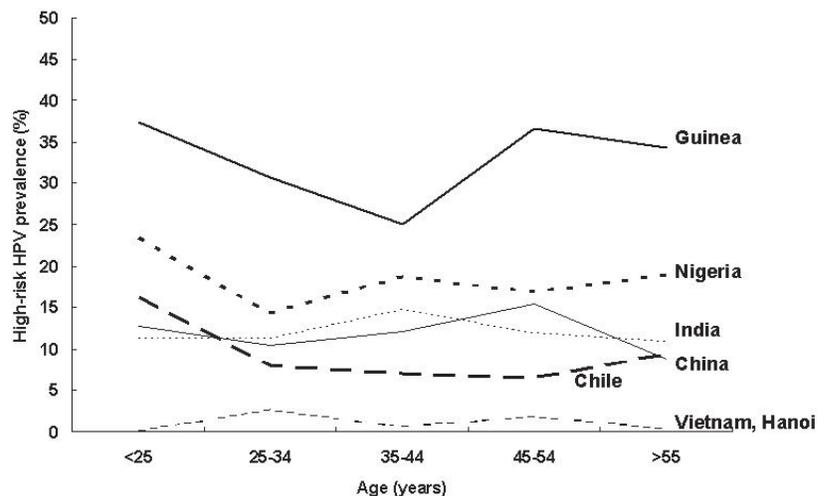


Figure 2. Age-specific prevalence of high-risk HPV types in some less-developed countries. IARC HPV Prevalence Surveys (\*Franceschi *et al.*, 2006).

Cancer, 2009; \*Louie *et al.*, 2009). The risk of cervical cancer increased with lifetime number of sexual partners, as expected. We also highlighted, however, the association with early age at first sexual intercourse after careful adjustment for confounding factors. It is conceivable that age at first intercourse

is related to invasive cervical cancer risk through HPV acquisition. One possibility is that cervical cancer risk may increase with duration of HPV infection. It is likely that women who have earlier first sexual intercourse are also exposed to HPV earlier, and might have longer duration of infection.

## BAYESIAN MODELS APPLIED TO CANCER ETIOLOGY

A natural history model for infection and clearance of HPV infection in the ASCUS-LSIL Triage Study (ALTS) demonstrated that distinct HPV types act as independent agents with no impact on incidence or clearance of other types (\*Plummer *et al.*, 2007). Further investigation of the determinants of HPV persistence showed that, contrary to some recent claims, newly appearing infections clear equally well among older and younger women (\*Maucort-Boulch *et al.*, 2009). Therefore, for persistent infection old age is a proxy of "old age" of HPV infection (i.e. a poor prognostic factor).

## HUMAN IMMUNODEFICIENCY VIRUS/ ACQUIRED IMMUNE DEFICIENCY SYNDROME (HIV/AIDS)

Cancer risk in people with HIV/AIDS (PWA) is a subject of great importance to ICE now that PWA have improved survival as a result of highly active antiretroviral therapy (HAART). ICE has used record-linkage and cohort studies in Switzerland and Italy to achieve both an adequate study power for uncommon neoplasms (e.g. hepatocellular carcinoma, Hodgkin lymphoma) and accurate information on markers of immunity and use of HAART (10 publications in 2008–2009 and several in press). A second line of research has focused on the way HIV infection modifies the cancer potential of HPV infections in countries at very high-risk for both infections (i.e., Kenya and Uganda) (\*De Vuyst *et al.*, 2008).

Significantly elevated risks in PWA versus the general population were found for Hodgkin lymphoma, hepatocellular carcinoma, cancers of the cervix, anus, liver, lip, mouth and pharynx, trachea and lung, multiple myeloma and non-melanomatous skin cancer (\*Dal Maso *et al.*, 2009). The incidence of non-Hodgkin lymphoma and Kaposi sarcoma were shown to have greatly decreased in the HAART era (\*Polesel *et al.*, 2008; \*Franceschi *et al.*, 2008). HAART use was associated with a substantial weakening of the predictive value of CD4+ cell count, supporting the strong efficacy of HAART regardless of the degree of immune

impairment when treatment begins. The beneficial effect remained strong up to 10 years after HAART initiation (\*Polesel *et al.*, 2008; \*Franceschi *et al.*, 2008). Hodgkin lymphoma risk did not appear to be increasing in recent years among PWA using HAART, and the best predictive marker was low CD4+/CD8+ ratio (\*Clifford *et al.*, 2009). In a matched nested case-control study, lower CD4+ cell counts were shown for the first time to be significantly associated with hepatocellular carcinoma risk (\*Clifford *et al.*, 2008). Excess risks for cervical cancer among PWA are particularly high in Italy (\*Dal Maso *et al.*, 2009) as also reported in Spain. Although access to HAART is widespread, cervical screening among HIV-positive women needs to be improved.

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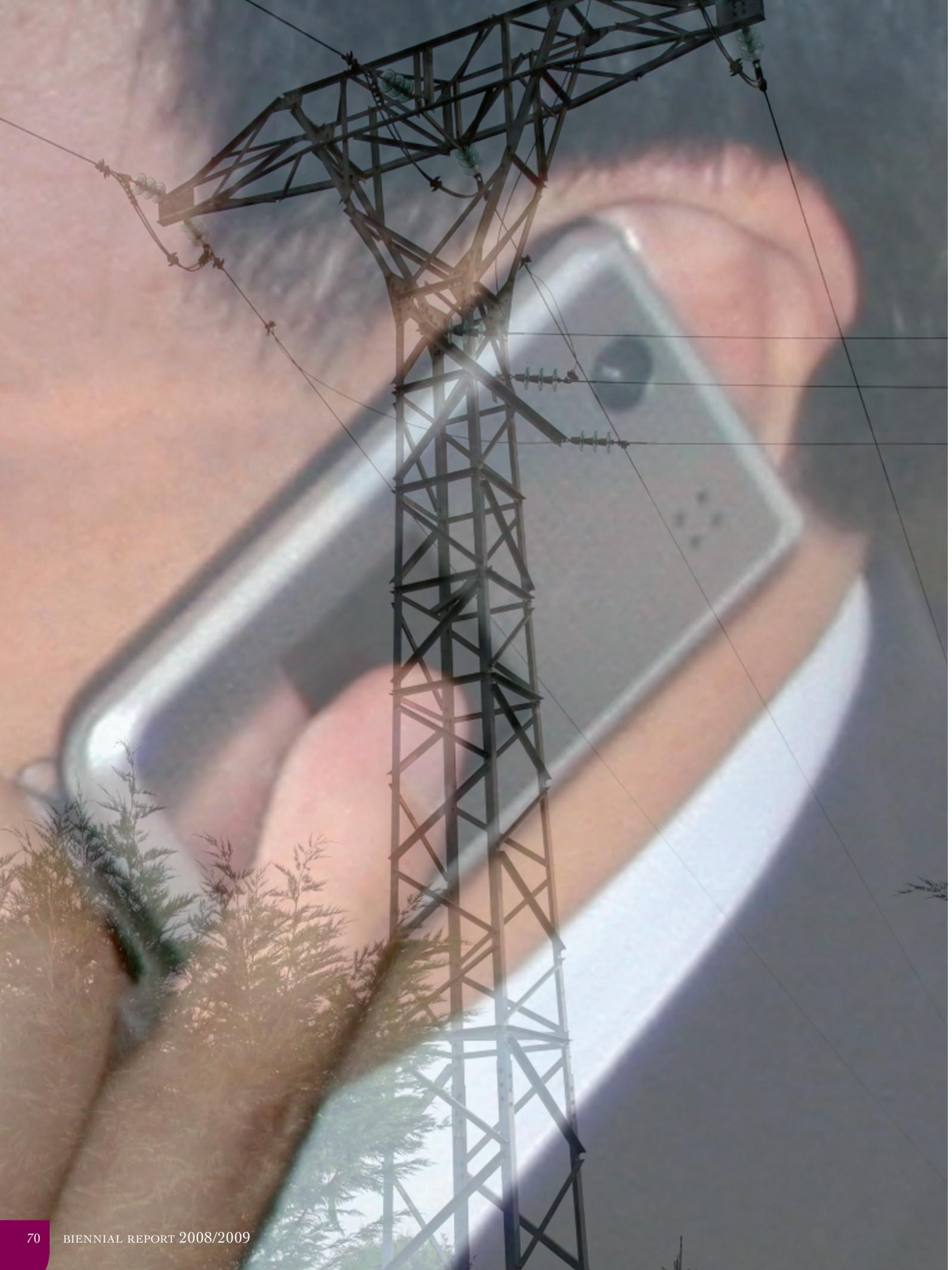
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## SECTION OF ENVIRONMENT (ENV)

**Section Head**  
Dr Paolo Boffetta

ENVIRONMENT, INCLUDING LIFESTYLE, ENCOMPASSES MANY MAJOR CAUSES OF HUMAN CANCER, INCLUDING TOBACCO USE, ALCOHOL DRINKING, OCCUPATIONAL EXPOSURES, ENVIRONMENTAL POLLUTANTS AND RADIATION.

IARC is well placed to address these important questions because of its ability to coordinate large-scale studies, which take advantage of the heterogeneity of cancer and cancer risk factors across human populations. IARC can also integrate epidemiological and biological techniques and contribute to programmes aimed at reviewing and evaluating the evidence of carcinogenicity of specific agents and interventions. Studies of the effects of ionising radiation are important for elucidating mechanisms of carcinogenesis, and can provide the scientific basis for radiation protection of the general public, patients and occupationally-exposed populations. In particular, uncertainties persist with regard to the health consequences of low doses and low dose rates, and host factors that can modify radiation-related cancer risk.



# LIFESTYLE AND CANCER GROUP (LCA)

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Mrs Rim Boudjema (Clerk, until April 2008)  
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Ms Ann Olsson  
Ms Sung-Shim Iani Park (July 2008–October 2008)  
Ms Lorenza Scotti (May 2008–August 2008)  
Ms Ding Wang (August 2009–October 2009)

RESEARCH IN THE LIFESTYLE AND CANCER GROUP (LCA) COMPLEMENTS THAT IN OTHER SECTIONS ACROSS IARC BY AIMING AT IDENTIFYING THE ENVIRONMENTAL CAUSES OF HUMAN CANCER AND THEIR INTERACTIONS WITH GENETIC FACTORS (BOFFETTA ET AL., 2008A; BOFFETTA ET AL., 2009A). IT ALSO AIMS TO CONTRIBUTE TO THE METHODOLOGICAL DEVELOPMENT OF THE FIELD OF MOLECULAR AND GENETIC EPIDEMIOLOGY, AND OF CANCER PREVENTION RESEARCH, IN PARTICULAR IN THE FIELD OF TOBACCO CONTROL. THE FOCUS IS ON CANCERS OF THE LUNG, THE UPPER AERODIGESTIVE TRACT, THE PANCREAS AND THE KIDNEY, AND ON LYMPHOMA. THE PROGRAMME CONSISTS OF MULTICENTRIC INTERNATIONAL STUDIES CARRIED OUT IN COLLABORATING CENTRES, THE COORDINATION OF NETWORKS OF INVESTIGATORS, THE USE OF EXISTING RESOURCES SUCH AS CANCER REGISTRY DATA, AND THE PREPARATION OF THE *IARC HANDBOOKS OF TOBACCO CONTROL*.

Different types of study design are used (case-control, cohort, record linkage), and all field studies include a biological component. During 2008–9 the group completed a series of analyses of risk factors for cancers of the lung, the upper aerodigestive tract (including the oral cavity, pharynx, larynx and esophagus) and the kidney, the colorectum, the breast and of lymphoma, based on large-scale case-control studies coordinated by the former Gene-Environment Epidemiology (GEE) Group and conducted in previous years in Europe and Latin America. Extensive genotyping of samples collected in these studies has been conducted by the GCS and GEP groups.

The full exploitation of this material will take several years; results reported during 2008–2009 include causes of cancer in France (Boffetta *et al.*, 2009b), UV radiation exposure and the risk of malignant lymphoma and multiple myeloma (Boffetta *et al.*, 2008b), various second primary cancers (Chuang *et al.*, 2008a; Chuang *et al.*, 2008b; Maule *et al.*, 2008), and risk factors for hypopharyngeal, laryngeal and breast cancers in India (Chuang *et al.*, 2008a; Chuang *et al.*, 2008b; Heck *et al.*, 2008; Mathew *et al.*, 2008; Mathew *et al.*, 2009; Sapkota *et al.*, 2007; Sapkota *et al.*, 2008). Results of analyses conducted in these studies on the effect of genetic variants on the risk of lung and head and neck cancer are contained in the report from the GEP group.

The work of the Group in the epidemiological studies described above has been extended to the coordination of international consortia, with the following goals: fast and coordinated replication of new findings; pooling of data for analysis for which large populations are needed, typically for gene-environment interactions; and setting standards for future epidemiological research. In

particular, during 2008–2009 the Group played a key role in coordinating consortia of studies of lymphoma (InterLymph), lung cancer (ILCCO) and head and neck cancer (INHANCE); important results were reported on the effect of tobacco and alcohol interactions, marijuana, involuntary smoking, and family history of cancer on head and neck cancer in the INHANCE Consortium (Berthiller *et al.*, 2009; Hashibe *et al.*, 2009; Lee *et al.*, 2008; Negri *et al.*, 2009). In addition, the group continues to be actively involved in a consortia of investigators involved in molecular and genetic epidemiology of pancreatic cancer (PANC4) and squamous cell carcinoma of the esophagus (ESC3). Finally, the group has been collaborating on projects within the Asia Cohort Consortium, comprising ongoing and new prospective studies in Asia and the Pacific region.

Another important area of research for the Group is the field of diet and nutrition and their association with various cancers. The Group was successful in obtaining pilot funding from the World Cancer Research Fund (WCRF) to study the feasibility of establishing a large-scale study on dietary and lifestyle factors and the risk of esophageal cancer in Kashmir, India, a high-risk region lying within the Asian Esophageal Cancer Belt. In addition, the group has been active in the European Prospective Investigation into Cancer and Nutrition (EPIC), a large cohort of over 520 000 subjects with dietary information and biological samples. In this respect, the group has conducted a study of vitamin D receptor polymorphisms (Jenab *et al.*, 2009a) as well as blood vitamin D levels and risk of colorectal cancer, showing a strong inverse risk association (Jenab *et al.*, 2008).

In order to address the conclusions of the 2007 WCRF expert report (World Cancer Research Fund, 2007), which called for further epidemiologic research on the potential association of fruits and vegetables with reduced cancer risk, the Group was involved in studies based on EPIC to examine the association of these important food groups with the risk of colorectal (van Duijnhoven *et al.*, 2009) and pancreatic (Vrieling *et al.*, 2009) cancers. In addition, the Group led a comprehensive analysis for fruit and vegetable intake and the risk of all cancers, showing a small but significant reduction in total cancer risk with higher consumption (Boffetta *et al.*, submitted).

In an effort to identify future horizons for the field of dietary biomarkers, the Group led a comprehensive review of this topic (Jenab *et al.*, 2009b). The review highlighted a need for discovery of new dietary biomarkers, and in view of this the Group led a large collaborative grant application with the objective of identifying metabolomic profiles specific to different foods, dietary patterns and lifestyle habits.

The Group is leading a comprehensive review and meta-analysis of alcohol consumption and cancer risk, focused primarily on the dose effects of lower intake levels and on cancer sites for which previous reports have been inconclusive (Baan *et al.*, 2007; World Cancer Research Fund, 2007). The first publication from this project shows an increased risk of pancreatic cancer for consumption of 3 or more drinks per day (Tramacere *et al.*, submitted).

Another important area of work for the Group was its support to the establishment of prospective studies of cancer in populations in transition. In addition to the cohort study in the Russian Federation described in the GEP



**IARC Handbooks on Tobacco Control, Volume 13:  
Evaluating the Effectiveness of Smoke-free Policies**  
31 March to 5 April 2008, Lyon, France



group, the prospective study established in the Golestan province of Northeastern Iran, an area with very high incidence of esophageal cancer, has been successful. Analyses of risk factors of esophageal cancer and other major

outcomes include socioeconomic status, high temperature beverages, tea drinking habits, tooth loss and oral hygiene, dietary habits, BRCA2 mutations and opium use (Abnet *et al.*, 2008; Akbari *et al.*, 2008; Hakami *et al.*, 2008; Islami *et al.*, 2009a; Islami *et al.*, 2009b; Islami *et al.*, 2009c; Nasrollahzadeh *et al.*, 2008; Pourshams *et al.*, 2009).

In the field of occupational cancer, a case-control study of lung cancer among European asphalt workers, aimed at clarifying whether the increased risk detected in the historical cohort phase of the study is due to exposure to bitumen fumes, exposure to other agents in the asphalt industry, or to confounders such as tobacco smoking and exposures in other industries, has been completed. The results are expected to be published in 2010–11.

For the SYNERGY project, ten case-control studies on lung cancer have been pooled to study the joint effects of selected occupational carcinogens (asbestos, PAH, chromium, nickel and crystalline silica) and tobacco smoking. A job-exposure matrix is currently being developed on the basis of measurements provided by major exposure databases of participating countries. The large dataset will also allow the investigation of many open questions in lung carcinogenesis, regarding occupational and other exposures. A close collaboration with ILCCO is anticipated, and the first results are expected in 2010.

During 2008–2009, with respect to tobacco prevention, the Group hosted one meeting (31 March–5 April 2008) of international experts to evaluate the evidence on the effectiveness of smoke-free legislation on reducing exposure to secondhand smoke, health effects and smoking behaviour, with the summary of the meeting's main conclusions published in *Lancet Oncology* in July of the same year (Pierce & Leon, 2008). The Group also completed the publication of two

volumes in the IARC series of Handbooks of Cancer Prevention on Tobacco Control; specifically, Volume 12 on *Methods for Evaluating Tobacco Control Policies* (IARC, 2008) and Volume 13 on *The Effectiveness of Smoke-free Policies* (IARC, 2009). Requests for partial translations of volume 12 into German and Japanese were received and granted. In addition, the Group coordinated a complete session on the main Handbook's findings on smoke-free policies at the 14<sup>th</sup> World Conference on Tobacco or Health, held in Mumbai in March of 2009. The Handbooks on Tobacco Control and concomitant dissemination efforts will support the implementation of WHO's Framework Convention on Tobacco Control. At present, planning for Volume 14 in the Handbooks series on *The Effectiveness of Tobacco Taxes in Controlling Tobacco Use* is proceeding, with the expert meeting scheduled for 17–22 May 2010 and the outline for the volume and corresponding authors already identified; publication of the volume is expected in 2011.

During the biennium, the Group has established preliminary contacts with researchers at the University of Sana'a and at the National Oncology Center in Sana'a, Yemen, and developed a preliminary study protocol to jointly plan and undertake a case-control study of lifestyle factors and aerodigestive tract cancer, with emphasis on the possible etiological role of khat chewing in oral, pharyngeal and esophageal cancers. This study will be the first to document if there is an association between khat use and upper digestive tract cancer in a country with a high incidence of oral cancer.

**Financial support from the following bodies is gratefully acknowledged:**

European Commission  
National Institutes of Health  
Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET), France  
Ligue contre le Cancer, comité du Rhône, France  
Région Rhône-Alpes, France  
INSERM, France  
Institut National du Cancer (INCA)  
Brescia University, Italy  
DGUV, Deutsche Gesetzliche Unfallversicherung  
World Cancer Research Fund, UK  
Nutricia Research Foundation, the Netherlands  
Conservation of Clean Air and Water in Europe (Concawe)  
European Bitumen Association (Eurobitume)  
European Asphalt Paving Association (EAPA)  
National Asphalt Pavement Association (NAPA), USA  
Asphalt Roofing Manufacturers Association (ARMA)  
National Roofing Contractors Association (NRCA), USA

**The Section of Environment is grateful to the following for their collaboration in its projects:**

Christian Abnet, Rockville, USA; Hans-Olov Adami, Stockholm, Sweden; Antonio Agudo, Barcelona, Spain; Wolfgang Ahrens, Bremen, Germany; Jane Allen, Washington, USA; Aage Andersen, Oslo, Norway; Nikolaus Becker, Heidelberg, Germany; Thomas Behrens, Bremen, Germany; Vladimir Bencko, Prague, Czech Republic; Simone Benhamou, Villejuif, France; Ingvar Bergdahl, Umea, Sweden; Douglas Bettcher, Geneva, Switzerland; Jillian M. Birch, Manchester, UK; Aaron Blair, Rockville, MD, USA; Stefania Boccia, Rome, Italy; Christine Bouchardy, Geneva, Switzerland; Freddie Bray, Oslo, Norway; David Brewster, Edinburgh, GB; Elizabeth Brown, Rockville, USA; Thomas Brüning, Bochum, Germany; Irene Brüske-Hohlfeld, Neuherberg, Germany; Patricia Buffler, Berkeley, USA; Igor Burstyn, Edmonton, Canada; Cristina Canova, Padova, Italy; Neil Caporaso, Bethesda, USA; Adrian Cassidy, Liverpool, UK; Xavier Castellsague, Barcelona, Spain; Frank Chaloupka, Chicago, USA; Chu Chen, Seattle, USA; Wong-Ho Chow, Bethesda, USA; Luke Clancy, Dublin, Ireland; Pier Luigi Cocco, Cagliari, Italy; Dario Consonni, Milan, Italy; David Christiani, Boston, USA; David Conway, Glasgow, UK; Giovanni Corrao, Milan, Italy; Dirk Dahmann, Bochum, Germany; Luigino Dal Maso, Aviano, Italy; Alexander Daudt, Porto Alegre, Brazil; Sandy Dawsey, Rockville, USA; Carolyn Dresler, Little Rock, USA; José Eluf-Neto, São Paulo, Brazil; Eleonóra Fabiánová, Banská Bystrica, Slovakia; Leticia Fernandez, Havana, Cuba; Esteve Fernandez, Barcelona, Spain; John Field, Liverpool, UK; Leticia Fernandez, Havana, Cuba; Joelle Fevotte, Lyon, France; Tony Fletcher, London, UK; Lenka Foretova, Brno, Czech Republic; Christina Funch Lassen, Copenhagen, Denmark; Silvano Gallus, Milan, Italy; Rainer van Gelder, Sankt Augustin, Germany; Maura Gillison, Baltimore, USA; Anna Gilmore, Bath, UK; Fiona Godfrey, Paris, France; Ellen Gritz, Houston, USA; Isabelle Groß, Bochum, Germany; Per Gustavsson, Stockholm, Sweden; Johnni Hansen, Copenhagen, Denmark; Joe Harford, Bethesda, MD, USA; Richard B. Hayes, Bethesda, USA; Dick Heederik, Utrecht, The Netherlands; Pirjo Heikkilä, Helsinki, Finland; Kari Hemminki, Huddinge, Sweden; Rolando Herrero, San José, Costa Rica; Ivana Holcatova, Prague, Czech Republic; Elisabeth Holly, San Francisco, USA; Mariette Hooiveld, Nijmegen, The Netherlands; Vladimir Janout, Olomouc, Czech Republic; Dhaval Jetly, Ahmedabad, India; Karl-Heinz Jöckel, Essen, Germany; Christoffer Johansen, Copenhagen, Denmark; Jøn G. Jønasson, Reykjavik, Iceland; Timo Kauppinen, Helsinki, Finland; Karl Kelsey, Boston, USA; Kristina Kjaerheim, Oslo, Norway; Sergio Koifman, Rio de Janeiro, Brazil; Pagona Lagiou, Athens, Greece; Maria Teresa Landi, Bethesda, USA; Jerome Lavoue, Lausanne, Switzerland; Hans Kromhout, Utrecht, The Netherlands; Pagona Lagiou, Athens, Greece; Sverre Langård, Oslo, Norway; Philip Lazarus, Hershey, USA; Fabio Levi, Lausanne, Switzerland; José Eduardo Levi, São Paulo, Brazil; David Levy, Calverstone, USA; Donghui Li, Houston, USA; Marja-Liisa Lindbohm, Helsinki, Finland; Jolanta Lissowska, Warsaw, Poland; Ray Lowry, Newcastle, UK; Danièle Luce, Villejuif, France; Gary Macfarlane, Manchester, UK; Manoj Mahimkar, Mumbai, India; Patrick Maisonneuve, Milan, Italy; Reza Malekzadeh, Tehran, Iran; Andrea 't Mannetje, Wellington, New Zealand; Dana Mates, Bucharest, Romania; Aleyamma Mathew, Trivandrum, India; Elena Matos, Buenos Aires, Argentina; Marc Maynadié, Dijon, France; Mary McBride, Vancouver, Canada; Bernard McCartan, Dublin, Ireland; Ana Menezes, Pelotas, Brazil; Sofia D. Merajver, Ann Arbor, USA; Franco Merletti, Turin, Italy; Andres Metspalu, Tartu, Estonia; Dario Mirabelli, Turin, Italy; Anush Moukeria,

Moscow, Russia; Joshua Muscat, Hershey, USA; Alexandra Nieters, Heidelberg, Germany; Hannu Norppa, Helsinki, Finland; Silvia Novello, Turin, Italy; Olof Nyrén, Stockholm, Sweden; Jørgen Olsen, Copenhagen, Denmark; Andrew Olshan, Chapel Hill, USA; Neil Pearce, Wellington, New Zealand; Markku Pekurinen, Helsinki, Finland; Armando Peruga, Geneva, Switzerland; Beate Pesch, Bochum, Germany; Susan Peters, Utrecht, the Netherlands; Gloria Petersen, Rochester, US; Richard Peto, Oxford, UK; John Pierce, San Diego, USA; Iris Pigeot, Bremen, Germany; Nils Plato, Stockholm, Sweden; Hermann Pohlman, Bremen, Germany; Lützen Portengen, Utrecht, The Netherlands; Akram Pourshams, Tehran, Iran; Eero Pukkala, Helsinki, Finland; Mark Purdue, Bethesda, USA; Lorenzo Richiardi, Turin, Italy; Marjorie Romkes, Pittsburgh, US; Peter Rudnai, Budapest, Hungary; Konrad Rydzynsky, Lodz, Poland; Suleeporn Sangrajrang, Bangkok, Thailand; Silvia de Sanjosé, Barcelona, Spain; Stephen Schwartz, Seattle, US; Chia Kee Seng, Singapore; Jack Siemiatycki, Montreal, Canada; Judith Shaham, Raanana, Israel; K. T. Shenoy, Trivandrum, India; Lorenzo Simonato, Padova, Italy; Elaine Smith, Iowa city, US; Amr Soliman, Ann Arbor, USA; Masoud Sotoudeh, Tehran, Iran; Margaret Spitz, Houston, USA; Anthony Staines, Dublin, Ireland; Eduardo De Stefani, Montevideo, Uruguay; Isabelle Stücker, Villejuif, France; Erich Sturgis, Houston, US; Sunil Surange, Bhopal, India; Ole Svane, Copenhagen, Denmark; Neonila Szeszenia-Dabrowska, Lodz, Poland; Renato Talamini, Aviano, Italy; Jon M. Tonita, Saskatchewan, Canada; Elizabeth Tracey, Kings Cross, Australia; Antonia Trichopoulou, Athens, Greece; Dimitrios Trichopoulos, Athens, Greece; Donna Vallone, Washington, USA; Lars Vatten, Oslo, Norway; Carlo La Vecchia, Milan, Italy; Gajalakshmi Vendhan, Chennai, India; Roel Vermeulen, Utrecht, the Netherlands; Paolo Vineis, Turin, Italy; Frank de Vocht, Manchester, UK; Martine Vornanen, Tampere, Finland; Qingyi Wei, Houston, US; Elisabete Weiderpass, Oslo, Norway; Denise Whitby, Frederick, USA; Heinz-Erich Wichmann, Neuherberg, Germany; Debbie Winn, Bethesda, USA; Victor Wünsch-Filho, São Paulo, Brazil; Ayda Yurekli, Geneva, Switzerland; David Zaridze, Moscow, Russia; Witold Zatonski, Warsaw, Poland; Zuo-Feng Zhang, Los Angeles, USA; Ariana Znaor, Zagreb, Croatia.

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# RADIATION GROUP (RAD)

## Head

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(until March 2008)

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Dr Martine Vrijheid  
(until January 2008)

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Mrs Monika Moissonnier  
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Ms H el ene Tardy (until June 2008)  
Ms Vanessa Tenet (until August 2009)

## Secretary

Mrs Catherine Chassin

## Visiting scientists and postdoctoral fellows

Dr Anne-Sophie Evrard  
(until January 2009)  
Dr Andrei Karotki

THE SCOPE OF THE WORK IN THE RADIATION GROUP ENCOMPASSES BOTH IONISING AND NON-IONISING RADIATION.

The main objective of the research on ionising radiation is to provide answers to some of the outstanding questions in radiation protection and radiation carcinogenesis, specifically the shape of the dose–response relationship at low doses, the effects of different types of radiation, and individual variability in cancer risk and genetic susceptibility to cancer.

An unprecedented increase in the use of sources of non-ionising electromagnetic fields in occupational and environmental settings has brought public concerns about possible health risks associated with their use. At IARC, work has mainly focused on exposure to the radio frequency (RF) radiation emitted by mobile telephones.

## IONISING RADIATION

**Case–control studies of haematological malignancies and thyroid cancer among Chernobyl liquidators** from Belarus, Estonia, Latvia, Lithuania and Russia have been finalised. The two studies included 107 cases of thyroid cancer and 117 cases of malignancies of lymphoid and hematopoietic tissue, and 904 controls. For all haematological malignancies combined, the Excess Relative Risk (ERR) per 100 mGy was 0.60 (90% confidence interval (CI): -0.02–2.35) (Kesminiene *et al.*, 2008). The corresponding estimates for leukaemia

excluding chronic lymphoid leukaemia (CLL), and for CLL were 0.50 (90% CI 0.38–5.7) and 0.47 (90% CI n.d.–7.6), respectively. A significantly elevated risk was observed for thyroid cancer, similar to that obtained in the recent studies of thyroid cancer following exposure to iodine-131 in childhood; the ERR per 100 mGy was 0.38 (95% CI 0.10–1.09) (Kesminiene *et al.*, submitted).

The **GENE-RAD-RISK** project was established to formally evaluate whether pathogenic alleles in DNA repair and damage recognition genes have an increased risk of breast cancer following exposure to ionising radiation, even at low doses. A multi-national study (France, Italy, the Netherlands and the UK) of pre-menopausal breast cancer risk is underway in populations chosen on the basis of their high prevalence of radiation exposure (childhood cancer and Hodgkin lymphoma survivors) and/or high prevalence of known mutations in susceptibility genes (BRCA1 and BRCA2 mutation carriers). More than 600 cases of breast cancer have been identified to date in the cancer survivor and Hodgkin lymphoma cohorts, and nearly 1500 cases in the mutation carrier cohorts. Data collection and dose reconstruction have been completed, and analyses are expected to be completed in early 2010.



Courtesy of J. Seppala, Turku University Hospital, Finland

Diagnostic radiation represents an indispensable, sometimes life-saving, tool in modern medicine. However, the growing use of diagnostic X-rays and of relatively high-dose techniques (CT scans, interventional procedures) is a topic of concern in radiological protection, especially in children and adolescents. The increasing use of paediatric diagnostic exposures is therefore a unique opportunity to address the possible health effects of low doses of radiation in an a priori particularly sensitive population. The **Child-Med-Rad** project is aiming to assess the feasibility of establishing trans-national cohorts suitable for long-term follow-up and to make recommendations concerning future research needs. The countries included in this project at the outset are: Denmark, Finland, France, Germany, the Netherlands, Spain, Sweden and the UK. Scientists from Australia, Canada, Israel, Japan, Korea, and the USA and from the WHO (Geneva) are also involved as experts to ensure that planned studies are fully harmonised with other existing or planned activities around the world.

Despite numerous studies, the exact consequences of the Chernobyl accident remain a matter of debate, and the future

direction of health research has been subject to wide differences of opinion. The **Agenda for Research on Chernobyl Health (ARCH) project** is conducting a 'scoping study' of all relevant research to determine where research efforts are most needed and to advise on the potential value of proposed studies to public-health decision making. The main output of ARCH will be a strategic research agenda (SRA) for short-, medium- and long-term research on the health consequences of the accident. The development of a sound SRA necessitates the coordinated efforts of a critical mass of experts with knowledge of the accident's impact on human health. Project partners are dispersed throughout Europe, including the three most affected countries, Belarus, the Russian Federation and Ukraine.

#### NON-IONISING RADIATION

The **INTERPHONE Study**, a series of multinational case-control studies established to determine whether mobile telephone use increases the risk of cancer and, specifically, whether the radio-frequency radiation emitted by mobile telephones is carcinogenic, has now been completed. Separate studies have

been carried out for acoustic neurinoma, glioma, meningioma and tumours of the parotid gland. These studies used a common core protocol and were carried out in Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK. Details of the study protocol and procedures have been published (Cardis *et al.*, 2007). A manuscript presenting the results of the international analyses of the relation between mobile phone use and risk of glioma and meningioma has been submitted for publication.

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## SECTION OF NUTRITION AND METABOLISM (NME)

### Head

Dr Silvia Franceschi

POOR NUTRITION IS AN IMPORTANT CANCER RISK FACTOR IN THE DEVELOPED WORLD, ALTHOUGH THE ROLE OF SPECIFIC NUTRITIONAL FACTORS AND THEIR MECHANISMS OF ACTION REMAIN ILL-UNDERSTOOD. OVERWEIGHT AND OBESITY REPRESENT A GLOBAL EPIDEMIC CONTRIBUTING TO A NUMBER OF COMMON CHRONIC DISEASES, INCLUDING CANCER. AT THE SAME TIME, LACK OF PHYSICAL ACTIVITY AND ENERGY BALANCE ARE INCREASINGLY RECOGNISED AS BEING IMPORTANT DETERMINANTS OF CANCER RISK. IN LOW- AND MIDDLE-INCOME COUNTRIES THE ROLE OF DIET IS FAR LESS STUDIED, AND FUTURE RESEARCH SHOULD INCLUDE UNDER-NUTRITION AS WELL AS OVER-NUTRITION.

In the recent re-organisation of the IARC scientific structure, a new Section of Nutrition and Metabolism was created. Its main objectives are to investigate the causes and prevention of cancer in association with diet (including biomarkers of diet), obesity, physical inactivity and endogenous hormones, through different existing (e.g. the EPIC study) and new epidemiological and clinical studies in developed and middle- and low-income countries. The NME section is also charged with investigating the role of nutrition and metabolism in cancer etiology using internal laboratory facilities and complementary expertise from internal and external support and collaborations.

Selection of a new section head is underway, and therefore new research activities for the next biennium are under discussion. As such, only activities related to the Dietary Exposure Assessment (DEX) Group (formerly the Nutrition and Hormone [NTR] Team) are reported here.



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Dr Aurelie Moskal  
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Dr Kimberley Bouckaert  
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Nicole Suty (until October 2008)

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Carine Biessy

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Jérôme Vignat

DIET IS CONSIDERED AN IMPORTANT ENVIRONMENTAL FACTOR IN THE ETIOLOGY OF SEVERAL MAJOR CANCERS. HOWEVER, THERE ARE STILL INCONSISTENT RESULTS ON THE RELATIONSHIPS BETWEEN DIET AND CANCER, LEADING TO A CRITICAL EVALUATION OF THE TRADITIONAL STUDY DESIGNS AND METHODOLOGICAL APPROACHES USED SO FAR. THE MAIN OBJECTIVES OF THE DEX GROUP ARE TO IMPROVE THE ACCURACY, UNDERSTANDING AND INTERPRETATION OF DIETARY EXPOSURE AND TO STRENGTHEN THE LIKELIHOOD OF DETECTING ASSOCIATIONS BETWEEN DIET AND CANCER AND OTHER INTERMEDIATE DISEASES IN INTERNATIONAL STUDY CONTEXTS. OVER THE LAST TWO YEARS, DEX HAD FIVE MAJOR AXES OF ACTIVITIES, DETAILED BELOW:

## 1. ADVANCED RESEARCH ON DIETARY METHODOLOGIES AND LABORATORY ACTIVITIES FOR INTERNATIONAL STUDIES

A focal point of the DEX Group is to develop methods for the standardisation of dietary data collection, data processing and statistical analyses in large international multi-centre studies. This involves the development of a standardised computerised 24-hour dietary recall programme (EPIC-Soft<sup>™</sup>) and the enrichment and maintenance of a large international standardised nutrient database (ENDB) and its related database management system program (EnMan). Over the last two years, the EPIC-Soft programme initially developed for EPIC in the early 1990s has been substantially restructured and extended so that it may be used as a standardised method and reference in future international studies. Furthermore, a comprehensive platform to be hosted on the IARC website is under development to facilitate the use and dissemination of the whole EPIC-Soft methodology. Discussions at the international level (the European Food

Safety Authority, the Directorate General for Health and Consumer Affairs [DG-SANCO], WHO, the European Food Information Resource [EuroFIR] Network) are ongoing to establish a network of future possible users of the platform and plan new inter-disciplinary projects on cancer research and prevention.

More recently, a new international methodological project has been initiated to compare different multivariate approaches (e.g. principal component analysis, cluster analysis) relevant to analyses of diet-disease associations in international study context. In this project the DEX group, in collaboration with the IARC Biostatistics Group (BST), is specifically in charge of the nutrient and biological pattern analyses, with already-planned applications to cancer and diabetes.



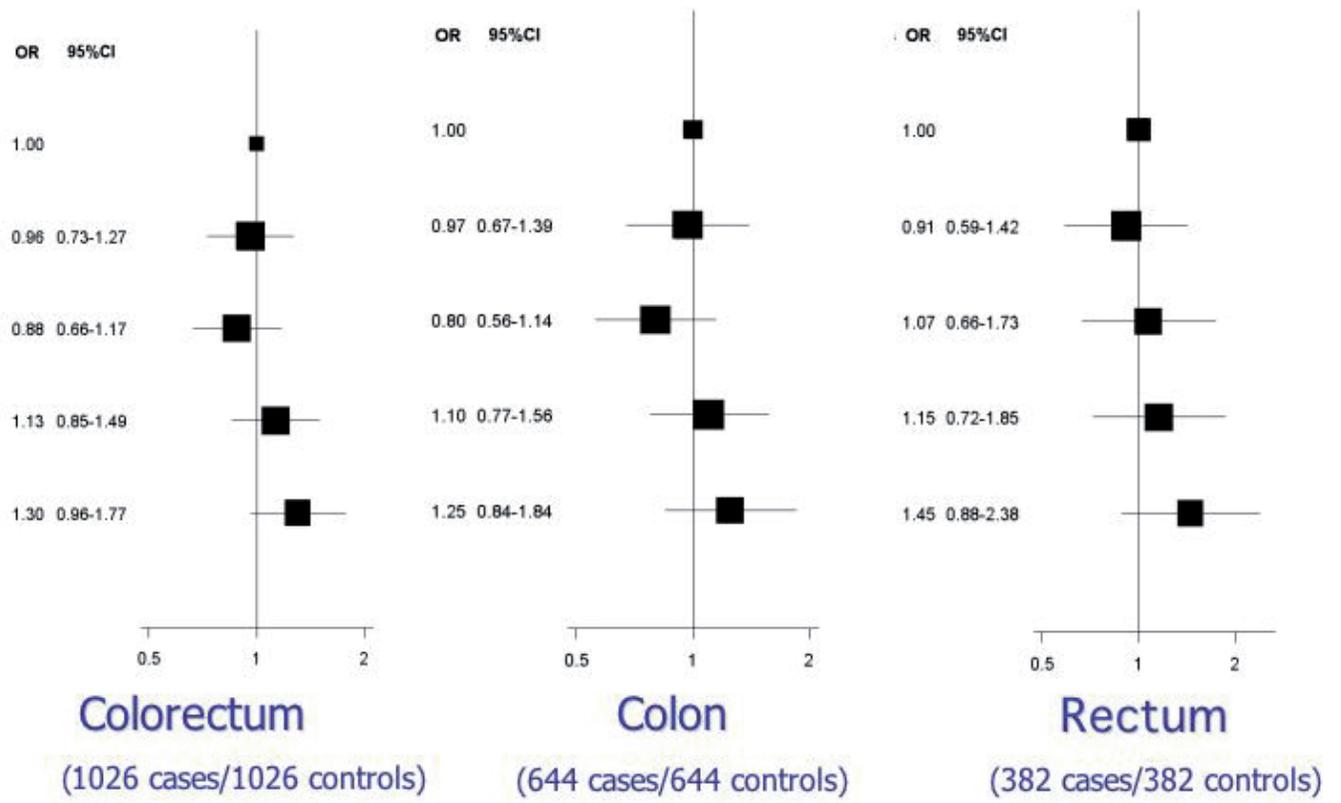


Figure 2. Glycated hemoglobin and risk of colorectal cancer: EPIC. Rinaldi et al., Cancer Epidemiol Biomarkers Prev. 2008

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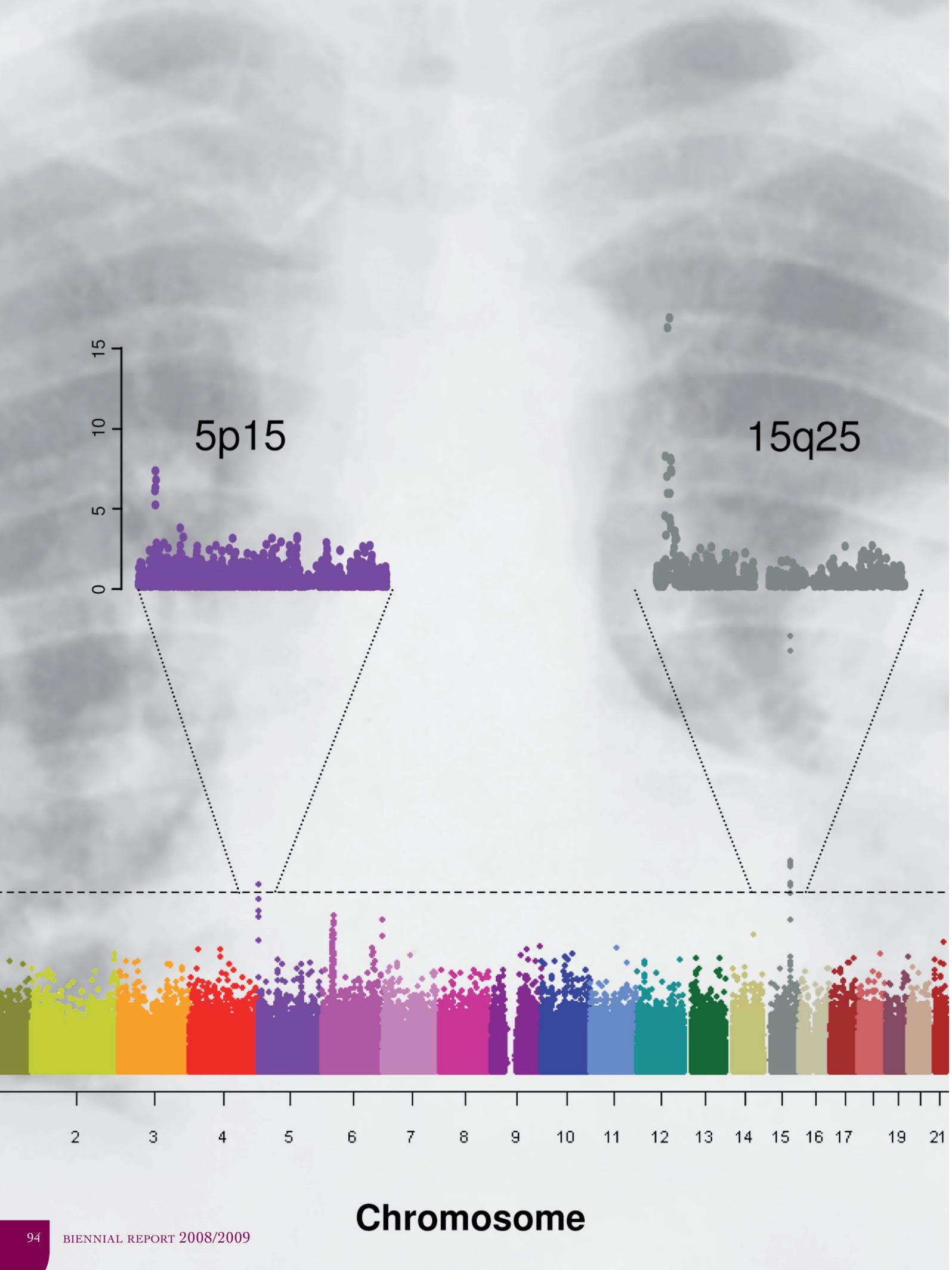
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# SECTION OF GENETICS (GEN)

**Section Head**  
Dr Paul Brennan

IDENTIFYING SPECIFIC GENES AND GENE VARIANTS THAT CONTRIBUTE TO THE DEVELOPMENT OF CANCER IS IMPORTANT FOR A NUMBER OF REASONS. THESE INCLUDE UNDERSTANDING IN GREATER DEPTH THE BIOLOGICAL PATHWAYS THAT ARE INVOLVED IN CANCER, ELUCIDATING HOW ENVIRONMENTAL FACTORS MAY EXERT THEIR EFFECTS IN COMBINATION WITH GENES, AND IDENTIFYING INDIVIDUALS WHO ARE AT HIGH ENOUGH RISK THAT THEY ARE LIKELY TO BENEFIT FROM EXISTING RISK REDUCTION STRATEGIES.

The Genetics Section comprises two Groups with the overall mission of identifying genes involved in cancer, characterising the spectrum of pathogenic sequence variants that they harbour, and understanding how they interact with non-genetic factors. These are the Genetic Epidemiology Group (GEP) and the Genetic Cancer Susceptibility Group (GCS). GEP is mainly involved in coordinating large population-based epidemiological studies and analysis of multiple common genetic variants in order to identify new susceptibility loci. Cancers of primary interest include those of the lung and upper aerodigestive tract (including the nasopharynx) as well as kidney cancer and rarer childhood cancers. GCS is mainly involved in identification of rare variants or mutations in known or strong candidate cancer loci that result in a substantial cancer risk. The main focus is on breast cancer, in particular basal-type breast tumours, with a growing interest in melanoma. Findings from the GCS Group may have direct prevention implications by resulting in more accurate analysis of clinical mutation screening data from high-risk susceptibility genes such as BRCA1, BRCA2, MLH1 and MSH2. GCS also provides a genotyping platform service for both Groups.



# GENETIC EPIDEMIOLOGY GROUP (GEP)

**Group Head**

Dr Paul Brennan

**Scientists**

Dr James McKay

Dr Ghislaine Scelo

**Staff**

Ms Amelie Chabrier

Ms Valerie Gaborieau

Ms Yvette Granjard

Ms Helene Renard

**Visiting scientists**

Dr A. Boroda (May 2009–June 2009)

**Postdoctoral fellows**

Dr D. Anantharaman (from January 2009)

Dr K. Braga Ribeiro (from October 2007)

Dr D. Chen

Dr J. Fachiroh

Dr M. Johansson (from September 2008)

Dr E. Lips (February 2008–January 2009)

Dr K. Szymanska (until April 2008)

Dr M. Timofeeva (from July 2009)

Dr T. Truong (from December 2007)

Dr K. Urayama

**Students**

M. Delahaye

Mr S. Oh (July 2008–October 2008)

J. Matyjasik (February 2008–July 2008)

M. Lener (February 2008–July 2008)

GEP is currently undertaking large multi-partner genetic epidemiology studies of cancers strongly related to tobacco and alcohol—principally lung and aerodigestive cancers, but also kidney cancers. These include candidate gene studies, and increasingly genomewide association studies.

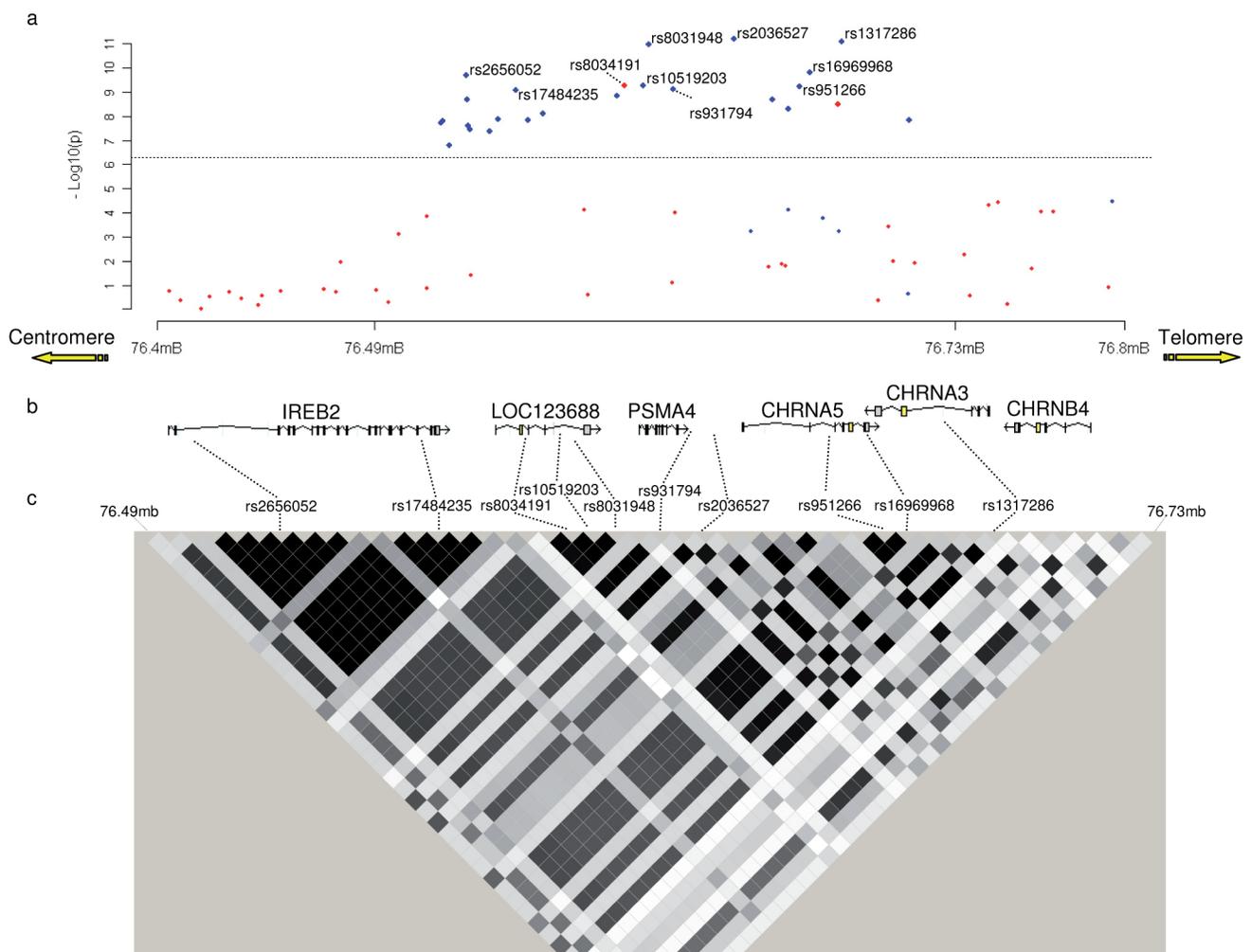
A series of large multicentre case-control studies of lung, upper aerodigestive and kidney cancers has been completed in

Europe and Latin America, comprising over 15 000 subjects. Genomewide association studies are currently underway in collaboration with the Centre National de Genotypage (Evry, France) to help identify new genes for these cancers, and the first results for lung cancer have been published (Hung *et al.*, Nature 2008; Mc Kay *et al.*, Nature Genetics, 2008).

The Group is also working with the International Lung Cancer Consortium (ILCCO) and the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, with the aim of pooling

information and results from all large studies of lung and aero-digestive cancers.

A large genome-wide study of kidney cancer is also underway in collaboration with the Centre National de Genotypage and the US National Cancer Institute. Complete results are expected before the end of 2009. Plans have also been developed in collaboration with the Centre International de Genotypage for a large-scale tumour sequencing project of kidney tumours (the CAGEKID project).



The 15q25 Lung cancer susceptibility locus identified by the IARC lung cancer genome-wide association study. This locus contains three nicotinic acetylcholine receptor genes, *CHRNA5*, *CHRNA3* and *CHRN4*. (a) P-values for SNPs genotyped in the 15q25 region (76.4-76.8mB). The blue line indicates the threshold of  $p < 5 \times 10^{-7}$  at which results were considered genome-wide significant. Points labeled with rs numbers have a  $p < 1 \times 10^{-9}$ . Points in red are genotyped in the 317K Illumina panel; points in blue indicate additional genotyped SNPs (Taqman). (b),(c) The high LD genomic region approximately delineated by rs4887053 (76.49 mB) and rs12594247 (76.73 mB) containing the SNPs strongly associated with lung cancer risk. (b) The positions of the 6 known genes. (c) The pairwise  $r^2$  estimates for the 46 common SNPs from 76.49mB and 76.73mB in controls of the central Europe IARC study, with increasing shades of grey indicating higher degree of  $r^2$  values. The majority of pairwise  $D'$  estimates for these SNPs exceed 0.8.

## RUSSIAN COHORT STUDY

We are coordinating a large cohort study in Russia, along with colleagues in the Cancer Research Centre of Moscow and the Clinical Trials Service Unit of the University of Oxford. Over 200 000 adults have already been recruited from 3 cities in Western Siberia (Barnaul, Biysk and Tomsk) with collection of extensive questionnaire information and DNA. Follow-up is underway to identify cancer and other chronic disease outcomes, and future analyses will focus on understanding the causes of the extremely high mortality rates among adults in middle age in this region. Initial analysis of over 50 000 people from these regions who died of various causes has provided strong evidence that alcohol is the cause of more than half of all Russian deaths at ages 15–54, and accounts for most of the recent large fluctuations in Russian mortality (Zaridze *et al.*, Lancet 2009).

## 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-fold higher. Endemic regions include the southern parts of China, other parts of Southeast Asia, and the Maghreb (Morocco, Algeria and Tunisia). Along with partners in Malaysia and Thailand, we are conducting studies on the role of genes and environmental factors in the etiology of NPC in Southeast Asia. This study aims to be one of the world's largest studies of NPC with at least 1000 case-control pairs as well as multi-case families. Currently the study sites consist of nationwide efforts in Thailand coordinated by the National Cancer Institute in Bangkok, and in the Sarawak region of Malaysia coordinated by the Kuching General Hospital. Upon completion of recruitment, we aim to conduct genome-wide studies of NPC to investigate genes associated with onset and survival.

## CANCER IN CHILDREN AND YOUNG ADULTS

We are helping to initiate pilot studies of non-central nervous system embryonal cancers that occur in childhood and young adulthood. Apart from most common cancers at these ages (leukemia and central nervous system tumours), there is a lack of large-scale etiological studies in all types of childhood cancers, and data on causes and mechanisms are very limited. With a large international study, we aim to investigate the role of exposure to suspected risk factors at different key periods (preconceptional, prenatal, and postnatal), genetic susceptibility factors and gene-environment interactions, as well as novel molecular markers (e.g. DNA methylation and repair capacity). The study will include retinoblastoma, Wilms' tumour, rhabdomyosarcoma, neuroblastoma, and hepatoblastoma.

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## MEETINGS HOSTED BY THE GENETIC EPIDEMIOLOGY GROUP

Central Europe studies on Pancreatic and Kidney Cancer Study Group Meeting – Prague, Czech Republic - 8 April 2008

Central Europe studies on Pancreatic and Kidney Cancer Study Group Meeting – Prague, Czech Republic - 3-4 March 2009

6th Annual ILCCO (International Lung Cancer Consortium) meeting – Paris, France - 23-24 March 2009

Kidney Cancer Genomics Meeting – Lyon, France - 19 October 2009



# GENETIC CANCER SUSCEPTIBILITY (GCS)

## Group Head

Dr Fabienne Lesueur (acting)  
Dr Sean Tavtigian  
(until October 2009)

## Secretary

Ms Antoinette Trochard

## Scientist

Dr Florence Le Calvez-Kelm

## Staff

Mr Geoffroy Durand  
Ms Nathalie Forey  
Ms Sandrine McKay-Chopin  
Ms Jocelyne Michelin  
Ms Nivonirina Robinot  
Ms Catherine Voegelé

## Visiting Scientists

Prof. A. Thomas  
(May 2009-June 2009)

## Postdoctoral fellows

Dr J. Ahmad  
Dr F. Damiola  
(from November 2008)  
Dr S. Garritano  
(until August 2008)

## Students

Ms A. Herkert  
(October 2008-November 2008)  
Ms B.T.T. Nguyen  
Ms C. Tessereau  
(February 2009-May 2009)  
Ms R. Tricarico  
(September 2009-October 2009)  
Mr M. Vallée

DURING THE 2008 AND 2009, THE GCS GROUP HAS BEEN ACTIVE IN FOUR AREAS: ANALYSIS OF UNCLASSIFIED VARIANTS IN HIGH-RISK CANCER SUSCEPTIBILITY GENES, CASE-CONTROL MUTATION SCREENING OF INTERMEDIATE-RISK BREAST CANCER SUSCEPTIBILITY GENES, THE GENETICS OF MELANOMA SUSCEPTIBILITY, AND DEVELOPMENT OF AN ARRAY SERVICES PLATFORM TO SUPPORT MULTI-GROUP COLLABORATIVE PROJECTS.

## ANALYSIS OF UNCLASSIFIED VARIANTS.

In North America, Europe, Australia and Japan, genetic testing of high-risk cancer susceptibility genes is becoming an increasingly important component of the clinical management of at-risk patients and their close relatives. The vast majority of genetic testing of cancer susceptibility genes is directed towards the established high-risk breast cancer and colon cancer susceptibility genes, especially BRCA1, BRCA2, MLH1 and MSH2. De novo testing of an at-risk patient usually involves a mutation screen of the coding exons and proximal splice junction regions of the underlying susceptibility gene(s), often augmented with a screen for duplications or deletions of individual exons (\*Tavtigian and Le Calvez-Kelm, 2007); consequently, the tests are technologically demanding and relatively expensive.

In addition to insertion-deletion mutations and other protein truncating sequence variants that are highly likely to damage protein function and are consequently generally classified as pathogenic *a priori*, mutation screening often reveals the presence of single nucleotide substitutions and other variants whose effects on gene function and disease risk are not immediately predictable. As a group, these are often referred to as

unclassified variants (UVs). Over the last several years, we have contributed to a consortium focusing on the analysis of UVs in BRCA1 and BRCA2. Three notable achievements of our consortium have been: (1) to create a Bayesian method for assessing UVs that combines data across several independent data types in order to calculate an integrated posterior probability that a sequence variant is pathogenic (\*Goldgar *et al.*, 2004, \*Easton *et al.*, 2007; \*Goldgar *et al.* 2008; \*Tavtigian *et al.*, 2008); (2) to convene in February 2008 an IARC Working Group on Unclassified Genetic Variants that resulted in clinically applicable guidelines for UV classification (\*Plon *et al.*, 2008) (Tables 1 and 2) and began the diffusion of our Bayesian integrated evaluation beyond the breast cancer genetics community; and (3) to convene in February 2009 an IARC Working Group on Unclassified Genetic Variants in the mismatch repair genes, with the specific intent of adapting the Bayesian integrated evaluation to the colon cancer susceptibility genes.

**Table 1. Proposed Classification System for Sequence Variants Identified by Genetic Testing**

Class	Description	Probability of being pathogenic
5	Definitely pathogenic	>0.99
4	Likely pathogenic	0.95–0.99
3	Uncertain	0.05–0.949
2	Likely not pathogenic or of little clinical significance	0.001–0.049
1	Not pathogenic or of no clinical significance	<0.001

**Table 2. Testing Recommendations Associated with Each Class of Variant**

Class	Clinical Testing	Surveillance recommendations if at-risk relative is positive	Research testing of family members
5	Test at-risk relatives for variant	Full high-risk surveillance guidelines	Not indicated
4	Test at-risk relatives for variant <sup>a</sup>	Full high-risk surveillance guidelines	May be helpful to further classify variant
3	Do not use for predictive testing in at-risk relatives <sup>a</sup>	Based on family history (and other risk factors)	May be helpful to further classify variant
2	Do not use for predictive testing in at-risk relatives <sup>a</sup>	Treat as “no mutation detected” for this disorder”	May be helpful to further classify variant
1	Do not use for predictive testing in at-risk relatives <sup>a</sup>	Treat as “no mutation detected” for this disorder”	Not indicated

<sup>a</sup>Recommend continuing to test proband for any additional testing modalities available for the disorder in question: e.g., rearrangement testing.

**CASE-CONTROL MUTATION SCREENING OF INTERMEDIATE-RISK BREAST CANCER SUSCEPTIBILITY GENES.** The known high-risk breast cancer susceptibility genes explain about 25% of the familial relative risk of breast cancer, and the common risk-SNPs detected by recent GWAS studies are not responsible for more than about 10% of the familial relative risk. Thus in breast cancer (as well as colon and prostate cancer) genetics, there is an emerging problem of «missing heritability» (Maher, 2008; Easton and Eeles, 2008). One strong possibility is that uncommon-to-rare variants in intermediate-risk susceptibility genes, typified by ATM and CHEK2, are responsible for an important component of the missing heritability.

We are just finishing Year 2 of a 5-year NIH-funded project to examine this hypothesis. The main approach of the project is full open reading frame mutation screening of carefully selected candidate genes from a series of 1250 breast cancer cases and a similar number of ethnically-matched controls. The candidate genes

are selected each year by an advisory committee, and the majority of the cases and controls are from the population centers of the NIH sponsored Breast Cancer Family Registries. Preliminary results have been encouraging. We have published a laboratory methods paper (\*Nguyen *et al.*, 2009) and an analysis of the intermediate risk susceptibility gene ATM (\*Tavtigian *et al.*, 2009). In the latter work we demonstrate the effectiveness of our bioinformatic approach to analysis of rare missense substitutions while also demonstrating the importance of rare missense substitutions in ATM to breast cancer susceptibility. Over the next three and a half years, we will be able to analyse a considerable number of candidate genes via this approach, and look forward to further elucidating the genetic basis of breast cancer susceptibility.

**GENETICS OF MELANOMA SUSCEPTIBILITY.** Mutations in two genes encoding cell cycle regulatory proteins have been shown to cause familial cutaneous malignant melanoma (CMM). About 20%

of melanoma-prone families bear a point mutation in the CDKN2A locus at 9p21, which encodes two unrelated proteins, p16 (INK4a) and p14 (ARF). Rare mutations in CDK4 have also been linked to the disease. Although the CDKN2A gene has been shown to be the major melanoma predisposing gene, there remains a significant proportion of melanoma kindreds linked to 9p21 in which germline mutations of CDKN2A have not been identified through direct exon sequencing. To assess the contribution of large rearrangements in CDKN2A to the disease, we performed multiplex ligation-dependent probe amplification (MLPA) in the French melanoma-prone families set. Overall, we showed that genomic deletions represent 2.1% of total mutations in this series (\*Lesueur *et al.*, 2008).

In melanoma-prone families, the effect of CDKN2A is modified by subject-related phenotypes such as skin type, nevus count and sun sensitivity, as well as genetic variants in the highly polymorphic

pigmentation gene MC1R. We have investigated the effect of the GST genes, which are involved in detoxification of metabolites after UV exposure, on melanoma risk in multigenerational melanoma-prone families with CDKN2A mutations. We found that the GSTT1 null allele modifies the risk of developing melanoma in carriers of a high-risk CDKN2A mutation, even after adjustment for MC1R genotype and host factors. Thus it is becoming clear that multiple genetic modifiers influence melanoma risk (\*Chaudru *et al.*, 2009).

Following a strategy similar to one we have developed to identify and analyse intermediate-risk genes for breast cancer, our next goal is to investigate strong candidate genes of the pigmentation pathway through a case-control mutation screening using subjects from the EPIC cohort.

**ARRAY SERVICES.** The GCS Group took delivery of an Illumina BeadArray reader/ Goldengate platform in April 2008. Workflows for SNP genotyping, methylation profiling and gene expression profiling have been validated, and GCS staff have been trained accordingly. Several projects have been executed on the Illumina platform. In support of a GCS breast cancer genetics project, we have created and validated a custom 384-SNP worldwide ancestry informative marker panel. In support of an EGE project, we used the Illumina Cancer Panel I methylation kit to profile the promoter methylation of 807 cancer-related genes in a series of hepatocellular, breast and esophageal carcinomas and surrounding tissues. Manuscripts related to the methylation studies are in preparation, and larger sample series will likely be analysed in the near future. In support of a MOC project, the Illumina Platform was used to perform gene expression profiling on a series of breast cancer cell lines to assess how p53 status affects the transcriptional response of these cells to estradiol or to the selective estrogen receptor modulator tamoxifen. Analyses are ongoing and a manuscript should follow.

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## MEETINGS HOSTED BY THE GENETIC CANCER SUSCEPTIBILITY GROUP

Unclassified Variants Clinical Interpretation Workshop – Lyon, France - 4-5 February 2008

Unclassified Variants in Mismatch Repair Genes Working Group – Lyon, France - 19-20 February 2009

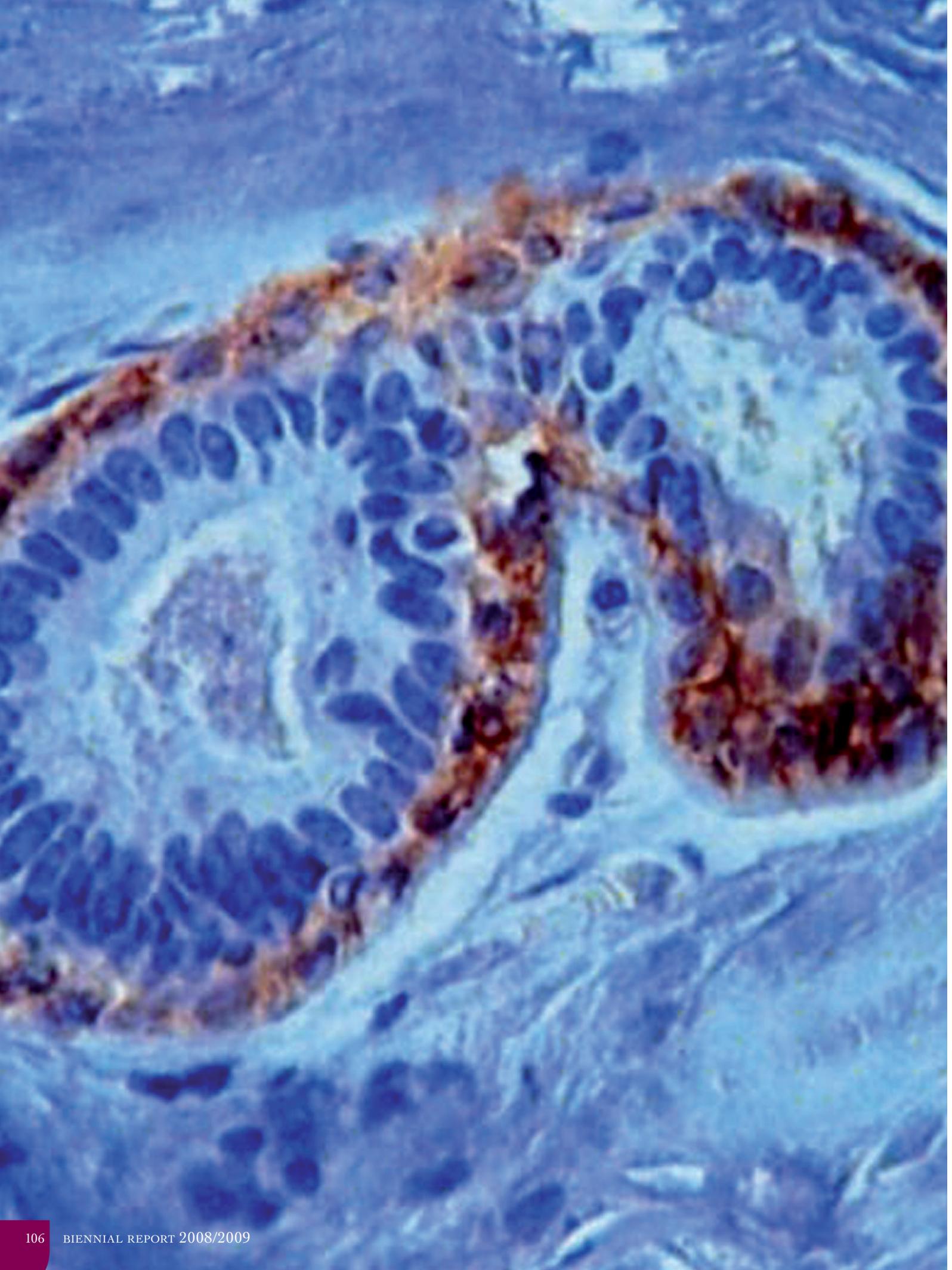
# SECTION OF EARLY DETECTION & PREVENTION (EDP)

## **Section Head**

Dr Rengaswamy Sankaranarayanan

THE SECTION OF EARLY DETECTION AND PREVENTION COMPRISES THREE GROUPS: THE PREVENTION GROUP (PRE), THE QUALITY ASSURANCE GROUP (QAS) AND THE SCREENING GROUP (SCR).

The Section seeks to provide evidence as to which primary and secondary prevention interventions are appropriate, effective and cost-effective in lowering the global burden of breast, cervical, oral, colorectal, skin and prostate cancers. This approach includes studying the means to implement integrated and quality-assured interventions in routine settings in different parts of the world. These research topics are in tune with the overall mission of the Agency in that they aim to reduce cancer burden by prevention.



# PREVENTION GROUP (PRE)

**Group Head**

Dr Philippe Autier

**Scientists**

Dr Mathieu Boniol

Dr Graham Byrnes (until April 2009-moved to CIN/BST)

**Secretariat**

Ms Asiedua Asante

Ms Anne Sophie Hameau (until March 2008)

Ms Laurence Marnat (February 2008-May 2008)

**Visiting scientists**

Prof Brian Cox (from June 2008 to December 2008)

Dr Jean-Francois Dore

Dr Jan Alvar Lindencrona (until March 2008)

Ms Carolyn Nickson (March 2009-May 2009)

Prof Peter Selby (July 2009-December 2009)

Ms Mary Jane Sneyd (June 2009-December 2009)

**Clerks**

Ms Murielle Colombet (until December 2008)

Myriam Adjal (until February 2009)

**Students**

Lorraine Bernard (February 2008-August 2008)

Maria Bota (July 2008-August 2008)

Anne Elie Carsin (January 2008-April 2008)

Gwendoline Chaize (May 2008-August 2008)

Clementine Joubert (March 2008-August 2008)

Alice Koechlin (May 2009-August 2009)

Anthony Montella (June 2008-August 2008)

**PhD students:**

Clarisse Hery (from June 2008)

Isabelle Chaillol (from October 2008)

## EXPOSURE TO ULTRAVIOLET RADIATION (UV) AND SKIN CANCER

The Prevention Group has international expertise on skin cancer and ultraviolet radiation, and regularly publishes on these topics. PRE staff are active members of international societies on skin cancer such as Euroskin and the EORTC Melanoma Group.

The main project in this domain in 2008–2009 is the Quantification of Sun Exposure in Europe and its Effects on Health (the Eurosun Project), a three-year project designed to monitor ultraviolet exposure in the European union and its effects on the incidence of skin cancers and cataracts. Meteorological satellite data will be used to calculate exposure to various UV wavelengths for European populations; these data will be used to produce an atlas of UV exposure in Europe, which will contain maps similar to the one displayed in Figure 1. These data will also serve to predict the global EU burden of UV-related diseases in the future. Concurrent with this project is a similar one, limited to France, funded by AFSSET (Agence Française de Sécurité Sanitaire de l'Environnement et du Travail, Paris).

The Prevention Group has a broad agenda on indoor tanning issues, and participated in the 2009 IARC Monographs Volume 100-D meeting on radiation that classified this exposure as a Group I carcinogen. Ongoing collaborations with the WHO aim to translate into public health terms the most recent scientific evidence on the deleterious effects of exposure to artificial UV radiation.

## VITAMIN D AND CANCER

An international IARC Working Group was established in 2007–2008 to investigate the current status of knowledge about the potential cause-effect relationship between an individual's vitamin D status and cancer and to determine if any anti-cancer benefit may be gained from increasing vitamin D status. Systematic reviews were undertaken, with meta-

analyses, and the results are available in a downloadable report:

[http://www.iarc.fr/en/content/download/10701/74064/file/Report\\_VitD.pdf](http://www.iarc.fr/en/content/download/10701/74064/file/Report_VitD.pdf)

In brief, increasing vitamin D status was associated with a reduced risk of colorectal cancer, and not of breast or prostate cancer. Other studies show no evidence for an association with ovarian or pancreatic cancer. Randomised trials testing vitamin D supplements did not show a protective effect against colorectal cancer, but our meta-analysis published in 2007 showed a reduction in all-cause mortality associated with taking these supplements (\*Autier and Gandini, 2007). The key issue now is to sort out whether vitamin D status is simply a marker or is causally associated with cancer and other chronic diseases.

## EUROCADET PROJECT (www.eurocadet.org)

The objective of this project is to estimate the effect of the successful implementation of prevention strategies on the incidence of cancer. Data were gathered in 30 European countries on key exogenous determinants of cancer: smoking, alcohol consumption, overweight and obesity, physical activity, use of post-menopause hormonal treatment, and fruit and vegetable consumption. The future burden of cancer incidence in Europe was also calculated. These exposure data and incidence prediction will serve as a basis for developing scenarios of public health interventions and their likely impact on the cancer burden in Europe.

## EVALUATION OF IMPACT OF SCREENING ACTIVITIES ON CANCER MORTALITY

In mid-2007 the Prevention Group began conducting evaluations of the impact of screening activities on the incidence of advanced cancer at diagnosis. Normally, if screening works and is widespread, the incidence of advanced cancer should

decrease. Such a decrease is independent of the effects of treatments and can provide information on the contribution of screening to changes in mortality. If this concept is largely accepted by the scientific community so far, it has only been correctly ascertained for cervical cancer screening. The Group hopes to have finished its evaluation of breast cancer screening by the end of 2009, and the first articles are already published or in press (\*Autier *et al.*, 2009). This first article shows that in randomised trials on mammography screening, the decreases in breast cancer mortality were preceded by similar decreases in the incidence of advanced breast cancer. The next cancer we will examine is colorectal cancer.

## TYROL STUDY ON PROSTATE CANCER

Prostate cancer screening activities have existed for the past 20 years in Tyrol, Austria. A large database has been put together by the Department for Urology at Innsbruck Medical University (Innsbruck, Austria) collecting the full pre-clinical and clinical history of men who were tested for prostate cancer. Analysis of this data will provide invaluable information on the natural course of this cancer.

## METHODOLOGICAL ISSUES

The Prevention Group has developed methodological expertise in the area of meta-analysis, mainly for observational studies, for which little guidance is available in the specialised literature. This has allowed us to produce original meta-analytic work for vitamin D and cancer and for mobile phones and cancer. These studies will be published as articles or reports in late 2009 and in 2010.

The Group is also involved in the methodological issues inherent in what exactly is meant by “cancer incidence” when a cancer can be screen-detected. The first result of this work was an article on the limitations of using cancer survival data in public health (\*Autier *et al.*, 2007).

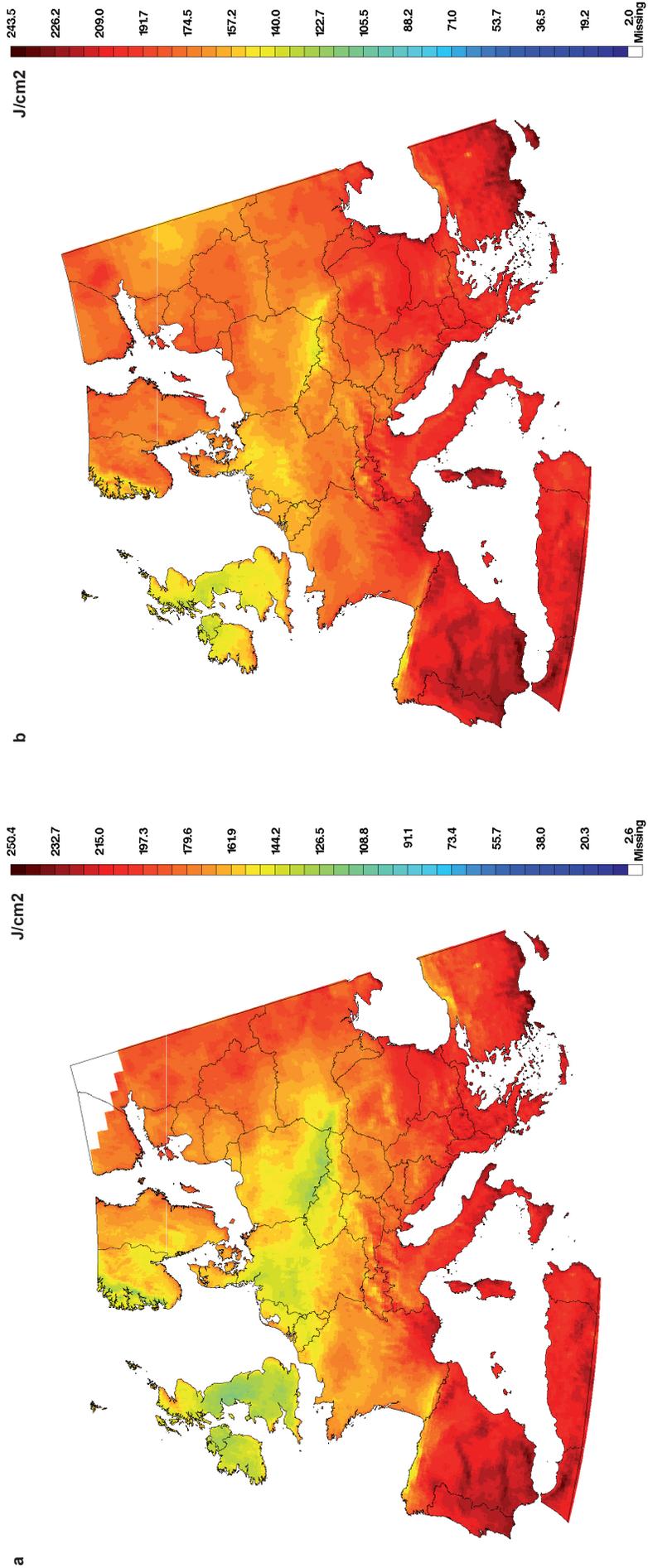


Figure 1. Daily mean of total UV irradiation averaged over 5-year periods in Europe during the month of June for the period 1998–2002 (a) and for the period 2003–2007 (b)

The ECO is an IARC-hosted website designed to present the number of cases and deaths by cancer in European countries in a user-friendly manner (<http://eu-cancer.iarc.fr>). The ECO site, launched on 5 May 2009, was developed by Philippe Autier (PRE group) and Jacques Ferlay (DEP group). Data presented on the site are those made publicly available by cancer registries and by national statistics agencies. The data on cancer cases are derived from data used for volumes I to VIII of the IARC Cancer Incidence in Five Continents Series. Data on mortality by cancer are derived from World Health Organization (WHO) data.

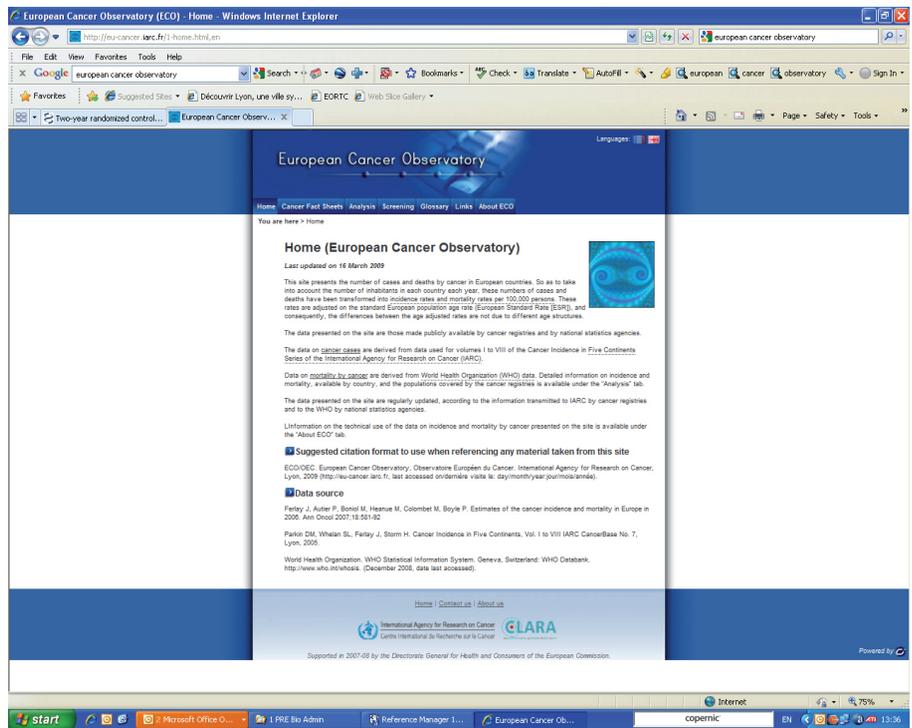


Figure 2. European Cancer Observatory website. <http://eu-cancer.iarc.fr>

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

- Belgian Cancer Registry, Brussels, Belgium
- The Epidemiology and Biostatistics Division of the European Institute of Oncology, Milan, Italy
- Icelandic Cancer Society, Reykjavik, Iceland
- Northern Ireland Cancer Registry, Belfast, UK
- The University of Innsbruck, Austria
- West Midlands Cancer Intelligence Unit, The University of Birmingham, Birmingham, UK

**FUNDING BODIES**

We are grateful for the funding received from DG SANCO and AFSSET.

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THE OBJECTIVE OF SCREENING GROUP PROJECTS IS TO GUIDE THE DEVELOPMENT OF EVIDENCE-BASED PUBLIC HEALTH POLICIES IN IMPLEMENTING CANCER SCREENING AND EARLY DIAGNOSIS IN A RANGE OF HEALTHCARE SETTINGS, PARTICULARLY IN LOW- AND MEDIUM-RESOURCE COUNTRIES, LEADING TO RATIONAL UTILISATION OF HEALTHCARE RESOURCES AND TO IMPROVING QUALITY OF LIFE. TO MEET THIS REQUIREMENT, OUR STUDIES ADDRESS THE ACCURACY, REPRODUCIBILITY, EFFICACY, BENEFITS, HARMFUL EFFECTS AND COST-EFFECTIVENESS OF DIFFERENT SCREENING INTERVENTIONS FOR BREAST, CERVICAL, ORAL AND OTHER CANCERS, AND DEVELOPMENT OF QUALITY ASSURANCE STANDARDS FOR SCREENING IN DIFFERENT SETTINGS, IN COLLABORATION WITH NATIONAL INSTITUTIONS IN DIFFERENT COUNTRIES.

## I. CERVICAL CANCER SCREENING

*Cluster-randomised controlled trial on the effectiveness of a single round of HPV testing, cytology testing or visual inspection with acetic acid in Osmanabad*

The efficacy and cost-effectiveness of a single round of screening using HPV testing or cervical cytology or visual inspection with acetic acid (VIA) in preventing cervical cancer cases and deaths as compared to a control group receiving routine care plus health education on cervical cancer prevention is being assessed in a cluster randomized trial in the Osmanabad district, India (\*Sankaranarayanan, Nene *et al.*, 2009). Screen-positive women had colposcopy and directed biopsies. Women with CIN were treated with cryotherapy by nurses, or loop excision by doctors. About 79% of the eligible women in the different groups were screened. About 60% of the patients in the HPV and cytology groups and 42% in the VIA group were diagnosed in stage I, as compared to 28% in the control group. There was a significant 53% reduction in the incidence rate of stage II or worse stages of invasive cervical cancer, and a significant 48% reduction in cervical cancer mortality in the HPV group as compared to the control group (Table 1). The significant reduction in the incidence of advanced cancers and cervical cancer

deaths associated with HPV testing is quite likely to be due to the fact that HPV testing detects more precancerous lesions, with a high potential for malignant transformation, as compared to VIA or cytology, and that HPV testing is more sensitive than the other two tests for true premalignant lesions, resulting in fewer subsequent cancers diagnosed among the HPV-negative women.

*Cryotherapy and loop electrosurgical excision procedure for treatment of cervical precancerous lesions*

The effectiveness, safety and acceptability of treatment of cervical intraepithelial neoplasia (CIN) using cryotherapy provided by midwives and using loop electrosurgical excision procedure (LEEP) by new trained physicians were assessed in three studies in rural India (Table 2) (\*Nene *et al.*, 2008; \*Rema *et al.*, 2008; \*Sankaranarayanan, Keshkar *et al.*, 2009). We reported 94% cure rates for CIN by cryotherapy and 87%–94% rates for LEEP. Similar results are observed in developed countries. Minor side effects and complications were reported in less than 10% of women; these treatments are judged to be effective, safe and acceptable to women.

**Table 1. Incidence rates of stage II or worse and mortality rate in the cervical cancer screening trial in Osmanabad District, India**

Variable	HPV testing	Cytology	VIA	Control
Incidence of stage II or worse cervical cancer (N)	39	58	86	82
Rate per 100 000 person-years	14.9	23.8	21.7	34.6
Hazard ratio (95% CI)	0.49 (0.33–0.72)	0.78 (0.52–1.17)	1.09 (0.76–1.58)	1.00
Deaths from cervical cancer (N)	34	54	56	64
Rate per 100 000 person-years	13.0	22.1	21.7	27.0
Hazard ratio (95% CI)	0.53 (0.33–0.86)	0.91 (0.63–1.30)	0.90 (0.63–1.28)	1.00

HPV: Human papillomavirus; VIA: visual inspection with acetic acid; CI: confidence interval

**Table 2. Follow-up details of histologically-proven CIN treated with cryotherapy of LEEP in 3 different studies in India**

	Study author (treatment offered)		
	Nene et al., 2008 (Cryotherapy)	Rema et al., 2008 (LEEP)	Sankaranarayanan, Keshkar et al., 2009
Number treated	728	311	634
Number followed up (%)	574 (78.8)	283 (91.0)	489 (77.1)
Number disease-free (%)	538 (93.7)	248 (87.6)	459 (93.9)
Number with minor side effects and complications (%)	40 (5.5)	39 (12.5)	39 (6.2)

LEEP: loop electrosurgical excision procedure

*The Screening Technologies to Advance Rapid Testing (START) project for cervical cancer prevention*

The START project for cervical cancer prevention aims to develop, evaluate and make available affordable and accurate biochemical tests for the early detection of CIN in public health and clinical practice in developing countries. This project is in collaboration with the Nargis Dutt Memorial Cancer Hospital (NDMCH), Barshi and the Tata Memorial Centre (TMC), Mumbai, contributing to the development, validation and future commercial availability of the new test formats. From September 2005 to August 2007 we screened 10 593 women and collected 35 900 cervical and vaginal samples for test development

and validation. A total of 407 biopsy specimens pertaining to all CIN cases and invasive cancer, as well as a sample of normal cases, were brought to Lyon for HPV genotyping and p16 immunostaining. We are currently analysing the data and investigating why the performance of fast HPV test in the Indian START component was inconsistent with that in China. In addition, results from HPV genotyping and p16 immunostaining will be used to reinforce the validity of histology diagnosis of CIN in our study.

*Multicentre HPV vaccine project*

This is a major randomised clinical trial in collaboration with 8 centres in India (Tata Memorial Centre, Mumbai; Nargis Dutt Memorial Cancer Hospital, Barshi;

Jehangir Clinical Development Centre, Pune; Christian Fellowship Community Health Centre, Ambillikai; Gujarat Cancer Research Institute, Ahmedabad; All India Institute of Medical Sciences, New Delhi; MNJ Cancer Institute, Hyderabad and Cancer Foundation of India, Kolkata) to generate scientific evidence on the clinical efficacy of two-dose HPV vaccination as compared the current standard three-dose to prevent persistent HPV infection and cervical neoplasia in order to guide public health policies for planning and implementing wide-scale, sustained HPV vaccination delivery to pre- and early adolescent girls. This study will involve around 20 000 girls aged 10–18 years, and is funded by the Bill & Melinda Gates Foundation. The study protocol received clearance from the Ethics committees

of IARC and our Indian collaborative centres, and from the Ministry of Health and the Drugs Controller General of India, and the vaccination process is underway.

### Training

The Group conducted six training courses in cervical cancer screening and prevention (1 in China, 2 in India, 1 in Tanzania, 1 in Gabon, and 1 in Morocco), training around 100 doctors and nurses from Asian and African countries. The group also published digital training manuals for cervical screening and treatment of CIN. Our collaborative cervical cancer prevention training schools in India, Angola, Guinea, Tanzania, Brazil and Peru are active in training human resources in their respective regions.

## 2. ORAL CANCER SCREENING

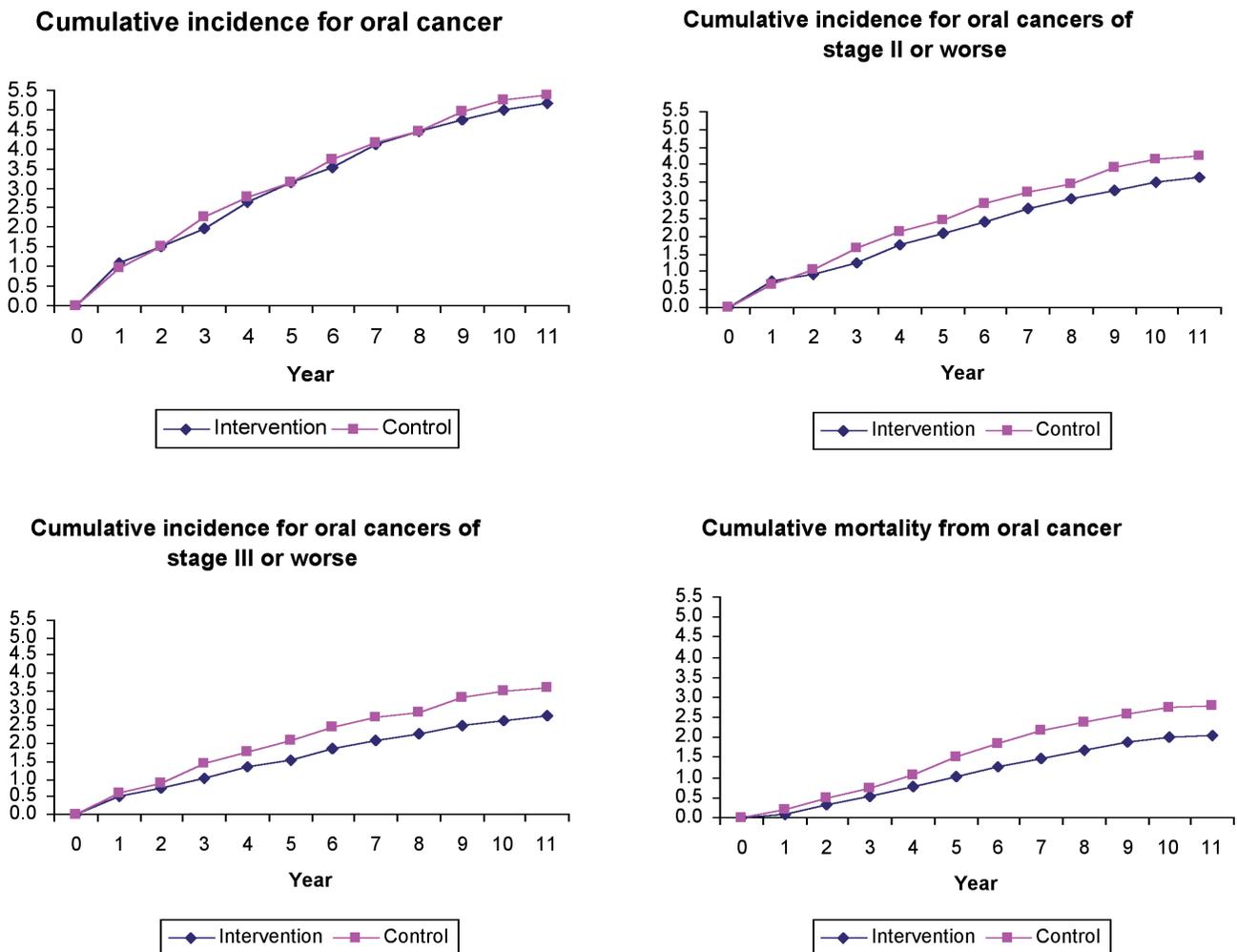
Following a 34% reduction in oral cancer mortality among tobacco and/or alcohol users observed in a randomised controlled screening trial involving 200 000 subjects in Trivandrum district, Kerala, India, we have now completed a single round of oral screening for the 100 000 control subjects, as part of our ethical obligation (\*Sankaranarayanan *et al.*, 2005). A similar trend in reduction of cancer burden is still being observed after 13 years of follow-up. Figure 1 shows similar cumulative cancer incidence during follow-up between the intervention and the control groups. However, the difference between the two groups increased with increasing cancer stage and with mortality. A study of the cost-effectiveness of oral cancer screening reported that the most cost-effective

approach was to focus on tobacco and/or alcohol users (\*Subramanian *et al.*, 2009). A clinical reference chart and web-based atlas to help in the detection of oral precancerous lesions and early diagnosis of oral cancer has been developed and will be validated.

## 3. BREAST CANCER SCREENING

A cluster-randomised controlled trial was initiated in Kerala, India in collaboration with the Regional Cancer Centre (RCC), 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 the clinical early detection and improved outcome of breast cancer. Around 56 000 women have been

Figure 1. Cumulative incidence and mortality rate curves of oral cancer in the Trivandrum Oral Cancer Study



recruited in the intervention arm to receive health education and clinical breast examination (CBE) by trained health workers, and 59 000 in the control arm to receive the currently existing health care in the region and health education on early detection and prevention of cervical cancer. Among the eligible women in the intervention arm, 90% received CBEs, of whom 6% were found to have abnormal breast symptoms and were referred for further investigations by physicians. Half of these women complied with the referral. During the first round, 74 breast cancer cases have been diagnosed in the intervention group (15% at stage I) and 61 in the control group (8% at stage I).

**Financial support from the following bodies is gratefully acknowledged:**

The Bill & Melinda Gates Foundation, Seattle, USA  
Program for Appropriate Technology in Health, Seattle, USA  
Association for International Cancer Research, St. Andrews, UK  
International Network for Cancer Treatment & Research, Brussels, Belgium  
African Regional Office of the World Health Organization, Brazzaville, Congo

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

Dr Adelaide de Carvalho, National Director of Public Health, Luanda, Angola  
Dr Miraldina da Ganda Manuel, Maternidade Lucrecia Paim, Luanda, Angola  
Dr Silvio Tatti, Faculty of Medicine, Buenos Aires, Argentina  
Dr Silvina Arrossi, CEDES, Buenos Aires, Argentina  
Dr Marc Arbyn, Scientific Institute of Public Health, Brussels, Belgium  
Dr Ian Magrath, International Network for Cancer Treatment & Research, Brussels, Belgium  
Dr Paulo Naud, Dr Jean Matos, Instituto de Prevencao du Cancer de Colo do Utero, Porte Alegre, Brazil  
Dr L. Santini, INCA, Rio de Janeiro, Brazil  
Dr Boblewende Sakande, Dr Marius Nacoulma, Centre Hospitalier National Yalgado Ouédraogo, Ouagadougou, Burkina Faso  
Dr Youlin Qiao, Cancer Institute of the Chinese Academy of Medical Sciences, Beijing, China  
Dr Yong-Bing Xiang, Shanghai Cancer Institute, Shanghai, China  
Dr Jiang-Guo Chen, Qidong Liver Cancer Institute, Qidong, China  
Dr Chen Kexin, Tianjin Cancer Registry, Tianjin, China  
Dr Chun-Key Law, Mr. Oscar Mang, Hong Kong Cancer Registry  
Dr Raul Murillo, Dr Carlos Vicente Rada Escobar,  
Dr Joaquin G. Luna Rios, Instituto Nacional de Cancerología, Bogota, Colombia  
Professeur Charles Gombe Mbalawa, Dr Judith Malanda-Mfinga Université Marien Nguouabi, Brazzaville  
Dr Joseph Kokolo, Brazzaville Cancer Registry, Brazzaville  
Dr Rolando Herrero, Dr Adolfo Ortiz, Ministry of Health, San Jose, Costa Rica  
Dr Leticia Fernandez Garrote, Dr Yaima Galan Alvarez, National Institute of Oncology and Radiobiology, Havana, Cuba  
Dr Lucien Frappart, Hopital Edourard Herriot, Lyon, France  
Dr Bernard Fontanière, Centre Leon Berard, Lyon, France  
Dr Thuy Tien Couty, Hospices Civils de Lyon, Lyon, France  
Dr Ebrima Bah, Gambia Cancer Registry, Banjul, The Gambia  
Dr. Michael Pawlita, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany  
Dr Moussa Koulibaly, Dr Namory Keita, CHU Donka, Conakry, Guinea  
Dr Ketayun Dinshaw, Dr Rajendra Badwe, Dr Surendra Shastri, Dr Roshan Chinoy, Dr Kedhar Deodhar, Dr Rohini Kelkar, Dr Rajesh Dikshit, Dr Sharmila Pimple, Dr Gauravi Mishra Dr. C. Patil, Dr. P. Uplap, Dr. N. Jambhekar, Dr. B. Rekhi, Dr. R. Mulherkar, Dr. S. Chiplunkar, Tata Memorial Centre, Mumbai, India  
Dr Bhagwan M. Nene, Mrs Kasturi Jayant, Mr M.K. Chauhan, Mr. Sanjay Hingmire, Mrs. Ruta Deshpande, Mrs. Aruna Chiwate, Dr Sylla G. Malvi, Nargis Dutt Memorial Cancer Hospital, Barshi, India.  
Dr Balakrishnan Rajan, Dr Kunnambathu Ramadas, Dr Paul Sebastian, Dr Ramani Wesley, Dr Thara Somanathan, Regional Cancer Centre, Trivandrum, India.  
Professor M. Radhakrishna Pillai, Mr Rajan Panicker IAA, Rajiv Gandhi Centre for Biotechnology, Trivandrum, India.  
Dr V. Shanta, Dr R. Swaminathan, Cancer Institute (WIA), Chennai, India  
Dr Neerja Bhatla, Dr Arti Gulati, Dr Shachi Vashist, Professor RC Deka, Professor P.P.Kotwal, Dr Alka Kriplani, Dr Sandeep Mathur, All India Institute of Medical Sciences, New Delhi, India

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Dr Partha Basu, Dr Ranajit Mandal, Chittaranjan National Cancer Institute, Kolkata, India

Dr Maqsood Siddiqi, Ms Sutapa Biswas, Cancer Foundation of India, Kolkata, India

Dr Eric Zomawia, Civil Hospital, Aizawl, Mizoram, India

Dr Yogesh Verma, STNM Hospital, Gangtok Sikkim, India

Dr Srabani Mittal, Mr Samiran Das, Saktipada Das Memorial Foundation, Kolkata, India

Dr Arun Kurkure, Dr Balakrishna Yeole, Indian Cancer Society, Mumbai, India

Dr Mary Cherian, Dr Pulikatil Okkaru Esmey, Mr Anil Kumar, Christian Fellowship Community Health Centre, Ambillikai, India

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Dr B.V. Bhat, Mr Krishnanandha Pai, Malabar Cancer Care Society, Kannur, India

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## QUALITY ASSURANCE GROUP (QAS)

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CANCER SCREENING AIMS TO REDUCE THE BURDEN OF DISEASE BY DETECTING AND TREATING CANCER, OR IN SOME CASES PRECANCEROUS LESIONS, BEFORE INDIVIDUALS SEEK TREATMENT DUE TO SELF-DETECTED SIGNS OR SYMPTOMS. FOR A NUMBER OF CANCER SITES, PARTICULARLY BREAST, CERVICAL AND COLORECTAL CANCER, WHICH ACCOUNT FOR APPROXIMATELY ONE OF FOUR CANCER DEATHS WORLDWIDE, POPULATION-BASED SCREENING IS CURRENTLY A COMPONENT OF CANCER CONTROL IMPLEMENTED IN MANY HIGH-RESOURCE COUNTRIES. EFFORTS ARE UNDERWAY TO DEVELOP SCREENING STRATEGIES APPROPRIATE TO MEDIUM- AND LOW-RESOURCE COUNTRIES.

The vast majority of the people invited to attend population-based screening programmes have low to medium risk of developing a target cancer. The screening process has to be optimised for individuals to adequately benefit from early detection and to avoid the potentially detrimental effects of unnecessary further examinations or treatment. Therefore, comprehensive quality assurance, encompassing all aspects of the process of cancer screening is of paramount importance (Perry et al. 2009; European Commission 2008; Arbyn et al., in press).

The screening process comprises complex activities extending from invitation of the eligible population to performance of a screening test, assessment of detected abnormalities and, if necessary, treatment. Even in countries with relatively small target populations, quality-assured introduction of nationwide screening programmes may take 10 years or more due to the need for feasibility testing and planning, piloting and quality-assured rollout of services across the regions served by a programme. International collaboration has therefore become a key factor for successful application and further development of the standards and procedures required to maintain the

effectiveness and the cost-effectiveness of cancer screening programmes.

Achieving and maintaining high quality at every step in the screening process requires an integrated, population-based approach to programme implementation. The population-based approach is essential in order to adequately monitor, evaluate and continuously improve performance, and in order to give all eligible people an equal chance of benefiting from screening. Nationwide implementation of population-based screening programmes of appropriate quality generally makes services performing to high standards accessible to the entire population, not just those persons eligible to attend screening. Large numbers of professionals undertake further specialisation and training in order to meet the screening quality standards. Consequently, these nationwide efforts also contribute to widespread improvement in the diagnosis and management of cancers that are detected outside of screening programmes. Implementation of cancer screening programmes of appropriate quality therefore has the additional potential to improve the entire range of cancer care.



Figure 1

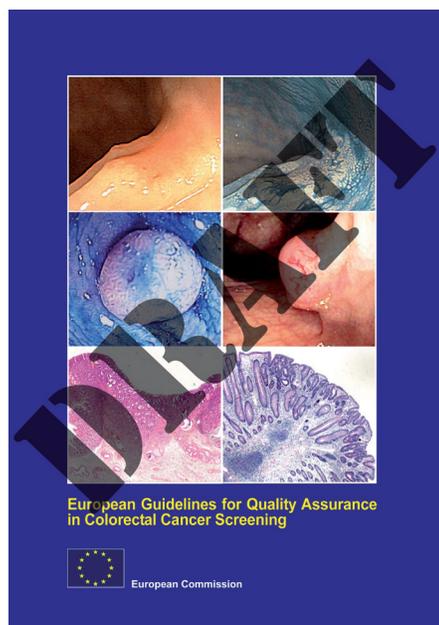


Figure 2

During the current biennium, the limited resources of the QAS group have been concentrated on further development and updating of European guidelines for quality assurance in breast, cervical and colorectal cancer screening (Figs. 1 and 2) and documentation of screening programme implementation in Europe (Fig. 3).<sup>1</sup>(Karsa et al. 2008; Anttila et al. 2009).<sup>1</sup> Due to the wide span of activities and the multidisciplinary scope of quality assurance guidelines for cancer screening, collaboration with experts from several IARC groups and the WHO are ongoing. The current status of cancer screening programmes reflects the substantial experience gained in Europe: 70 breast, cervical or colorectal cancer screening programmes, 50 of which follow the population-based approach, had been implemented in the

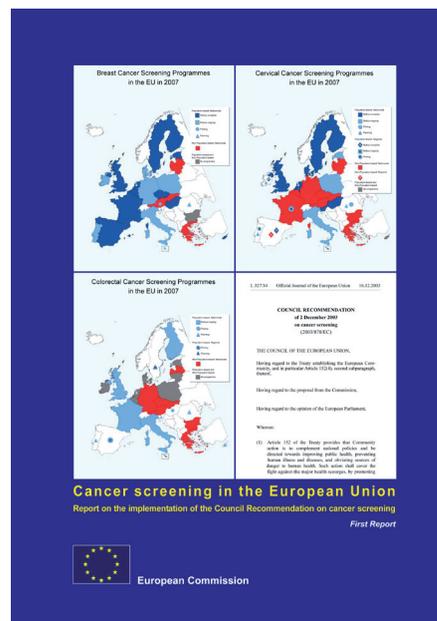


Figure 3

<sup>1</sup> These activities have been co-financed by the EU Health Programme through the projects: *European Cancer Network (ECN)*, grant no. 2004309, *European Network for Information on Cancer (EUNICE)* grant no. 2004114, *Development of Guidelines for Quality Assurance of Colorectal Cancer Screening*, grant no. 2005317, and *European Cooperation for development and implementation of Cancer screening and prevention Guidelines (ECCG-ECN)*, grant no. 2006322.

Associated partners in the project for updating the EU Guidelines for Quality Assurance of Breast and Cervical Cancer Screening are: *ARCADES*, France; *EUROPA DONNA*, *The European Breast Cancer Coalition*, Italy; *Stichting Landelijk Referentie Centrum voor Bevolkingsonderzoek, (LRCB-EUREF)*, The Netherlands; *Queen Mary & Westfield College*, United Kingdom; *Scientific Institute of Public Health*, Belgium; *Royal Surrey County Hospital NHS Trust*, United Kingdom. Associated partners in the project to develop quality assurance guidelines for colorectal cancer screening are: *University of Oxford*, United Kingdom; *Azienda Ospedaliera San Giovanni Battista and CPO*, Turin, Italy; *Public Association for Healthy People (PROEMBER)*, Budapest, Hungary; *European Cancer Patient Coalition (ECPC)*, Utrecht, The Netherlands.

EU by the end of 2007. At current levels, over 500 million screening tests will be performed in publicly mandated cancer screening programmes in the EU over the next 10 years. Due to the expansion of the current programmes, this volume is likely to double in the foreseeable future. Europe therefore offers a unique opportunity to deal with the challenges of implementation of population-based cancer screening programmes on a scale that is not likely to be encountered in other regions of the world until ten or more years from now. Colleagues from around the world have therefore been invited to collaborate with European experts in the efforts of the QAS group to further develop and to facilitate implementation

of quality assurance guidelines for population-based programmes for cancer screening.

A truly integrated approach to quality assurance in implementation of secondary prevention should be based on comprehensive efforts to control cancer and other chronic disease. During the current biennium, an increasing amount of attention has been devoted to expanding the evidence base to improve implementation of primary prevention strategies that are complementary to cancer screening. These include, for example, vaccination against human papilloma virus infection to prevent cervical cancer, as well as strategies to

effectively promote a healthy lifestyle by lowering risk factors such as smoking or lack of exercise. These activities have been co-financed through grants from the EU Health Programme to update cervical cancer screening and prevention guidelines and to update the European Code Against Cancer.<sup>2</sup> The EU project to develop guidelines on HPV vaccination will provide an important source of evidence and expertise for recently initiated efforts of the WHO, the French National Cancer Institute and IARC to collaborate in updating and expanding previous WHO guidelines on cervical cancer control.

<sup>2</sup> These activities have been co-financed by the EU Health Programme through the *ECCG-ECN* project (for details see footnote 1) and through a direct contract between the Directorate General and Consumers and IARC in 2008/2009. The project to update the European Code Against Cancer is conducted in collaboration with *Azienda Ospedaliera San Giovanni Battista and CPO*, Turin, Italy;

#### **The QAS Group is grateful to the following for their collaboration in its projects:**

Silvina Arrossi, Buenos Aires, Argentina

Michael Bourke, Queensland, Graeme P. Young, Adelaide, Australia;

Reinhard Horvat, Barbara Schleicher, Theresia Unger, Helene G. Wiener, Vienna, Austria;

Marc Arbyn, Pieter Vandenbulcke, Brussels; Hilde Bosmans, Leuven; Karen Fredrix, Anne Vandenbroucke, Belgium;

René Aloisio da Costa Vieira, São Paulo; Ana Ramalho, Rio de Janeiro, Brazil;

Shemuel Danon, Valerianova, Zdravka, Sofia, Bulgaria;

Linda Rabeneck, Bob Riddell, Toronto, Canada;

Wei-Min Tong, Min Dai, Beijing; Ji-guang Li, Shenyang, Shengqing Lu, Chongqing, China;

Magdalena Grce, Zagreb, Croatia;

Maria Nicolaidou, Vayios Partassides, Larnaca; Pavlos Pavlou, Nicosia; Marija Petkovi\_, Cyprus;

Adam Svobodnik, Brno; Jan Danes, Ruth Tachezy, Miroslav Zavoral, Prague; Miroslava Skovajsova, Czech Republic;

Elsebeth Lynge, Iben Holten, Copenhagen, Denmark;

Auni Aasmaa, Tallin, Estonia;

Ahti Anttila, Nea Malila, Pekka Nieminen, Martti Pamilo, Helsinki; Matti Hakama, Tampere; Peter B. Dean, Stefan Lönnberg, Eero Suonio, Turku, Finland;

Jérôme Viguier, Boulogne-Billancourt; Christine Bergeron, Cergy-Pontoise; Guy Launoy, Caen; Jean Faivre, Dijon; Jean-Pierre Bader, Issy-les-Moulineaux; Philip Davies, Lyon; Patrice Heid, Brigitte Seradour, Marseille; Rosemary Ancelle-Park, Paris; Jean-François Rey, St Laurent du Var; Jean-Jacques Baldauf, Muriel Fender, Strasbourg, France;

Michael Vieth, Bayreuth; Lutz Altenhofen, Monika Mund, Berlin; Christian P. Pox, Wolff Schmiegel, Bochum; Hermann Brenner, Magnus von Knebel Doeberitz, Michael Pawlita, Heidelberg; Siegfried Schach; Leverkusen; Jutta Pfeiffer, Meinhard; Meinhard Classen, Ulrich Schenck, Munich; Thomas Iftner, Tübingen; Margrit Reichel, Wiesbaden, Germany;

Elena Riza, Athens, Charles Anthony, Ormylia, Emmanuel Diakomanolis, Greece;

Szilvia Madai, Zoltan Péntek, Laszlo Vass, Budapest, Hungary;

Maqsood Siddiqi, Kolkata, India;

Walter Prendiville, Coombe; Niall Phelan, Dublin; Marian O'Reilly, Limerick, Ireland;

Gad Rennert, Dafna Kutner, Haifa, Israel;

Mohannad Alnsour, Jordan;

Mauro Risio, Candiolo-Torino; Marco Zappa, Florence; Susan Ballenger Knox, Lorenzo Thione, Milan; Giorgio Minoli, Montorfano; Paola Armaroli, Livia Giordano, Silvia Minozzi, Antonio Ponti, Guglielmo Ronco, Nereo Segnan, Carlo Senore, Turin, Italy;

Hiroshi Saito, Tokyo, Japan;

Mohannad Alnsour, Jordan;

Hee Sung Ha, Seo-Jeong Ha, Won Chul Lee, Seoul, Korea;

Labiba Temmim, Salmya, Kuwait;  
Ludmila Engele, Marcis Leja, Riga, Latvia;  
Juozas Kurtinaitis, Vilnius; Viaceslavas Zaksas, Lithuania;  
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Miriam Dalmas, Nadine Delicata, Joseph Psaila, Malta;  
Geir Hoff, Solveig Hofvind, Elisabete Weiderpass, Michael Bretthauer, Oslo, Norway;  
Barbara Dabrowska, Wenancjusz Domagala, Andrej Nowakowsky, Jaroslaw Regula, Witold A. Zato\_ski, Warsaw, Poland;  
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Luciana Neamtiu, Florian A. Nicula, Cluj-Napoca, Romania;  
Vadim G. Ivanov, Vladimir F. Semiglazov, St. Petersburg; David Zaridze, Moscow, Russian Federation;  
Kamil Pohlodek, Darina Sedlakova, Bratislava, Slovakia;  
Snje\_ana Frkovi\_-Grazio, Kristijana Hertl, Maksimilijan Kadivec, Mateja Krajc, Blanka Mikl Meznar, Maja Primic Zakelj, Jozica Maucec Zakotnik, Janez Zgajnar, Ljubljana, Slovenia;  
Silvia De Sanjose, Mercè Peris, Barcelona; Nieves Ascunce Elizaga, Pamplona; Montserrat Corujo Quinteiro, Santiago de Compostela; Dolores Cuevas, Lola Salas Trejo, Valencia; Raquel Zubizarreta, Spain;  
Joakim Dillner, Lena Dillner, Malmö; Lennarth Nystrom, Umea; Pär Sparen, Uppsala; Sven Törnberg, Stockholm, Sweden;  
Chris de Wolf, Fribourg, Hanspeter Ischi, Bern-Wabern, Switzerland;  
Chris Meijer, Peter Snijders, Amsterdam; Paul Klinkhamer, Eindhoven; Mireille Broeders, Johan Bulten, Roland Holland, Erik Puthaar, Henny Rijken, Martin Thijssen, Nijmegen; Jacques Fracheboud, Ernst Kuipers, Iris Lansdorp Vogelaar, Marjolein Van Ballegooijen, Rotterdam; Dan J. Dronkers, Velp, The Netherlands;  
Joseph Jordan, Birmingham; Steve Smith, Coventry; Robert Steele, Dundee; Euphemia McGoogan, Edinburgh; Stephen Halloran, Kenneth Young, Guildford; Pierre Martin-Hirsh, Lancaster; Phil Quirke, Leeds; Roland Valori, Leicester; Wendy Atkin, Jack Cuzick, Amanda Herbert, Roger Leicester, Clare Monk, Nick Perry, Anne Szarewski, Graham Talbot, Clive Wells, London; Joan Austoker, Paul Hewitson, Julietta Patnick, Patricia Villain, Joanna Watson, Premila Webster, Oxford; Sue Moss, Robin Wilson, Sutton; Lynn Faulds Wood, Twickenham, United Kingdom  
Robert A. Smith, Atlanta; Rachel Ballard-Barbash, Bethesda; David F. Ransohoff, Chapel Hill; Bernard Levin, Houston; Sidney J. Winawer, New York, David Lieberman, Portland; Berta M. Geller, Vermont, United States of America.

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### JOURNAL ARTICLES

Anttila A, Karsa L v, Aasmaa A, Fender M, Patnick J, Rebolj M, Nicula F, Vass L, Valerianova Z, Voti L, Sauvaget C, Ronco G. Cervical cancer screening policies and coverage in Europe. *Eur J Cancer* 2009 45(15): 2649-2658

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## PUBLICATIONS/EDITING SERVICE

The COM Group assists all scientific Groups in disseminating their research results by providing editorial support and guidance, including publication of articles, papers and op-ed pieces in international scientific journals, supported by graphic services, both for illustrations of publications and posters, and for the layout of the finished print-ready products. The Editor takes an active part in the preparation of manuscripts for submission of scientific papers, as well as for volumes in the book production series. He now also forms part of the faculty of the IARC Summer School, and has developed a courses on writing journal articles, annual reports, poster presentations and abstracts. In the future these classes may be offered to all IARC trainees in addition to Summer School students.

## NEW DEVELOPMENTS FOR THE DISSEMINATION OF IARC PUBLICATIONS

Since the dissemination of IARC publications was passed on to our parent Organization in 2006, the agreement that governed IARC's relations with WHO Press was renegotiated in 2009, thus rejuvenating the Publications program and enabling it to fund sustained efforts, particularly in the areas of the WHO Classification of Tumours ("Blue Books") series, which remain the Agency's best-sellers, and are among the top-selling titles for WHO Press. Further, a new mechanism agreed by the Governing Council now allows a larger share of the revenue from the sale of IARC publications to be transferred back into the program. In addition, the agreed re-establishment of the Advisory Committee on Publications, with terms of reference updated to reflect the new strategic vision set forth for the Agency from 2009, was given priority for managing and planning publications projects in the longer term.

## NEW IARC PUBLICATIONS

The Agency published a number of publications under the IARC imprint in the period under review:

- One digital aide for diagnosis, by the IARC Screening Group: *Digital Manual for the Early Diagnosis of Oral Neoplasia* (IARC, 2008);
- the second volume of the **WHO Classification of Tumours, Fourth Edition** (2008) (*Tumours of Haematopoietic and Lymphoid Tissues*);
- two **Working Group Reports** (Volume 5, *Vitamin D and Cancer* (IARC, 2008) and *IARC Code of Good Scientific Practice* (IARC, 2008));
- the **World Cancer Report 2008** (IARC, 2008);
- one new volume in the **IARC Monographs on the Evaluation of Carcinogenic Risks to Humans** (Vol. 97, *1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide)* (IARC, 2008));
- one **IARC Scientific Publication** (*Atlas of Cancer Mortality in the European Union and the European Economic Area, 1993-1997* (IARC, 2008));
- and two volumes of the **IARC Handbooks of Cancer Prevention**, entitled *Methods for Evaluating Tobacco Control Policies* (IARC, 2008) —Volume 12— and *Evaluating the Effectiveness of Smoke-free Policies* (IARC, 2009) —Volume 13.

A number of these titles have been posted on the IARC website in digital format, either coinciding with their print publication or shortly thereafter (see <http://www.iarc.fr/en/publications/pdfs-online/>). In addition, a major overhaul of *Cancer Incidence in Five Continents, Volume IX* was undertaken early in 2009 to correct a large number of errors in the initial print run. The reprinted title and its pdf version have now been available since mid-2009.

## WEB SERVICES

The COM Group maintains the Agency's bilingual internet site. It has become clear that modern knowledge sharing and transfer should rest on modern communications technology, mostly

web-based. In this area also, 2009 has seen a major and very quick overhaul of the IARC facilities. More publications are now accessible through the main website, while a number of ancillary websites are being developed with other Groups in-house. The IARC website is the core of the Agency's outward communications effort, and should move into a content management system architecture in the near future.

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. From early on in 2009, it was assessed that these large efforts, which are expected to carry over into the next biennium and beyond, called for additional human resources, and a professional webmaster position was advertised in the fourth quarter of 2009.

## PUBLIC AND MEDIA RELATIONS

The Public Relations Service ensures relations between the Agency and the media, writing and distributing press releases, and organising press conferences. By means of a database of media contacts around the world, the service dispatches press releases to about 3500 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.

## 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 website is the gateway for the delivery of information services and resources to the IARC community, and it too is being redesigned to accommodate more functionality and respond to growing needs of modern research. 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 specialised libraries in Lyon and by welcoming reference enquiries from the public.

In 2009 the Library led a reflection on the nature and definition of Key Performance Indicators, and on the way these can relate to the new Medium-term Strategy for the Agency and what is expected of IARC's research as accountability and sustainability are of increasing relevance and importance to Participating States.

## 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 organises successful language courses in both working languages for the Agency's staff, as well as administering the United Nations language proficiency examinations.

# IARC EDUCATION AND TRAINING

**Dr P. Boffetta, Responsible Officer, Fellowship and Courses Programme** (until August 2009)

**Dr Z. Herceg, Responsible Officer, Fellowship Programme** (from September 2009)

**Miss M. Heanue, Coordinator, Courses Programme**

**Mrs E. El Akroud, Assistant, Fellowships**

**Mrs S. Anthony, Assistant, Courses Programme**

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.

## IARC RESEARCH TRAINING FELLOWSHIPS

The aim of this programme is to provide young scientists with training in a research Group at the Agency 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. The fellowships are especially intended for scientists from low- and medium-resource countries or for scientists from other countries with projects of benefit to low- and medium-resource countries. Heavy demand means there is strong competition, and fellows are chosen by a selection committee of both IARC and external scientists.

### *Postdoctoral Fellowships*

In the 2008-2009 biennial period, postdoctoral fellowships were awarded to junior scientists from Bulgaria, the People's Republic of China, India, Indonesia, Mongolia, the Russian Federation and Thailand. Postdoctoral fellowships are awarded for one year, and can be extended for a second year pending satisfactory performance. A small grant towards starting a collaborative research project is awarded to selected fellows upon completion of their fellowship. Since 2004, when the programme was restructured to focus on low- and medium-resource countries, 46 fellowships have been awarded, 39% to scientists in the field of epidemiology and 65% to scientists from Asian countries.



*Master's/PhD Fellowships  
(up to four years)*

Two PhD fellowships were awarded in 2008, to a junior scientist from Jordan, under joint supervision with the University of Glasgow, UK, and to a junior scientist from the People's Republic of China, under joint supervision with Innsbruck University, Austria.

The Italian Association for Cancer Research continued its generous support of the Fellowships Programme and an application for funding from the EC- FP7 Marie Curie Actions - People - COFUND programme was successful.

**EXPERTISE TRANSFER FELLOWSHIP**

This fellowship is 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. In 2008, the fellowship was awarded

to Professor Robert J. Biggar (State Serum Institute, Copenhagen, Denmark, formerly National Cancer Institute Viral Epidemiology Branch, Bethesda, MD, USA) to spend a total of eight months in the L.V. Prasad Eye Institute, Hyderabad, India.

**VISITING SCIENTIST AWARD**

No Award was made in 2008. In 2009 the Award was given to Professor Julian Peto (London School of Hygiene and Tropical Medicine, London, UK) to spend six months in the Infections and Cancer Epidemiology Group and to Professor David B. Richardson (University of North Carolina, Chapel Hill, NC, USA) to spend six months jointly in the Biostatistics Group and in the Radiation Group.

**TRAINEES, STUDENTS, POSTDOCS AND SENIOR VISITING SCIENTISTS AT IARC**

It is part of 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 provide some complementary support to the Agency's activities. With that in mind, in addition to the fellowship programme, IARC welcomes a substantial number of trainees, master's/doctoral students, technical students, postdocs and visiting scientists each year (between 80 and 100), who come with either outside funds or who are funded in part or in total by the Agency.

In the future, IARC will place more emphasis on developing an integrated and expanded programme of education and training, and these activities will include the strengthening of the Fellowships Programme. Young scientists from high-income countries will be encouraged to devote a career to international cancer research, which can complement the direct training of researchers from these regions. To this end, IARC will seek partnerships with other providers in order to maximise its contribution without duplication of effort and resources.

The main activity of the courses programme has been the IARC Summer School, organised in Lyon, which has been supplemented by specialised courses outside Lyon.

*IARC Summer School on Cancer Epidemiology, Lyon, France  
2-27 June 2008 and 15 June-3 July 2009*

The IARC Summer School has continued to evolve since its introduction in 2005. The programme is advertised toward the end of each year and has recorded up to 250 applications. About one half of the suitable candidates are retained on the basis of their background, their involvement in cancer research and the potential benefit of the training for their own institute and country. Participation is possible in one or more modules, depending on interest and expertise of the applicants and availability of resources.

In 2008 the basic programme remained the same; the first module on Cancer Registration, and the second module a 2-week course on Introduction to Cancer Epidemiology. There was also an advanced module on Methodological Issues in the Design and Analysis of Gene and Environment Studies.

There were a total of 81 participants from 41 different countries: Albania (1), Algeria (1), Argentina (2), Austria (1), Brazil (6), Bulgaria (1), Canada (1), China (5), Egypt (2), Estonia (1), Finland (1), France (1), Germany (2), Gambia (1), India (5), Indonesia (1), Iran (1), Ireland (1), Italy (7), Jordan (2), Malaysia (1), Nepal (1), the Netherlands (3), Nicaragua (1), Pakistan (1), Peru (2), the Philippines (1), Poland (2), Seychelles (2), Singapore (2), Spain (1), Sri Lanka (2), Sudan (2), Sweden (1), Syria (1), Taiwan, China (1), Thailand (2), Turkey (4), United Kingdom (1), USA (4), Vietnam (2) and Yemen (1).

Forty-one participants were from low- and medium-resource countries, and 36 received partial or full financial support. IARC participants originated from 12 countries: Algeria, Brazil, China, France, Germany, Iran, Italy, Netherland,

Pakistan, Poland, Sweden, Taiwan, China and the USA.

In 2009 only the first module on Cancer Registration, and the second module, a two-week course on Introduction to Cancer Epidemiology, were offered.

There were a total of 54 participants from 35 different countries: Australia (1), Austria (2), Bahrain (1), Barbados (1), Belarus (1), Brazil (4), Bulgaria (1), Cameroon (1), Chile (1), China (3), India (8), Iran (1), Italy (1), DPR Korea (2), Republic of Korea (1), Lithuania (1), Malaysia (1), Mongolia (1), Netherlands (2), Nigeria (1), Peru (1), the Philippines (1), Romania (1), Serbia (1), Slovakia (1), South Africa (1), Sri Lanka (1), Sweden (1), Switzerland (3), Tanzania (1), Thailand (4), Togo (1), Turkey (1) and Vietnam (1).

Twenty-seven participants were from low- and medium-resource countries, and 23 received partial or full financial support. IARC participants originated from 9 countries: Belarus, Brazil, Cameroon, China, India, Iran, Mongolia, the Netherlands and Thailand.

Financial support for these courses was received from the U.S. National Cancer Institute, the European Commission (through the ECNIS Network of Excellence), the International Atomic Energy Agency, the Alliance for Cervical Cancer Prevention and various WHO Regional Offices.

*International Course on Introduction to Cancer Registration and its Application to Cancer Epidemiology, Seoul, Republic of Korea, 22 to 27 September 2008*

This course, developed specifically for cancer registry staff, was held in conjunction with National Cancer Center of the Republic of Korea. The aim was to provide an intensive introduction to the methodology of cancer registration and the use of cancer registry data, and to provide instruction in the epidemiological methods that are appropriate to this purpose. Priority was given to participants from Asia and the Pacific.

There were 29 participants from 12 countries (Cambodia, China, India, Indonesia, Japan, Korea, Mongolia, Nepal, New Caledonia, the Philippines, Sri Lanka and Vietnam).

*International Course on Introduction to Cancer Registration and its Application to Cancer Epidemiology, Beijing, People's Republic of China, 14 to 18 September 2009*

This course was held in conjunction with the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS), with aims similar to those of the course held in 2008 in Korea. There were 34 participants from four different countries (China, Mongolia, the Philippines and Vietnam).

## SCIENTIFIC COORDINATION OFFICE (SCO)

UNTIL EARLY 2009, THE SCIENTIFIC COORDINATION OFFICE (SCO) WAS RESPONSIBLE FOR COORDINATION OF THE ETHICS COMMITTEES (THE IARC INSTITUTIONAL REVIEW BOARD AND THE ETHICS REVIEW COMMITTEE), SPECIFICALLY ARRANGING FOR REGULAR MEETINGS OF THE TWO COMMITTEES, WITH LOGISTICS ASSISTANCE FROM THE DOCUMENTS OFFICE. SCO ALSO LIAISED WITH THE IARC SCIENTIFIC COUNCIL, SUPERVISED THE GRANTS OFFICE AND MAINTAINED RELATIONS WITH CURRENT AND PROSPECTIVE PARTICIPATING STATES AND OTHER INSTITUTIONS. DURING 2009 THE SUPPORT STRUCTURES TO THE DIRECTOR'S OFFICE WERE RESTRUCTURED AND THE SCO WAS ABOLISHED, BEING REPLACED BY DEVOLVED RESPONSIBILITIES TO OTHER STAFF.

The two-tiered ethical review structure introduced in 2005 improved operational procedures and documentation of the ethical review process but, as noted in the Director's introductory remarks, it consumed considerable resources, and thus it was transformed into a single Institutional Review Board following consultation with the Scientific and Governing Councils of the Agency and others. The new single-body Institutional Review Board for 2010 will have an independent Chairperson and Vice-Chairperson, three Agency staff members, and seven members from other bodies including the WHO Research Ethics Review Committee, and including members from low- and middle-income countries.

In addition, in order to save valuable resources, new videoconferencing facilities were installed at the Agency in 2009, enabling members to participate in the meetings more fully and increase the diversity of expertise within the Board. A small ad hoc group of international experts will be appointed, with whom the Board may consult occasionally on issues deemed to be beyond its own expertise.

The IARC Grants Office (IGO), previously a part of SCO and now supervised by the DAF, is dedicated to supporting IARC researchers in securing external grants. In this regard, it acts as a liaison between IARC and funding agencies, and supports researchers in their competitive bids. To this aim, a dedicated grants office intranet site with a range of information on funders and deadlines has been developed and a newsletter service put in place that reminds scientists about upcoming deadlines of relevant funders dedicated to cancer research. IGO has set up a central repository of all information on grants as from 1 January 2003. This information is available to all staff through the intranet, and it is planned to display some of the information on the IARC external web site in the near future. IGO offers materials for grant writing including books, articles and hyperlinks, and runs a series of general and specialized workshops on grant writing. In addition, the grants office has been established as the focal point to ensure compliance with necessary registrations and miscellaneous funder requirements. As regards individualised services, IGO now offers funding opportunity analyses that are carried out with a particular project idea in mind. Several applications have been submitted in the recent past following this targeted approach. Finally, researchers at IARC will find help with externally funded projects on any issue that might arise in regards to application

procedures and forms, eligibility criteria, negotiations of grant or consortium agreements, project transfers or periodic and final reports.

## THE GAMBIA HEPATITIS INTERVENTION STUDY

INITIATED IN 1986, THE GAMBIA HEPATITIS INTERVENTION STUDY (GHIS) IS A JOINT ENDEAVOUR OF IARC, THE MEDICAL RESEARCH COUNCIL OF THE UK AND THE GOVERNMENT OF THE REPUBLIC OF THE GAMBIA, AIMED AT ASSESSING THE PROTECTIVE EFFICACY OF INFANT HEPATITIS B VIRUS (HBV) VACCINATION OF INFANTS AGAINST CHRONIC LIVER DISEASE AND LIVER CANCER IN ADULTS. THE GAMBIA, IN WEST AFRICA, IS A COUNTRY OF HIGH ENDEMICITY FOR CHRONIC HBV CARRIAGE. CONTAMINATION OF THE DIET BY AFLATOXIN, A CARCINOGENIC MYCOTOXIN, IS WIDESPREAD. THESE TWO FACTORS HAVE A SYNERGISTIC EFFECT ON THE RISK OF HEPATOCELLULAR CARCINOMA (HCC).



Childhood vaccination in The Gambia

The design of this trial is based on the long-term follow-up of a cohort of 125 000 subjects born between 1986 and 1990, the four years of progressive introduction of HB vaccination in the country. The main instrument for follow-up is the National Cancer Registry. Based on current data, we foresee that the final outcome of this trial will be measurable between 2015 and 2020.

Over the past two years, efforts have concentrated on improving the detection and diagnosis of cancer disease (with particular focus on chronic liver diseases and liver cancer) and on assessing the

long-term immunity against HBV in vaccinated adolescents. A large cross-sectional study in the GHIS cohort has shown that although protection against HBV infection has decreased, the protection against acquisition of the carrier status, the risk factor for HCC, remains remarkably high. In addition, a survey of those vaccinated since 1990 shows that the Government vaccination programme has reduced the prevalence of carriage to less than 1% in those under five years of age. The surveys are compatible with a significant reduction of the burden of chronic liver diseases in the forthcoming years.

Current work focuses on developing operational protocols for identifying vaccinated subjects through record linkage strategies using the vaccination database developed between 1986 and 1990. Research priorities concentrate on the study of the natural history of liver cancer, and in particular on the assessment of the role of cirrhosis as a precursor disease in early cancer. In the long term, we plan to develop interventions aimed at improving early diagnosis, controlling viral replication in chronically infected subjects, managing chronic liver disease and, whenever feasible, proposing appropriate treatment to liver cancer patients.

The study was moved from the Cluster on Pathology and Prevention to the Director's Office in 2009 in order to place increased priority on this flagship project. The Governing Council in May 2009 agreed additional support to permit recruitment of a clinician (hepatologist) to provide leadership to the project in The Gambia during the next critical phase.



# ETHICS REVIEW COMMITTEE (ERC)

IN 2006, A NEW IARC ETHICS REVIEW SYSTEM WAS CREATED WITH TWO DISTINCT COMPONENTS, THE INSTITUTIONAL REVIEW BOARD (IRB) AND THE ETHICS REVIEW COMMITTEE (ERC).

## THE IARC INSTITUTIONAL REVIEW BOARD (IRB)

The IRB met every two months in Lyon for ethical evaluation of all IARC projects. The IRB was composed of nine members, five members from outside the Agency and four from the Agency staff. Its membership for the period of the biennium was as follows:

- Professor Jean-Pierre Boissel, Professor of Clinical Pharmacology, Claude Bernard University
- Dr Paul Brennan, Head, Genetic Epidemiology Group, IARC
- Dr Marc Guerrier, Deputy Director, Department of Ethics Research, University Paris 11
- Ambassador Mireille Guigaz (Chair)
- Ms Ghyslaine Martel-Planche, Molecular Carcinogenesis and Biomarkers Group, IARC
- Mr Bernard Pedeux, former Head of Human Resources, COFRADEL Group
- Dr Martyn Plummer, Infections and Cancer Epidemiology Group, IARC
- Dr Pierre-Jean Souquet, Head, Pneumology & Thoracic Oncology Unit, Lyon-Sud Hospital
- Dr Bakary Sylla, Infections and Cancer Biology Group, IARC

## THE IARC ETHICS REVIEW COMMITTEE (ERC)

The ERC was composed of nine senior members from the international community, with the aim of ensuring international consistency and completeness in ethical approval. Its membership for the period of the biennium was as follows:

- Professor Clement Adebamowo (Nigeria), surgeon and bioethicist
- Dr Kazem Behbehani (Kuwait), former Assistant Director-General at WHO/HQ
- Mr David Byrne (Ireland) (Chair), former Commissioner of the European Union
- Professor Ketayun Dinshaw (India), former Director of Tata Memorial Cancer Centre in Mumbai
- Ambassador Mireille Guigaz (France) (Chair, IRB), Ambassador of France to the FAO, former Déléguée Générale of Cancéropôle Lyon-Auvergne-Rhône-Alpes
- Lord Mackay of Clashfern (United Kingdom), former Lord High Chancellor of Great Britain
- Professor Edith Olah (Hungary), oncologist and President Emeritus of the European Association for Cancer Research (EACR)

- Professor Jae-Gahb Park (Republic of Korea), former President of the Korean National Cancer Center
- Dr Luis Pinillos Ashton (Peru), former Director-General of the Peruvian National Cancer Institute and Minister of Health in Peru

In the period from 2006, the IRB met five to six times per year in Lyon. The ERC met twice per year, with one meeting held in Lyon in conjunction with the IRB meetings and one in one of the WHO Regions. In the current biennium, meetings were held in Mumbai, India (16–17 January 2008) and Dasman, Kuwait (15–16 December 2008), with a joint meeting of the ERC and IRB at IARC on 23–24 June 2008.

During 2008–2009, the IRB met eight times (up to September 2009). During this period, 61 applications were processed. Forty-eight were cleared after ethical review, 8 were requested to be resubmitted, 2 were rejected, 1 was given conditional clearance contingent upon the principal investigator making some modifications before the study began, and 2 were considered not to be within the competence of the IRB (submitted after study completion).



Joint Meeting of the IARC Ethics Review Committee and Institutional Review Board  
LYON, 23-24 June 2008



The incoming Director asked the Scientific Council in its 45<sup>th</sup> Session in 2009 to review the work of the ERC and whether the two-tier system of ethical review was still optimal for the Agency's needs. As a consequence the Scientific Council invited the Director to prepare recommendations to the Governing Council to adapt the ethics review process by establishing a single committee, the IARC Institutional Review Board (IRB) to both:

- provide an ethical evaluation of all IARC projects, and
- ensure international consistency and completeness regarding ethical approval.

This proposal was approved by the Governing Council in May 2009 at its 51<sup>st</sup> Session. The new Committee will comprise 12 members from diverse backgrounds: an independent chair and vice chair (both external), three members of IARC staff and seven additional

members external to the Agency. Among these it is proposed that one should be from the local cancer research community, one should be a general medical practitioner or senior nurse preferably with experience of practice in an ethnically diverse community, one lay member having no professional experience of science or medicine, one from the WHO Research Ethics Review Committee (WHO ERC), one member with bioethics training, and two members from low- and medium-income countries with backgrounds in science, law or other relevant areas. Recent investment in modern video-conferencing facilities at the Agency will help circumvent the problem of attendance by participants from outside of France.

The appointments to the new IRB will be made by the Chairman of the Governing Council. The new structure will be implemented in January 2010.

# IARC GOVERNING COUNCIL AND SCIENTIFIC COUNCIL



THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) IS GOVERNED BY ITS OWN GOVERNING BODIES, THE IARC GOVERNING COUNCIL AND THE IARC SCIENTIFIC COUNCIL.

## GOVERNING COUNCIL

IARC's general policy is directed by a Governing Council, composed of the Director-General of the World Health Organization and Representatives of the Participating States. It meets every year in ordinary session in Lyon, usually the week prior to the WHO World Health Assembly. The Council elected Dr Christopher Wild in May 2008, to serve a five-year term; he took office on January 1, 2009. The Chairperson of the Governing Council prepares the meetings together with the Secretariat, and advises the Director throughout the year.

## SCIENTIFIC COUNCIL

The Scientific Council consists of highly qualified scientists selected on the basis of their technical competence in cancer research and allied fields. Members of the Scientific Council are appointed as experts and not as representatives of Participating States. When a vacancy arises on the Scientific Council, the Participating State that nominated the departing member may nominate up to two experts to replace that member.

Scientific Council members are appointed for four-year terms by the Governing Council. The Scientific Council reviews the scientific activities of the Agency and makes recommendations on its programme of permanent activities and priorities. The Scientific Council meets every year in ordinary session in late January-early February.

## BUDGET

For the biennium 2008–2009, the IARC Governing Council voted a regular budget of US\$ 44 751 000. Of this, 75.42% was allocated to research programmes. A number of projects are also funded by extrabudgetary sources, both national and international. In the 2006–2007 biennium, 34.25% of the Agency's overall expenditure was financed by extrabudgetary funds.

# PARTICIPATING STATES AND REPRESENTATIVES AT IARC GOVERNING COUNCILS

## FIFTIETH SESSION, 14–16 MAY 2008

### NORWAY

Dr Lars E. Hanssen, Chairperson  
The Norwegian Board of Health  
Oslo

Ms Henrietta Blankson  
The Research Council of Norway  
Oslo

### FINLAND

Professor Pekka Puska,  
Vice-Chairperson  
National Public Health Institute  
Helsinki

### UNITED KINGDOM OF GREAT BRITAIN

AND NORTHERN IRELAND  
Dr Mark Palmer, Rapporteur  
Medical Research Council  
London

### AUSTRALIA

Dr Julie Hall  
Department of Health and Ageing  
Canberra

### AUSTRIA

Dr Hemma Bauer  
Austrian Federal Ministry of Science and  
Research  
Vienna

### BELGIUM

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SPF Santé publique, Sécurité de la  
Chaîne alimentaire et Environnement  
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Mr Nick Previsich  
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Ministry of Health, Labour and Welfare  
Tokyo

Dr Hajime Inoue  
Tokyo

### NETHERLANDS

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Ministry of Health, Welfare and Sport  
The Hague

Mr Jeroen Hulleman  
Ministry of Health, Welfare and Sport  
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Vice-Chairperson, Scientific Council

Dr Elaine Ron  
Chairperson, 44th Session of IARC  
Scientific Council

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Mr S.B. Pillay  
Office of the Comptroller and Auditor  
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FIFTY-FIRST SESSION, 14–15 MAY 2009

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Dr Raymond Pamphile

Conseiller scientifique pour les  
affaires internationales auprès du  
Directeur général de la recherche et de  
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Ms Raphaëlle Godart (until June 2009)

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Ms Maria Teresita Fernan (Clerk, until  
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Dr Annie Robert (until December 2008)

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# IARC STAFF PUBLICATIONS 2008–2009

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