International Agency for Research on Cancer

World Health Organization

Biennial Report

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International Agency for Research on Cancer 2010–2011

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Table of Contents

Introduction

Dr Christopher Wild

It is my great pleasure to introduce the Biennial Report 2010–2011 of the International Agency for Research on Cancer (IARC). This Report is being written as the final preparations are made for a high-level meeting of the United Nations General Assembly in New York on the topic of noncommunicable diseases. This is only the second time that Heads of State have assembled at this level at the United Nations to address a health topic, the first being in relation to HIV/AIDS in 2001. At the time when such an influential meeting considers the control of noncommunicable diseases, it is important to recognize the direct relevance and value of the cancer research described in this Report to that global challenge. Based on its expertise, international status and reputation, IARC is in an ideal position to play a significant role in the response on several different, complementary levels, particularly in low- and medium-resource countries where the greatest increases in cancer burden will occur over the next 20 years. Notably:

• The Agency helps to set the cancer control agenda. IARC contributed to the 2011 First Global Ministerial Conference on Healthy Lifestyles and Noncommunicable Disease Control in Moscow in April 2011. Working closely with the World Health Organization (WHO), they also played a key role in a 2010 meeting in New York to prepare the first global status report on noncommunicable diseases (WHO, 2011). This Report sets out the challenge of the worldwide burden of noncommunicable diseases, associated risk factors and prevention strategies, and highlights several important cancer-specific issues.

• Through close collaborations with cancer registries worldwide, IARC provides vital data on global cancer burden, which is an essential element for development of national cancer control plans. Improving the coverage and quality of cancer statistics remains a priority, especially in Africa, Asia and Latin America.

• The Agency's research into the causes of cancer provides the evidence-base for cancer prevention. Information on risks associated with exposures such as infectious agents, radiation, environmental pollutants, diet, metabolic imbalance (including obesity), and genetics is a vital platform for prevention. Evaluating interventions and how they may be implemented in health care settings is also critical in translating research into public health action.

• IARC scientists have focused on cancer in developing countries since the creation of the organization in 1965. The result is a unique collaborative network based on relationships of trust, which provides a foundation for future work. With this opportunity, however,

comes a responsibility to contribute to the necessary collaboration, training and support to develop cancer research capabilities in these regions, in tandem with the research projects themselves.

There are many examples of each of these areas of activity in the current Biennial Report organized under the different Research Sections.

During the current biennium, the Agency has completed major new analyses of global cancer burden, for example through its GLOBOCAN project, which projects striking rises in cancer incidence and mortality worldwide over the coming 20 years. In addition, the Agency provides technical support and training to cancer registries, working closely with the International Association of Cancer Registries. Of interest, the Agency's quality criteria were recognized by the signing of a new South African regulation requiring that the national cancer registry conform to cancer registration norms and standards as determined by IARC. In addition to incidence and mortality, the Agency examined international differences in survival among cancer patients. The scientific publication entitled "Cancer survival in Africa, Asia, the Caribbean and Central America," represented a landmark study which illustrated the desperate inequalities in cancer survival that still persist depending on where people live. At the same time, the study brought hope by revealing the significant benefits of early detection and treatment even in resource-limited settings.

The IARC Monographs Programme continues to be used widely by regulatory agencies and it provided updated monographs on over 100 Group 1 human carcinogens during the biennium. This in-depth review, involving 130 scientists from 28 countries, established new associations between individual agents and cancer in specific organs.

The Agency worked worldwide to identify cancer risk factors and to evaluate prevention strategies, with many examples summarized in the Report. This research covered a wide range of different risk factors, some of specific interest in particular geographic regions where little work has been conducted to date.

Cancer epidemiology cannot afford to ignore the advances in knowledge of mechanisms of carcinogenesis, for example in genomics and epigenomics, which is transforming cancer research. Agency scientists are taking this new knowledge, and the associated technology, back into population studies in interdisciplinary studies to elucidate the risk factors leading to those molecular alterations evident in pre-cancerous and cancerous lesions. Also, when associations are made, for example between a polymorphism at a specific gene locus and cancer risk, Agency laboratory scientists are able to study the functional consequences of that polymorphism and the interplay with environmental risk factors. This shuttling back-and-forth between population and laboratory offers great potential in relation to cancer prevention.

The Biennial Report reveals quite clearly the complementarities between the Agency's research and associated projects which naturally find their home here, due to the credibility of IARC researchers to provide leadership in key areas. Current examples include the continued production of the 4th Series of the WHO Classification of Tumours Series (WHO Blue Books) and the release in 2011 of the new EU Guidelines on Colorectal Cancer Screening and Diagnosis.

The volume and diversity of research and related activities in this Report represents an impressive body of work of the highest quality. At the same time, it is characterized by certain features which are inherent to the approach to cancer research taken by the Agency. These include the focus on international collaboration; interdisciplinary research; and research training and capacity building, both through the research projects themselves as well as more formal delivery of courses and awarding of fellowships. These underlying principles are what drives the Agency in its choices and, for this reason, examples from across the organization are provided in more detail in several brief articles at the beginning of this Report.

The Agency's activities are founded on a combination of a clear vision and excellent staff. Over the last two years, the scientific research programme has been redefined and presented in the Medium-Term Strategy 2010–2014. The same period has seen the recruitment of a significant number of outstanding senior scientists to provide leadership to this programme, as well as a wealth of younger, mid-career researchers who bring fresh ideas and enthusiasm. This blend is one of the most encouraging trends of the past biennium. The presence of an increasing number of eminent Senior Visiting Scientists, who have chosen to spend time at IARC, is a further sign of a stimulating scientific environment with an open, collaborative atmosphere. This environment is one where Masters and PhD students and post-doctoral scientists from around the world can not only do research, but also absorb a way of doing research: with courtesy, honesty and generosity in collaborations.

Cancer research is changing. Not only at a micro level in terms of understanding molecular mechanisms, but also at a macro level with respect to where research is being conducted. The global cancer research community is growing. The Agency has direct evidence of this through the creation of its own IARC alumni list this year, which includes invitations to over 500 past IARC Post-doctoral Fellows to remain in contact with us. Many of those past Fellows work in parts of the world where cancer research is increasingly a priority, for example in Latin America, parts of Asia, the Middle East and Africa. It is in these regions that national cancer institutes and other research centres are being established with local and regional priorities, but with a desire for international cooperation.

The above development offers the Agency exciting research opportunities through its collaborative approach. At the same time we need to reflect this changing world in the governance of the organization and to encourage these regions to set the international cancer research agenda through becoming Participating States of IARC and thus members of the Governing Council. In this regard it was an enormous pleasure to welcome Turkey as the 22nd Participating States of IARC in May 2011.

Finally, by way of introduction to the Biennial Report 2010–2011, I would like to acknowledge how privileged I feel to lead this Agency. The output is prodigious by any standard, especially given the resources available. More importantly, the quality and impact of the work is remarkable. However, overriding even these points in forming my own impression is the dedication and commitment of the IARC staff to the goals of this Agency. It is a community of people from 50 countries that looks to its international responsibilities with pride and determination. It is with this approach to our work that the last outstanding biennium was delivered and which will stand the organization in good stead for the one to come.

Publications

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International Agency for Research on Cancer
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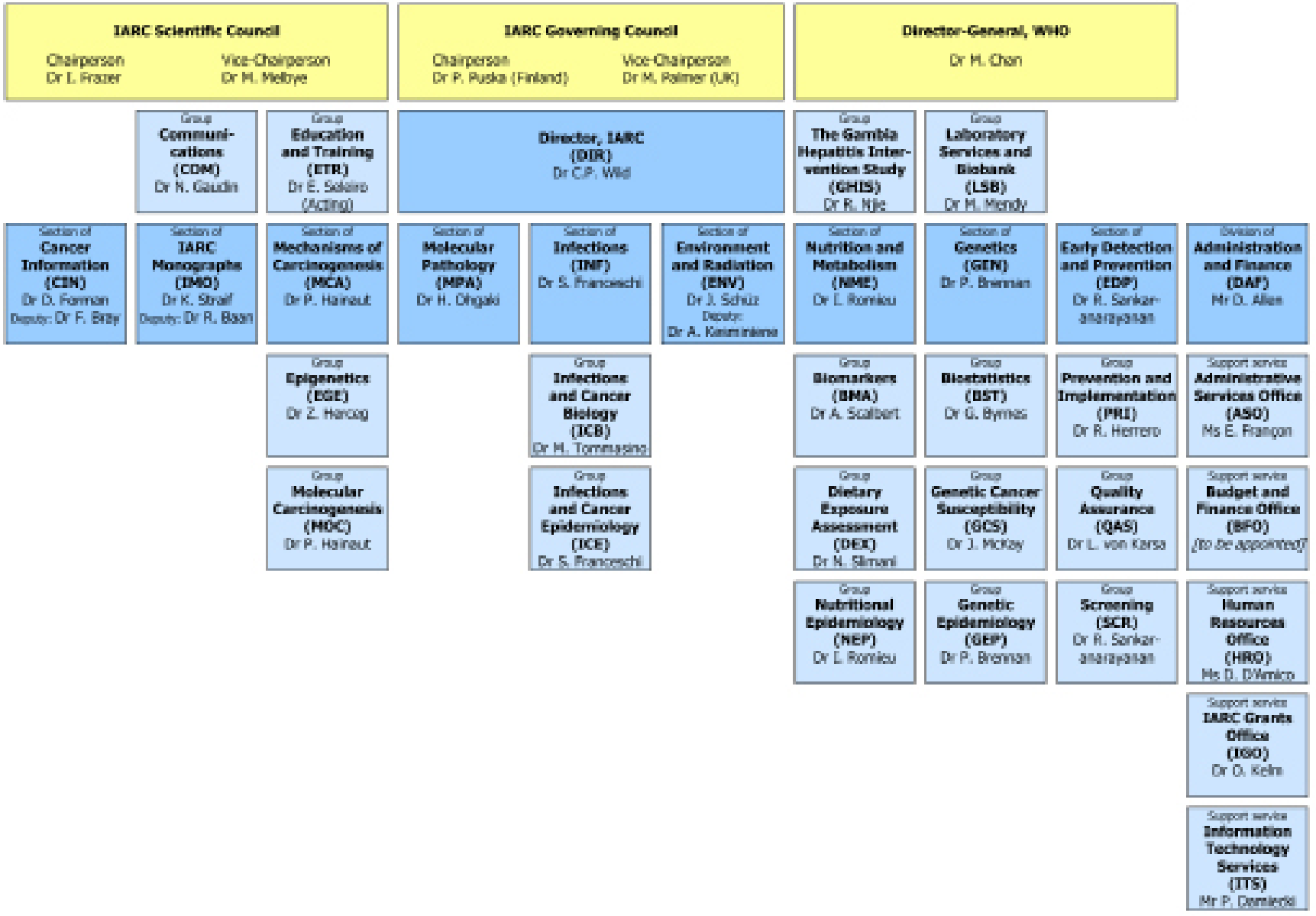
1 December 2011



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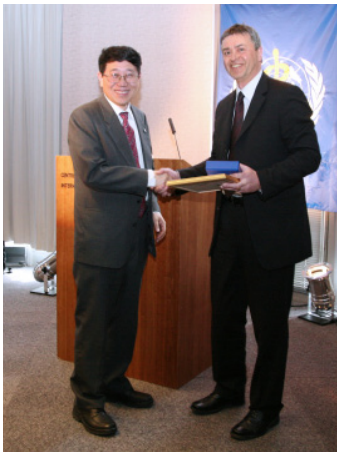


IARC Medals of Honour

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
2010 Gerald N. Wogan (Massachusetts Institute of Technology, Cambridge, USA) – Aflatoxins and human liver cancer
2011 Robert A. Smith (American Cancer Society, USA) – The challenge and potential of early detection to reduce the global burden of cancer

Richard Doll Lecture

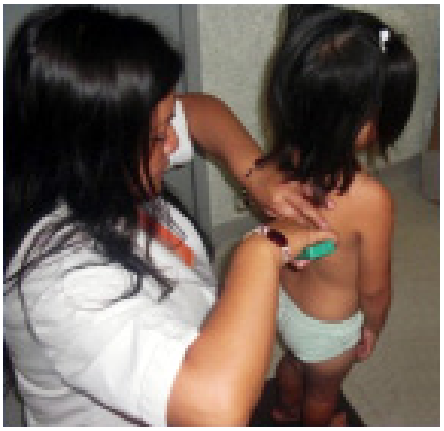
2004 Richard Doll (London, UK) – Fifty years follow-up of British doctors
2005 Brian MacMahon (Needham, MA, USA) – Epidemiology and the causes of breast cancer
2006 Joseph Fraumeni Jr (National Institutes of Health, USA) – Genes and the Environment in Cancer Causation: An Epidemiologic Perspective
2007 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
2010 Julian Peto (London School of Hygiene and Tropical Medicine and the Institute of Cancer Research, UK) – Future cancer mortality due to past and continuing worldwide asbestos use
2011 You-Lin Qiao (Chinese Academy of Medical Sciences & Peking Union Medical College, China) – Implementation of cancer screening and prevention in China – evidence and reality

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

Collaborative Research: examples of multicentre studies

The need for an organization with a worldwide mandate to promote and lead international collaborations in cancer research was one of the main driving forces behind the creation of IARC. Today, the Agency's extensive network of collaborations is widely recognized as one of its major strengths, and the promotion of collaborative research in cancer remains one of the guiding principles for its programmes.



One area where the Agency's contribution has been particularly significant is the coordination of large, international, multicentre epidemiological studies. As epidemiology focuses on identifying risk factors with small effect sizes, one of the requirements is to increase the scale of studies to have the requisite statistical power in the analysis; such scale can, for the most part, only be achieved through large, international, multicentre collaborative studies.

A particular priority for the Agency has been the establishment and coordination of this type of study in low- and medium-income countries (LMICs). These studies are of particular importance as the knowledge of the etiology of cancers more prevalent in these regions is often limited. In addition, they provide the opportunity to study the consistency of effects in different populations, and to test the applicability of approaches for prevention in different socioeconomic and cultural settings. Large-scale collaborative consortia also offer opportunities for designing more efficient studies which optimize the use of limited international, national and local resources.

The remainder of this section describes some of the current examples of multicentre, international, collaborative epidemiological studies and consortia coordinated by the Agency. These include collaborative efforts studying genetic susceptibility or occupational exposures, as well as examples of a new consortia of birth cohorts and the development of laboratory capacity in a LMIC.

Transdisciplinary Research in Cancer of the Lung (TRICL) consortium

Genome-wide association (GWA) studies aim to identify relevant genetic susceptibility variants by genotyping up to 1 000 000 genetic variants (or SNPs). While GWA studies do not require prior knowledge of the functional significance of the variants studied, they do require very large sample sizes, typically thousands of cancer cases and controls.

In 2008 and 2009, multiple independent groups reported results of GWA studies of lung cancer (Hung *et al.*, 2008; Thorgeirsson *et al.*, 2008; Amos *et al.*, 2008). These included studies

coordinated by the IARC GEN Section, MD Anderson Cancer Center (USA), DeCode Genetics (Iceland) and the Institute of Cancer Research (United Kingdom), which jointly comprised over 5000 cases and an even greater number of controls. These studies all provided strong evidence of a susceptibility region in chromosome 15, with an extremely consistent measure of effect between the studies (Fig 1). Two other susceptibility loci were identified in the larger studies, including a region on chromosome 6 (which includes the HLA region that largely comprises immune function-related genes) and on chromosome 5 (including the telomerase gene). Subsequent large studies coordinated by the US National Cancer Institute (NCI), including over 5000 cases and controls, failed to identify further susceptibility loci (Landi *et al.*, 2009).

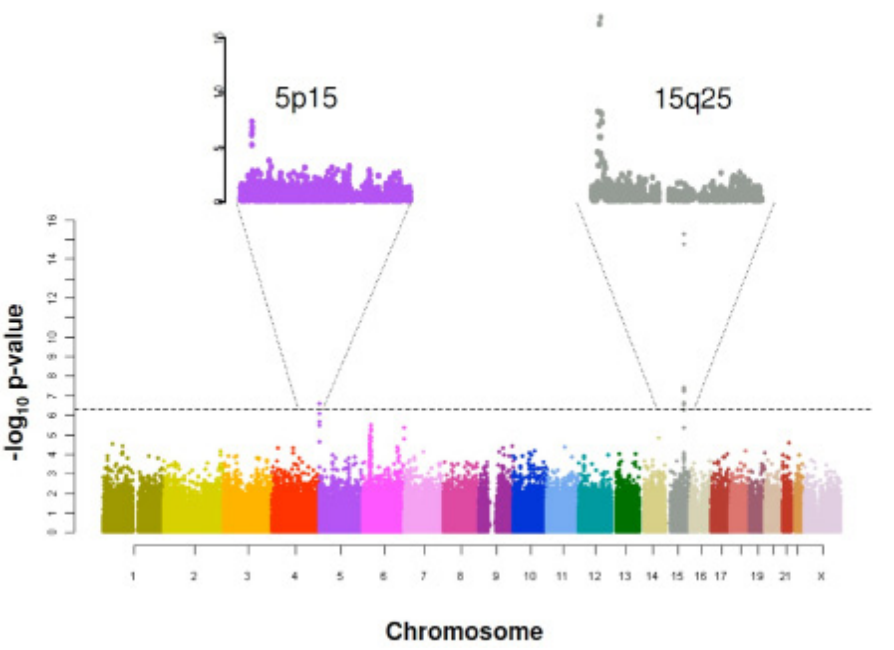


Figure 1. Scatter plot of p-values in –log scale from the trend test for 315 956 variants comparing 2971 lung cancer cases and 3745 controls, showing susceptibility loci in chromosomes 5 and 15

As part of an NCI-led initiative to follow-up on results from GWA studies of cancer, the TRICL consortium was established and started work in 2010. The primary objectives of the consortium are to: further elucidate genetic susceptibility for lung cancer by bringing together all previous studies; follow-up with functional research to help identify causal variants; and identify measures of population risk.

IARC scientists have been instrumental in leading the first objective by bringing together and conducting a meta-analysis of nine separate GWA studies of lung cancer, as well as looking for genetic susceptibility restricted to certain subgroups (e.g. among never smokers or by histological group). The final pooled dataset includes genome-wide results on approximately 15 000 cases and 30 000 controls, of which about 25% originate from IARC-led studies. New potential susceptibility loci have been identified and are being validated in other large lung cancer studies before publication. Other major partners in this initiative include MD Anderson Cancer Center, USA; the Institute of Cancer Research, United Kingdom; and the NCI, USA.

The SYNERGY consortium

A particular challenge in assessing the cancer risk associated with occupational exposures is that few independent studies would be large enough to have the power to correctly assess the joint effect of multiple risk factors.

The SYNERGY project was started in January 2007 to study the joint effects of five selected occupational exposures (polycyclic aromatic hydrocarbons, asbestos, crystalline silica, chromium and nickel) and smoking in the development of lung cancer. The ENV Section of IARC, the Institute for Prevention and Occupational Medicine (IPA, Germany) and the Institute for Risk Assessment Sciences (IRAS, Netherlands) coordinate the project, and IRAS is, in addition, responsible for exposure assessment. Investigators with relevant case-control data on occupational exposures were contacted with the suggestion to pool information.

So far, data from 14 case-control studies from Europe and North America have been pooled. The epidemiological database currently includes relevant demographic information and lifetime occupational and smoking history from 17 705 cases and 21 813 controls, which makes it the world's largest database of its kind. The data were collected between 1985 and 2009, and include around 20% women and 822 never-smoking cases. Another unique feature of the SYNERGY project has been the methodological development of SYNJEM – a country, year and job-specific job-exposure matrix with exposure estimates modelled from extensive quantitative exposure measurements from 21 countries.

The SYNERGY project has developed into a scientific platform for occupational lung cancer research, with main and parallel analyses, as well as for collaboration with other consortia and partners. The results will provide evidence for creating fair compensation schemes for occupational lung cancer and the introduction of more efficient prevention measures.

The Latin American Birth Cohort Consortium on Healthy Growth and Development

The effects of changes in lifestyle and of the rapid nutritional transition from traditional to Western type diets, observed in many LMICs around the world, are fast becoming a major health concern. However, the effects of these changes on children are not well established. Early exposure to poor diet, sedentary lifestyle, tobacco smoke and other environmental factors can alter infants' and children's growth patterns and may result in altered metabolism,

obesity and risk of chronic disease in adulthood.

The Latin American Birth Cohort Consortium on Healthy Growth and Development (BCCHGD) will combine data from established birth cohorts from three Latin American countries – Brazil, Chile and Mexico – with the primary aim of evaluating early life factors associated with optimal growth and developmental patterns and with the prevention of obesity and metabolic disorders.

One of the first activities of the consortium will be to explore the role of maternal anthropometry on the health and growth of offspring. In addition, the Consortium aims to evaluate the effects of maternal and infant nutrition and its interaction with environmental and genetic factors on early markers of cancer risk, epigenetic changes, and on biological and metabolic profiles in children as predictors of disease status at different life stages.

The BCCHGD is being established through a collaboration between scientists from IARC, the 'Centro de Pesquisas Epidemiológicas da Universidade Federal de Pelotas' (CPE-FPel, Brazil), the 'Instituto de Nutrición y Tecnología de los Alimentos' (INTA, Chile) and the 'Instituto Nacional de Salud Pública' (INSP, Mexico).

Establishing HPV serology and genotyping laboratories in Trivandrum, India

Increasingly, epidemiological studies rely on advanced laboratory assays to measure a range of biomarkers to improve disease definition, exposure assessment, or to identify susceptible individuals. The lack of state-of-the art laboratory facilities in many LMICs hinders the development of research led from such regions. The incorporation of capacity-building is a valuable feature of IARC collaborative studies.

Collaboration led by the IARC SCR and ICE Groups, together with the German Cancer Research Centre (DKFZ) and local partners, recently established dedicated HPV serology and HPV genotyping laboratories at the Rajiv Gandhi Centre for Biotechnology (RGCB) in Trivandrum, India. The RGCB HPV laboratories will support the analysis of plasma samples and cervical cells collected from 20 000 participants in the multicentre randomized clinical trial in India evaluating the comparative efficacy of 2-doses versus 3-doses of HPV vaccination in preventing cervical neoplasia.

Figure 2. HPV typing laboratory at the Rajiv Gandhi Centre for Biotechnology in Trivandrum, India

DKFZ trained two staff members from RGCB in HPV serology analyses using a competitive Luminex® immunoassay (CLIA), and provided the technical support for the transfer of CLIA technology to the RGCB. The first trial run of the serology testing facility at the RGCB was carried out in 2011. The assay procedure has been validated and currently large numbers of samples from the study are being processed to evaluate the antibody response following the different regimes.

The ICE Group of IARC trained two staff members from RGCB in the use of a multiplex PCR/APEX assay, a highly sensitive method for the detection and typing of 19 high-risk mucosal HPV types. The use of this methodology at the RGCB has now been validated. The assay will be used for testing the large numbers of cervical cell samples obtained from the participants of the IARC multicentre HPV vaccine trial to evaluate the efficacy of the two different dose regimes in preventing HPV infection. Financial support for this training was provided by the Union for International Cancer Control and IARC.

Publications

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Interdisciplinary Research: where laboratory and epidemiology combine and complement

One of the key features of the Agency's strategy has been the emphasis placed on conducting research that integrates laboratory sciences and population-based studies. The importance of interdisciplinary research to IARC's mission was recognized from its inception and the Agency's pioneering approach in this area was, and remains, one of the main contributors to its success.

Increasingly, the expanding knowledge about mechanisms of carcinogenesis in relation to genetic and epigenetic alterations, combined with the development of 'omics' technologies, is opening new possibilities for combining laboratory-based and epidemiological research. These developments present unprecedented opportunities to further the understanding of both the causes and mechanisms of cancer, as well as providing the scientific rationale for its prevention and, thus, for the translation of research findings from the laboratory to the population. Indeed, it is this approach which promises to provide new impetus to epidemiological studies which seek to detect small effect sizes in exposure-disease associations.

Research that cuts across groups and different specialities within the Agency is highlighted here to provide some specific examples where this interdisciplinary approach is yielding valuable insights. These include not only epidemiological studies incorporating biomarkers, but, of equal importance, studies where observations in the population led to subsequent laboratory studies aimed at explaining those observations.

Role of nicotinic acetylcholine receptors in tobacco-induced lung cancer

Genome-wide association studies, coordinated by Agency scientists, identified a susceptibility locus in chromosome region 15q25 that is strongly associated with lung cancer. Among the genes in this region were three encoding nicotinic acetylcholine receptor (nAChR) subunits (CHRNA5, CHRNA3 and CHRNB4); one variant of CHRNA5 was among the markers with the strongest disease association (Hung *et al.*, 2008).

nAChRs bind to nicotine and tobacco nitrosamines (such as N'-nitrosonornicotine) as well as to other potential lung carcinogens. Certain nAChR subunit alleles have been shown to be associated with a small but significant increased risk of lung cancer in smokers, but no clear association is observed in non-smokers or with other tobacco-related cancers (pancreas, bladder). Given these epidemiological observations, there is a need to understand the functional consequences of the polymorphisms identified to interpret the significance in relation to cancer prevention.

A research consortium coordinated by IARC scientists (BioSILC) and involving the IARC MOC and EGE Groups, the 'Institut Pasteur' in Paris and INSERM in Reims, demonstrated that the association between nAChR genes, tobacco and lung cancer risk is mediated through a complex interaction of multiple mechanisms: polymorphisms in CHRNA5 predispose to nicotine dependence with some alleles strongly associated with tobacco use (Frahm *et al.*, 2011); CHRNA5 expression in bronchial cells modulates cell adhesion and motility, and regulates the expression of p63, a potential oncogene in squamous cell carcinoma (SCC) (Krais *et al.*, 2011); CHRNA3 gene expression is frequently reduced in lung cancer cells, through DNA hypermethylation, and restoring CHRNA3 expression in these cells induces apoptotic cell death, providing a possible novel mechanism for lung cancer therapy (Paliwal *et al.*, 2010).

Role of ß cutaneous HPV types in skin carcinogenesis

Another good example of the complementarity between laboratory sciences and epidemiology at the

Agency is provided by the study of the role of β cutaneous HPV types in skin carcinogenesis, carried out by the IARC ICB Group in collaboration with researchers from the German Cancer Research Centre (DKFZ) (for a more detailed summary of this study see pg. 80 below).

Epidemiological and biological data suggested a role for solar exposure and immune impairment in the etiology of non-melanoma skin cancer (NMSC). Additional evidence pointed to cutaneous β HPV types as the infectious agents possibly responsible for the observed association with immune status, although it remained unclear whether they played a direct role.

In a first series of experiments, the expression of the main oncoproteins of cutaneous β HPV types (HPV38 E6 and E7 proteins) was shown to disrupt several key signalling pathways involved in the control of cellular proliferation and apoptosis (Accardi *et al.* 2011; Hussain *et al.* 2011; Yue *et al.* 2011). These results were confirmed by the observation of increased cellular proliferation in the epidermis of transgenic mice expressing HPV38 oncoproteins in the skin under the control of the keratin 14 promoter. More significantly, chronic UV exposure induced the formation of pre-malignant skin lesions and SCC in a significant proportion of transgenic animals, but not in wild-type animals. Moreover, the pre-malignant skin lesions induced by UV irradiation in the transgenic mice resembled actinic keratosis lesions in humans, which are considered as precursors of SCC (Viarisio *et al.*, 2011).

This work demonstrates that the oncoproteins of β HPV types can promote the development of SCC in mouse skin by enhancing the carcinogenic effect of UV irradiation. These data further support the role of β HPV types in the development of NMSC in humans.

The two studies described above provide particularly good examples of Agency research where data from genomics and/or epidemiological studies led to the development of novel hypotheses and guided the design of functional studies which, in turn, provided significant insights into some of the mechanisms of carcinogenesis associated with important risk factors for two common human cancers.

Use of biomarkers in epidemiological studies

Advances in our understanding of the mechanisms of carcinogenesis have led to the development of new or improved biomarkers of exposure, susceptibility and diagnosis or staging of cancer, which are transforming epidemiological research. However, the use of biomarkers in the context of large epidemiological studies is technically demanding, requiring methods which combine high sensitivity, high-throughput, robustness and limited cost.

The activities of the BMA Group are focused specifically on the development of assays which can be applied to large cohort and case–control studies of cancer. Both immunoassays and chromatographic analyses for the accurate measurement of biomarkers of nutrition (fatty acids and carotenoids), metabolism (sex steroids, growth factors, insulin and obesity-related hormones and thyroid hormones) and inflammation (cytokines) have been established.

The assays mentioned above have been successfully applied to major existing cohorts with biological specimens (the European Prospective Investigation into Cancer and Nutrition (EPIC), the New York University Women's Health Study, The Multiethnic Cohort, the Northern Sweden Health and Disease Study, the DOM cohort and the Study of Hormones and Diet in the Etiology of Breast Cancer-ORDET) to study the etiology of many cancers (breast, endometrial, ovary, prostate, colorectal, cervical and thyroid). A total of about 12 000 analyses on 3500 samples have been carried out over the last biennium, mainly focusing on hormone analyses for studies on cervical and thyroid cancers (in collaboration with the ICE Group) within the EPIC cohort.

Among the main results of these studies is the finding that testosterone, and possibly estradiol, may be implicated in the etiology of invasive cervical carcinoma (Rinaldi *et al.*, submitted) These results suggest that the use of modulators of sex steroid hormones may help to improve the treatment of invasive cervical cancer by decreasing recurrences of cancerous and precancerous lesions.

Research leadership forums

Finally, a new initiative to promote interdisciplinary research at the Agency was introduced at the end of the biennium. The Research Leadership Forums consist of one day meetings of senior scientific staff at a location in or around Lyon, with the purpose of discussing the Agency's scientific strategy and activities in specific areas of cancer research. The aim of these meetings is to stimulate discussion between IARC Groups and promote the development of research projects that cut across individual areas of research. The first of these meetings took place in December 2011 and focused on the Agency's strategy on breast cancer.

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Research & Health Service Development: research leads to service delivery improvements

Health services refers to all structured and interrelated organizations, actions and resource personnel whose primary interests are to help individuals and communities maintain good health by providing preventive and promotive health intervention, and to restore health by diagnosis and treatment of illness. They generally denote government-owned and -promoted facilities that provide, among other things, funds, staff, equipment and consumables, such as drugs. Efficiency of health services in a country is measured by the extent of access, availability, coverage and quality of service delivery, as well as how they are organized and managed. It is important that they be organized around people's needs and expectations and lead to the progressive reduction in exclusion and socio-demographic disparities in health. They should also have a sound financing system and infrastructure to ensure that resources are used equitably and efficiently.

The way health (basic, clinical and epidemiological) research can directly improve public health services through introducing new concepts and practice patterns and by augmenting infrastructure and human resources, has increasingly come to the attention of governments, health care policy-makers and administrators in recent years. From this perspective, it is worthwhile to evaluate the impact and contribution of IARC's prevention and early detection research activities in improving service delivery in national health services in low- and medium-resource countries.

The Gambia Hepatitis Intervention Study (GHIS) was jointly established in 1986 by the Government of The Gambia, the Medical Research Council, United Kingdom and IARC, to evaluate the protective effectiveness of infant hepatitis B immunization in the prevention of chronic liver disease, particularly hepatocellular carcinoma. This long-term IARC study has markedly strengthened the capability of The Gambia to deliver the Expanded Programme on Immunization (EPI) and improve the coverage of hepatitis B vaccination leading to reduced prevalence of hepatitis B surface antigen (Plymoth *et al.*, 2009; Viviani *et al.*, 2008).

Over the last two decades, IARC has organized several trials in developing countries to evaluate various screening options to facilitate development of cost-effective strategies and suitable public health policies for early detection and control of cervical, breast, colorectal and oral cancers in low- and medium-resource countries, such as Angola, Burkina Faso, Guinea, India, Lao People's Democratic Republic, Mali, Mauritania, Nepal, Niger, Republic of Congo, United Republic of Tanzania and Thailand (Deerasamee *et al.*, 2007; Muwonge *et al.*, 2009; Muwonge *et al.*, 2010; Nene *et al.*, 2008; Nessa *et al.*, 2010; Ngoma *et al.*, 2010; Rema *et al.*, 2008; Sankaranarayanan *et al.*, 2004; Sankaranarayanan *et al.*, 2005; Sankaranarayanan *et al.*, 2007a,b; Sankaranarayanan *et al.*, 2009a,b; Sankaranarayanan *et al.*, 2011a; Screening Group, 2011; Teguete *et al.*, 2011). From the start, these studies aimed not only to answer research questions, but also to contribute to improving the infrastructure and skilled human resources of the local health services. Funding agencies, such as the Bill & Melinda Gates Foundation, Association for International Cancer Research (AICR), and Cancer Research, United Kingdom, and organizations, such

as the Union for International Cancer Control (UICC), African Regional Office of the World Health Organization (WHO-AFRO) and Program for Appropriate Technology in Health (PATH), played a major catalytic role by supporting these studies.

Our cervical cancer screening studies have instigated the wider availability of: visual screening and colposcopy; improved histopathology services; treatment of precursor lesions with cryotherapy, cold coagulation, and loop electrosurgical excision procedure (LEEP); cold knife conization; and improved the capacity for delivering radical cancer surgery services for stage I cervix cancer. Augmented human resources and infrastructure deliver the above services in several sub-Saharan African countries such as Angola, Burkina Faso, Guinea, Mali, Republic of Congo, and United Republic of Tanzania, and Asian countries such as Bangladesh, Bhutan, Cambodia, India, Nepal and Lao People's Democratic Republic (Sankaranarayanan *et al.*, 2011b; Teguete *et al.*, 2011). Medical and nursing personnel, who were trained and worked as part of the IARC studies, have evolved as master trainers in screening, diagnosis and treatment and impart their skills to other providers in their countries/regions. The governments of Angola, Guinea and the United Republic of Tanzania have sustained the evolution of these cervical cancer screening training centres by supporting construction of the training facilities, equipping them and providing support for on-going training activities.

Between 1999 and 2011, IARC organized 49 courses on cervical cancer screening in 16 countries, which resulted in the training of 860 doctors in visual screening techniques, colposcopy and treatment with cryotherapy, cold coagulation and LEEP. Some received training in radical surgical procedures and providing colposcopy and LEEP, while 229 nurses, midwives and health workers received education in visual screening and cryotherapy (Tables 1 and 2). Most have evolved as master trainers in their countries thanks to experience acquired through training, retraining and the considerable hands-on opportunities. Nine regional training centres have been set-up and supported by local institutions and governments. IARC continues to provide assistance to facilitate the exchange of master trainers from different countries in the regions. The training facilities have contributed to the instruction of master trainers from Nepal, Bangladesh, China, Thailand, Cambodia, Lao People's Democratic Republic, Vanuatu, Guatemala, El Salvador, Paraguay, Equator, Guinea Bissau, Cape Verde, Comoros islands, among others. The training courses organized by the Cancer Institute of the Chinese Academy of Medical Sciences, in collaboration with IARC during 2003–2007, have resulted in instructing more than 120 master trainers in colposcopy and LEEP in China. They, in turn, have trained a large number of providers over the past five years, resulting in the establishment of several new colposcopy, LEEP and opportunistic VIA screening services within China and in the region.

It is anticipated that the large evidence base and resources generated by IARC and other researchers will, in due course, lead to scaling up of screening and treatment availability and options through organized programmes in health services of low- and medium-resource countries. It is also hoped that the wide variation in survival from treatable forms of cancers between different low- and medium-resource countries/regions will catalyse urgent investments in improving awareness, population-based cancer registration, early detection programmes, health services infrastructure and human resources, so that the disparities in availability, access to diagnostic/treatment services and survival outcomes will be rapidly reduced (Sankaranarayanan *et al.*, 2010; Sankaranarayanan & Swaminathan, 2011c).

Table 1. Training courses on early detection and treatment of cervical cancer (1999–2011)

Country and year of training (# of courses)	Early detection (VIA, VILI, HPV-DNA testing, colposcopy) Number of participants	Treatment (LEEP, cryotherapy, +/− radical surgery) Number of participants
Africa		
Angola (2002)	13	13
Congo (2001; 2003)	27	-
Egypt (2011)	-	20
Gabon (2009)	24	17
Guinea (2000; 2001(2); 2002; 2003; 2007)	67	64
Mali (2001; 2004)	60	-
Mauritania (2002)	18	18
Morocco (2009)	22	-
United Republic of Tanzania (2002; 2009)	48	36
Asia		
China (2004; 2006; 2008)	68	31
India (1999; 2000 (3); 2001 (5); 2002 (2); 2003 (2); 2006; 2007 (2); 2008 (2); 2010; 2011 (2)	630	294
Lao People's Democratic Republic (2002)	15	15
Nepal (2003)	8	8
Thailand (2006; 2007)	54	30
Europe		
France (2000; 2003)	5	5
Oceania		
Vanuatu (2007)	10	10
Total	**1069**	**561**

Table 2. Training resources on early detection and treatment of cervical, breast and oral cancers

Cervical cancer
A practical manual on visual screening for cervical neoplasia
A training course in colposcopy
A training course in Loop Electrosurgical Excision Procedure (LEEP) – practical
A training course in Loop Electrosurgical Excision Procedure (LEEP) – theory
A training course in Visual Inspection using 4% Acetic Acid (VIA) – theory and practice (movie)
A training course in Visual Inspection using Lugol's Iodine solution (VILI) – theory and practice
Colposcopy and treatment of cervical intraepithelial neoplasia: a beginner's manual.
Course in visual methods for cervical cancer screening: visual inspection with acetic acid and Lugol's iodine
Cytopathology of the uterine cervix – digital atlas
Digital learning series – A training course in cryotherapy
Digital learning series – A training course in Loop Electrosurgical Excision Procedure (LEEP)
Digital learning series – A training course in Visual Inspection with 5% Acetic Acid (VIA)
Digital learning series – A training course in Visual Inspection with Lugol's Iodine solution (VILI)
Histopathology of the uterine cervix – digital atlas
Quick clinical reference chart for Visual Inspection with Acetic Acid (VIA)
Quick clinical reference chart for Visual Inspection with Lugol's Iodine (VILI)
Breast cancer
Digital training resource for clinical breast examination and breast awareness
Quick reference chart for clinical breast examination
Oral cancer
A digital manual for the early diagnosis of oral neoplasia
Detecting Oral Cancer – A guide for health care professionals
Quick clinical reference chart for visual inspection of the oral cavity to detect precancerous lesions and invasive cancers

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Education and Training: a historic perspective

Education and Training has been a statutory activity of the Agency since its inception. The Research Training Fellowship Programme was the first activity to be set up when the Agency was created in 1965, before any of the scientific areas were established. At that time, and for a significant period after, IARC Fellowships were one of only a few international fellowships in cancer research, enabling researchers to train in a major institute in a different country. The Fellowship Programme was therefore a vital means of promoting IARC as a new international organization and of enhancing its image and visibility worldwide, as well as promoting cancer research in areas of interest to the Agency.

The aim of the IARC Fellowships Programme is to provide young postdoctoral scientists from any country in the world with training in aspects of cancer research, ranging from biostatistics and epidemiology to mechanisms of carcinogenesis, so that they can return to their own country to develop and implement programmes in cancer research and/or cancer control. Historically, special emphasis has been given to the field of epidemiology and on training of benefit to low- and medium-income countries (LMICs).

With the start of the Courses Programme in 1968, IARC became a pioneer in holding basic epidemiology courses in countries with little or no experience in this area (e.g. China, Cuba, etc.). One course per year was usually organized in a different region of WHO. These courses were instrumental in stimulating interest in cancer epidemiology and in encouraging, identifying and supplying Fellows for further training. In addition to basic epidemiology training courses, the IARC Courses Programme has broadened to include courses in the fields of cancer registration and screening, as well as more methodology-based courses covering a wide range of subjects at both basic and advanced levels.

The current activities of the Education and Training Group, including fellowships and courses, are described elsewhere in this report; in the following sections a brief historical perspective of the IARC Fellowship Programme is provided.

Fellowship Programme

Since 1966, IARC has awarded 570 fellowships to talented young scientists from 73 countries. Of the fellowships awarded, 23% have been in the areas of epidemiology or biostatistics with the remaining 77% split among various laboratory-oriented disciplines. In the first 30 years of the programme the Fellows were predominantly male (~80%), however in the past 10 years the number of women receiving IARC Fellowships has increased to 54%. Approximately 85% of Fellows return to their home country on completion of their training, and around 82% remain active in cancer research .

Director, IARC, opening a session of the Fellowships Selection Committee in a room put at the disposal of the Agency by the Mayor of Lyon.

Figure 1. Dr Higginson, first Director of the Agency, chairing a Fellowship Selection Committee at the Lyon City Hall in 1967.

IARC Fellowships are governed by WHO Fellowship rules and regulations, adapted to meet IARC's specific needs. Since the beginning of the Programme, Fellows have been selected on the basis of scientific excellence by a selection committee composed of external scientists of international reputation in the field of cancer research, together with scientists working at IARC and representatives from WHO and from the Union for International Cancer Control (UICC). The UICC has been a partner since the first days of the Programme and runs a cancer research fellowship programme complementary to that of IARC.

Given the importance of epidemiology for research in cancer etiology and cancer control, and as one of the core components of IARC's activities, particularly in developing countries, the IARC Fellowship Programme has traditionally given considerable

emphasis to this discipline. During the first decades of the Programme, IARC Fellowships were one of the few international fellowships to provide training in cancer epidemiology. At that time in most regions of the world, including various countries in western Europe, there was a virtual absence of graduate training programmes in chronic disease epidemiology, and the Programme funded several Fellows to obtain a formal degree in epidemiology from international schools of public health.

From 1966 to 2004, the IARC Fellowships were aimed at postdoctoral scientists, from any country in the world, who wished to receive training in another country in an area relevant to the etiology and pathogenesis of cancer. During this period, 528 fellowships were awarded, with 80% hosted in laboratories in the USA, the United Kingdom and France, and 11% at IARC. Although the majority of Fellows over this period came from developed countries (64%), the Programme made a significant impact by training candidates from former eastern European countries (18%) and LMICs (19%). It should be noted that, up to 1990, the IARC Fellowship Programme was one of the few programmes that permitted young scientists from eastern Europe to visit other countries and maintain a scientific link with the international research community.

The Education and Training Programme was restructured in 2004, with the goal of ensuring IARC's resources were devoted to providing a unique contribution to training in cancer research, by refocusing the benefit of the Programme to LMICs. Because of this, IARC Fellowships were restricted to LMIC candidates and uniquely tenable at the Agency. From 2005 to 2009, 28 fellowships were awarded. The fellowship duration was extended to two years and a return grant (seed grant) introduced, to enable the Fellow to set up a collaborative research project upon return to their home country.

In 2010, after successfully securing the award of a grant (0.84 million Euros over a period of four years) from the European Union's 7th RTD Framework Programme (Marie Curie COFUND), and to increase the number and quality of applications received, the fellowships were opened again to candidates from any country wishing to be trained at IARC. However, the focus on LMICs was maintained by giving priority to candidates from, or with projects of benefit to, LMICs. Approximately 6–8 new fellowships are awarded annually, with the same number of extensions for a second year (Figure 2)

Following interest expressed by the Agency's participating states, two new elements were introduced to the Programme in 2010–2011: the IARC-Australia Postdoctoral Fellowships, sponsored by Cancer Council Australia, based on the established two year fellowship model; and the IARC-Ireland Postdoctoral Fellowships, sponsored by the Irish Cancer Society, offering a three-year fellowship.

Figure 2. Committee members and IARC Fellows

The Agency continues to actively pursue means of developing and enhancing the Programme, a major step forward being the introduction in September 2011 of the Postdoctoral Fellowship Charter. This is a useful tool in the training of future Fellows. The objective being to reinforce generic training and to provide a more structured approach to performance evaluation and career development.

Other features

A Senior Visiting Scientist Award was introduced in 1983 to enable a senior scientist to spend a sabbatical period at IARC, bringing innovative research, not only to the host research Group, but to IARC's programmes at large. To date, 34 awards have been made.

In an effort to reinforce IARC's mission to enhance cancer research and cancer prevention in LMICs, the Expertise Transfer Fellowship was begun in 2006 to enable a senior scientist to transfer their knowledge and expertise to a host institute in an LMIC. Four fellowships have been awarded to date, all in the area of epidemiology.

Funding

As a core activity, the Education and Training Programme is mainly financed through IARC's budget, however, it has enjoyed support over time from several external sources. With specific regard to the Fellowship Programme, support has been received from the Italian Association for Research on Cancer (AICR), the EU 7th RTD Framework Programme (Marie Curie COFUND), the Cancer Council Australia and the Irish Cancer Society.

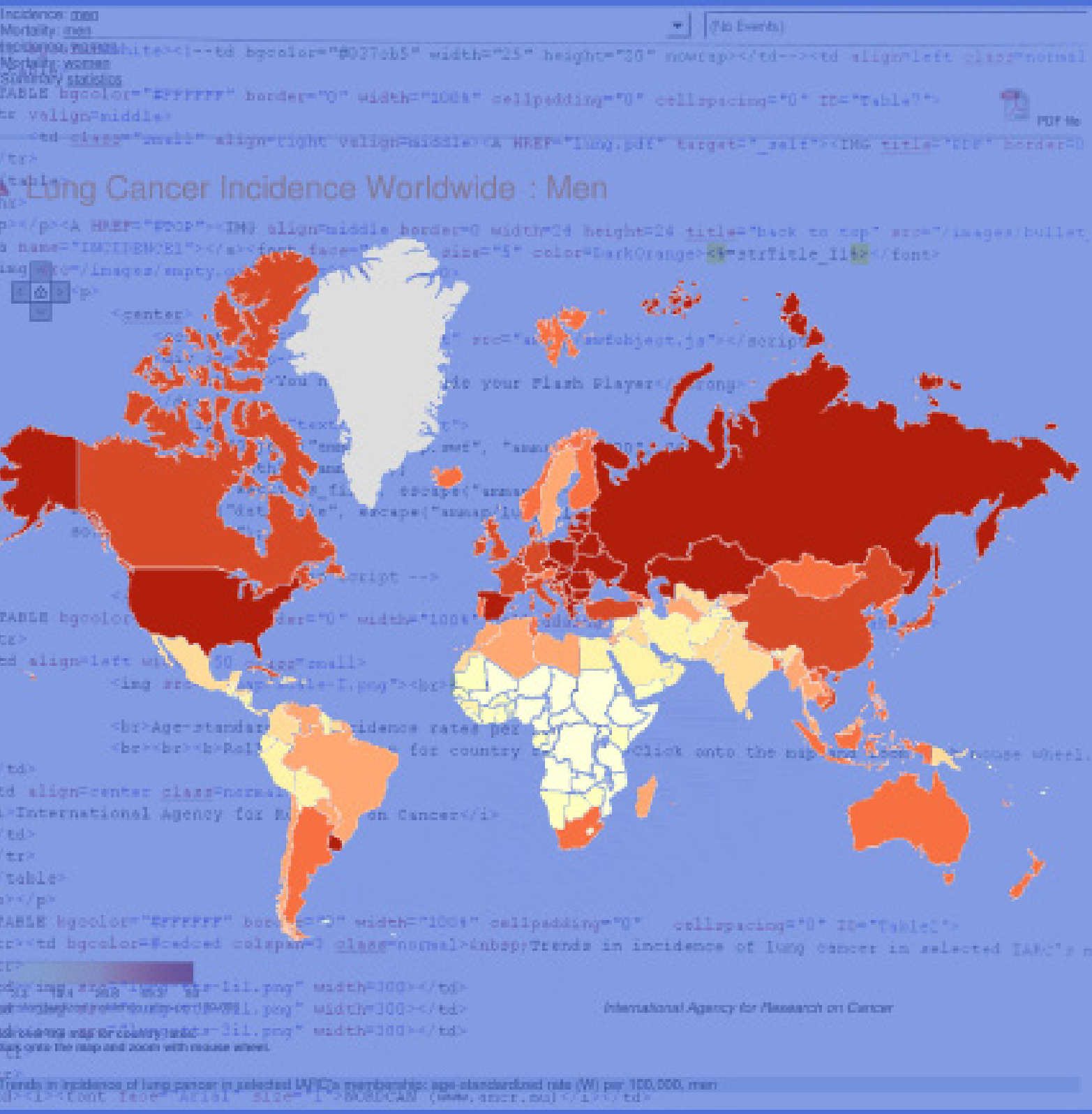
Alumni

The IARC Alumni Group was created in 2011 within the LinkedIn® social network, with the purpose of bringing together former Agency staff, visiting scientists, fellows, postdocs and students. It provides a way of creating a community of people who have spent time at IARC in the past, promoting informal discussion and networking and a means for keeping the members informed of activities and opportunities at the Agency.

IARC Alumni Group page: http://www.linkedin.com/groups?mostPopular=&gid=3713610

Conclusion

Over the past 45 years, IARC's Education and Training Programme has made a substantial contribution to the development of cancer research programmes in many countries, especially in the field of cancer epidemiology, with special emphasis on LMICs. In particular, the Fellowship Programme has played a major role in shaping the Agency's research strategy and activities and contributed significantly to building IARC's wide network of collaborators. Over the years it has provided the first contact with the Agency for several scientists who would later become some of its most senior staff members.


Lung Cancer Incidence Worldwide : Men
International Agency for Research on Cancer

Section of Cancer Information (CIN)

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Deputy section head
Dr Freddie Bray

Scientists
Dr Maria-Paula Curado
(until July 2010)
Dr Hai Rim Shin (until June 2010)
Dr Isabelle Soerjomataram
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Mr Eric Masuyer

Clerks (informatics)
Mr Emmanuel Giraud
Clerks (statistics)
Ms Murielle Colombet
Ms Joannie Tieulent

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Visiting scientists
Ms Graciela Cristina Nicolas
Dr Cristina Stefan
Postdoctoral fellows
Dr Jiansong Ren
Dr Suzanne Moore

Students
Mr Mohannad AlNsour
Mr Dyego Bezerra de Souza
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Ms Marianna de Camargo Cancela
(until March 2011)
Ms Marine Castaing (until July 2011)
Ms Karima Chaabna
Ms Stephanie Gehring
(until August 2010)
Ms Clarisse Héry (until February 2010)

The Section of Cancer Information (CIN) has the overall goal of maintaining IARC as the definitive reference source for the provision of information concerning worldwide cancer statistics. CIN was created in 2009 and, in March 2010, two of the three existing Groups, Descriptive Epidemiology Production (DEP) and Data Analysis and Interpretation (DEA), were amalgamated to constitute an integrated Section. The third, Biostatistics Group (BST), previously in CIN, was moved to the Section of Genetics (GEN).

In April 2010, Dr David Forman joined IARC from the University of Leeds, United Kingdom to become Section Head, and Dr Freddie Bray joined IARC from the Cancer Registry of Norway as a Staff Scientist. In October 2010, Dr Bray was appointed as Deputy Section Head. The previous Group Heads, Dr Maria Paula Curado (DEP) and Dr Hai-Rim Shin (DEA), left IARC in July 2010.

CIN works to fulfil a series of linked objectives consistent with the goal of the Section and with the IARC medium-term strategy. The primary objective is the collection, analysis and dissemination of information concerning the global cancer burden. This is accomplished through collaboration with and provision of support to cancer registries worldwide and the International Association of Cancer Registries (IACR). Information obtained is published in the serial definitive reference volume, Cancer

Incidence in Five Continents, and in online global cancer statistics tools, including GLOBOCAN, available on the CancerMondial website (http://www-dep.iarc.fr/). CIN provides support to cancer registries worldwide in terms of development, staff training, promotion of common standards for coding and classification and ensuring effective use of data produced. There is a relative deficit of cancer registries in low- and middle-income countries (LMIC). CIN is responsible for leading a new IARC Global Initiative for Cancer Registration in LMIC (GICR) in collaboration with several international partners. CIN conducts a research programme in the descriptive epidemiology of cancer, which includes geographic analyses, studies of time trends and the estimation of the future burden of the disease. Components of the research programme include the use of new sources of information concerning the burden of cancer and novel methodological approaches to the analysis of registration and mortality data.

The global burden of cancer

GLOBOCAN 2008

Accurate statistics on cancer occurrence and outcome are essential, both for the purposes of research and for the planning and evaluation of programmes for cancer control. IARC provides regular updates of the cancer burden worldwide through its GLOBOCAN series (http://globocan.iarc.fr). This has now been updated to 2008 for incidence, mortality (Ferlay *et al.*, 2010) and prevalence (Bray *et al.*, submitted). Estimates have been prepared for 27 major cancers by sex and ten age groups in 184 countries. The new release of GLOBOCAN has benefited from a comprehensive review of the estimation procedures and from new sources of data. A hierarchy of methods is employed in building up the global profile of cancer, and are dependent on the availability and accuracy of country-specific data. National sources of incidence and mortality were used wherever possible, with local data and statistical modelling used in their absence. For developing countries where no vital statistics were available, cancer-specific mortality was approximated using the estimated incidence for 2008 and cancer survival probabilities modelled by GDP per capita, and scaled to the WHO estimates.

Overall in 2008 there were an estimated 12.7 million new cancer cases, 7.6 million cancer deaths and 28.8 million persons alive with cancer (within five years of diagnosis). Lung cancer remains the most common cancer in the world in terms of both new cases (1.6 million cases, 12.7% of the total cancer incidence burden) and deaths (1.4 million deaths, 18.2% of the total mortality burden). Breast cancer is the second most common cancer overall (1.4 million cases, 10.9%) and ranks fifth in terms of cause of cancer death (458 000 deaths, 6.1%). Cancers of the colon and rectum (1.2 million cases, 608 000 deaths), stomach (990 000 cases,738 000 deaths), prostate (913 000 cases, 261 000 deaths) and liver (748 000 cases, 695 000 deaths) rank third to sixth respectively in terms of global frequency of new cases. With respect to prevalence, the most common cancers are breast cancer (5.2 million women surviving up to five years after diagnosis), colorectal cancer (3.3 million persons) and prostate cancer (3.2 million men). Figure 1 illustrates the striking variations from region-to-region in the patterns of occurrence of cancer, while Figure 2 provides a breakdown of the total burden of cancer incidence, mortality and prevalence by continent.

Figure 1. Global maps of the 2008 age-standardized incidence rates per 100 000, all ages. Contrasting patterns for (a) male colorectal cancer and (b) cervical cancer

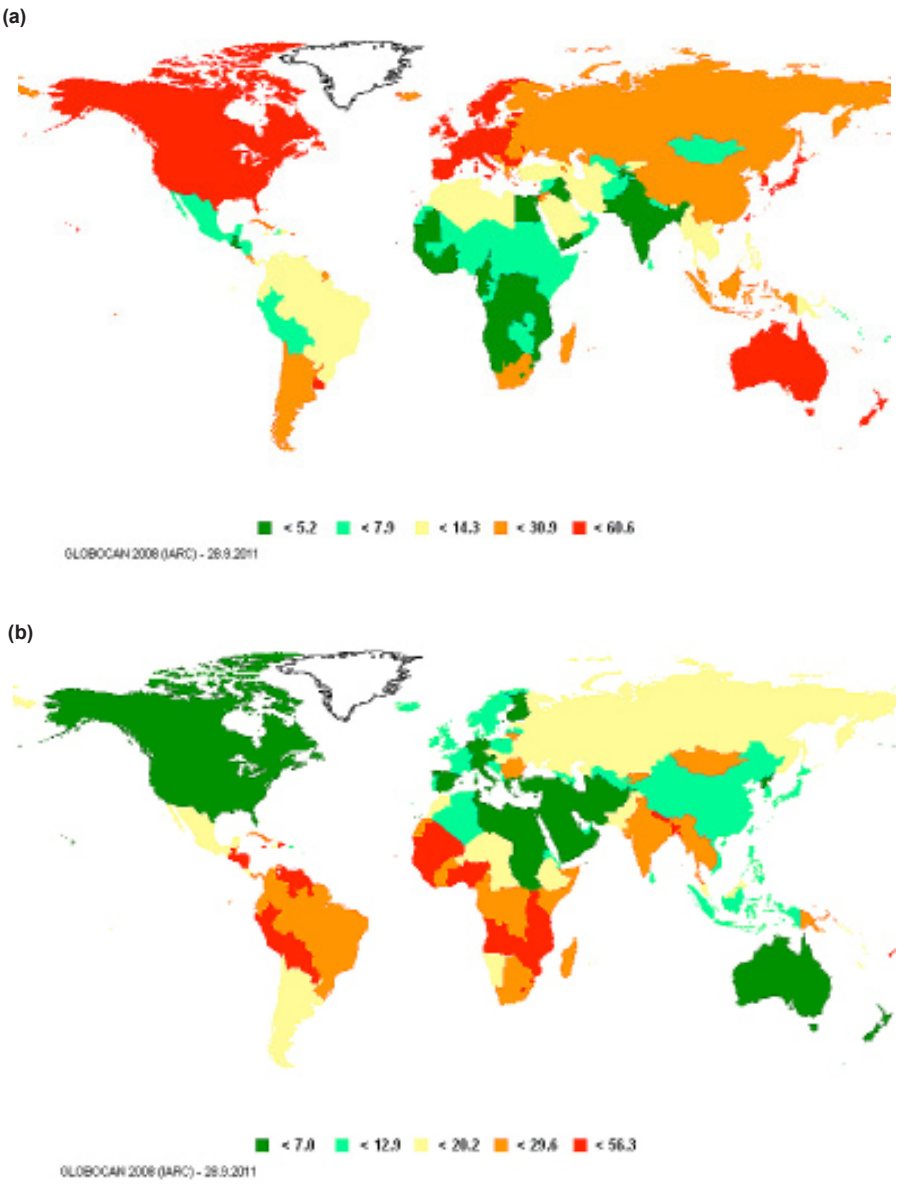


Figure 2. Estimated cancer incidence, mortality and prevalence worldwide in 2008 by continent

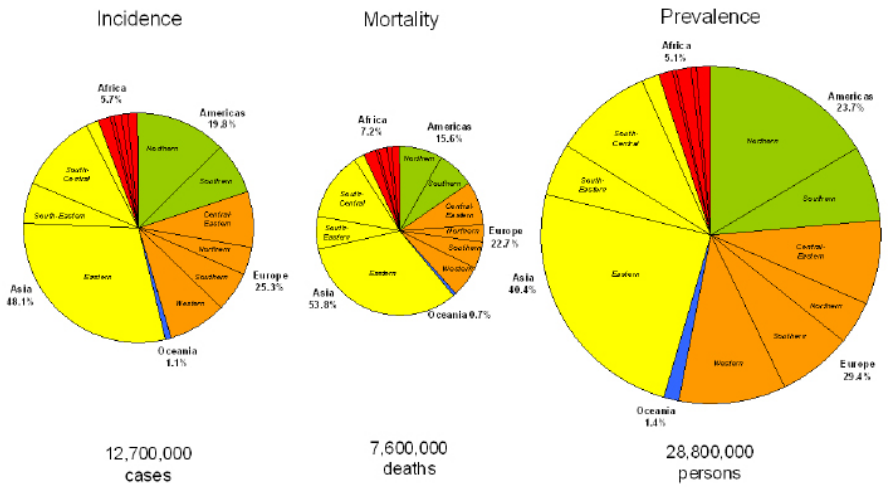
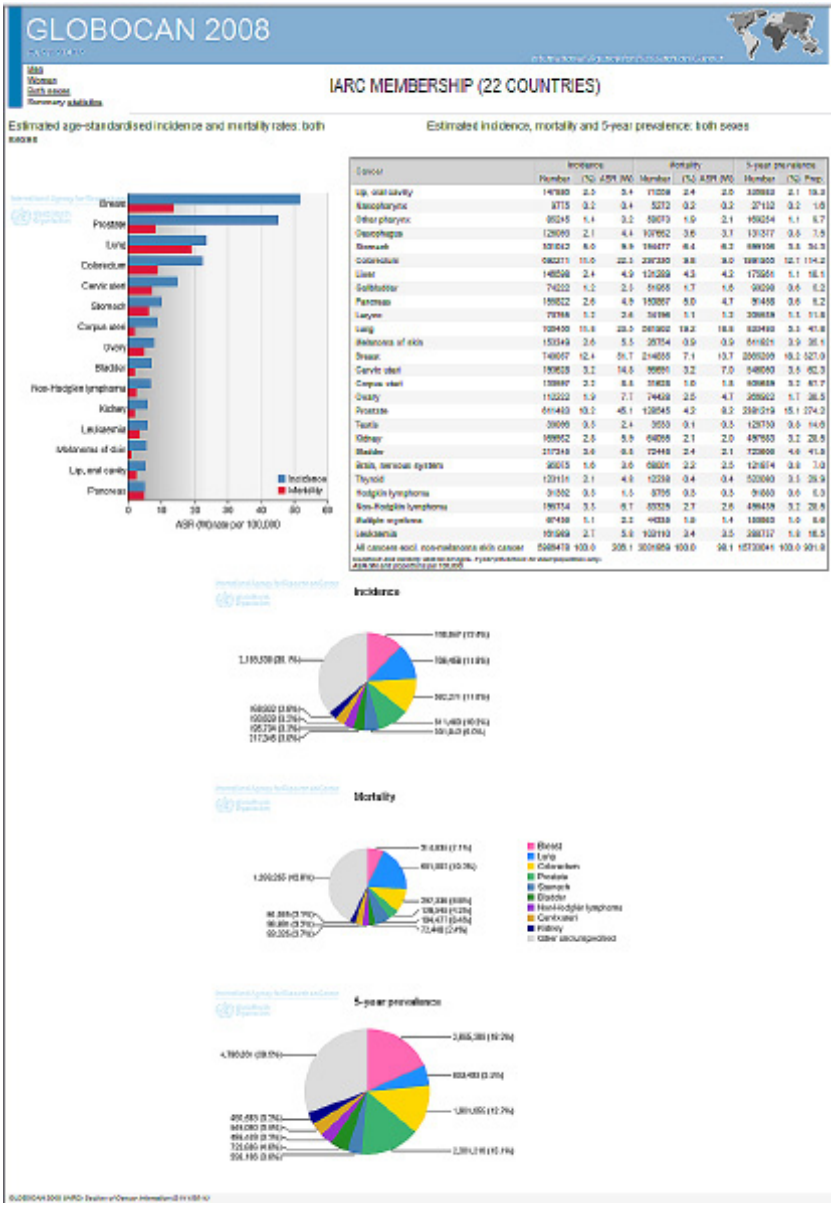


Figure 3. Example of country fact sheets available at the GLOBOCAN 2008 website (http://www.globocan.iarc.fr)



Facilities for the tabulation and visual description of the current and future cancer burden in each country of the world, and according to world region, can be accessed via the website. This also provides a series of cancer site and country-specific factsheets (e.g. Figure 3).

Cancer Incidence in Five Continents

Recent work on *Cancer Incidence in Five Continents* (CI5) has brought together results from all nine previously published volumes (Parkin *et al.*, 2010). *CI5 I–IX* comprises two public domain websites, *CI5 I–IX* and CI5plus (http://ci5.iarc.fr). The *CI5 I–IX* application contains data exactly as published in the nine volumes of CI5. The *CI5plus* database contains unpublished annual data for 101 selected populations from 86 cancer registries published in CI5, for the longest period available (up to 2002), and for 27 major cancer sites and all cancers combined. In addition, combined groups of cancer registries in the same country have been added for 11 countries. An *online analysis* option allows creation of tables of incidence rates for a selected population or cancer similar to those of CI5 I–IX. Graphic options are also available, allowing creation of age-specific incidence curves (e.g. Figure 4), or time trends (e.g. Figure 5). A downloadable page gives access to the tabulated annual data used in the online application (*summary* database) or to a subset of the summary database, including incidence data for 88 selected populations for which histological data were available for a minimum of 15 consecutive years (*detailed* database).

In March 2011, an Editorial Board was convened to prepare for volume X of CI5. Members of the Editorial Board representing IACR are: David Brewster (United Kingdom), Charles Gombe-Mbalawa (Republic of Congo), Betsy Kohler (USA), Marion Piñeros-Petersen (Colombia) and Rajaraman Swaminathan (India) and, representing IARC: Freddie Bray, Jacques Ferlay, David Forman and Eva Steliarova-Foucher. A call for volume X data was sent to cancer registries in September 2011. Volume X will include data for cancers diagnosed in the period 2003–2007 and will be published in 2012.

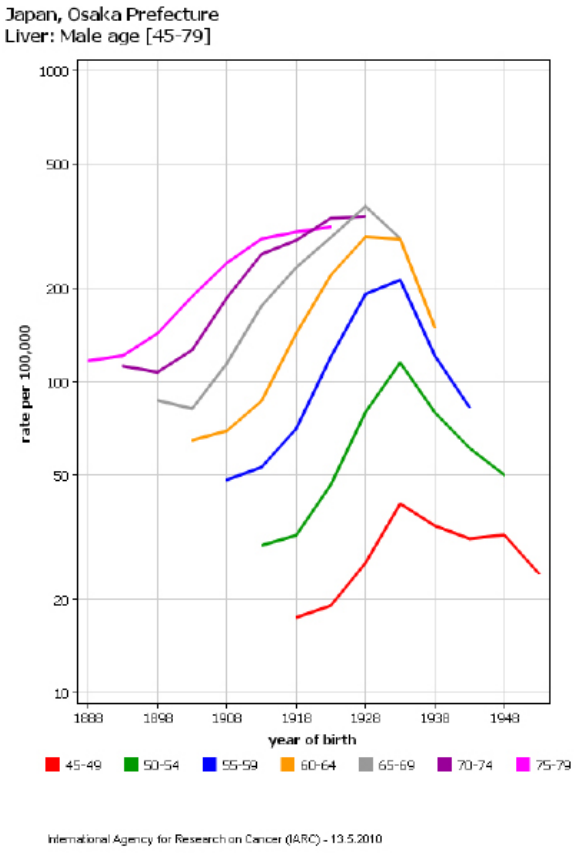


Figure 4. Trends in incidence of liver cancer in males (age 45-79) Osaka, Japan, by period of birth

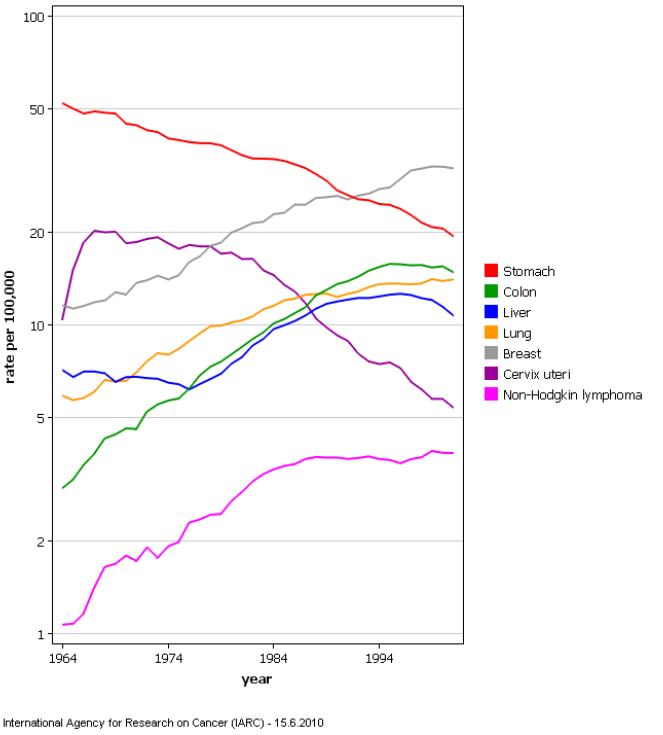


Figure 5. Trends in age-standardized incidence of selected cancers in females (all ages) Osaka, Japan, 1964-2004

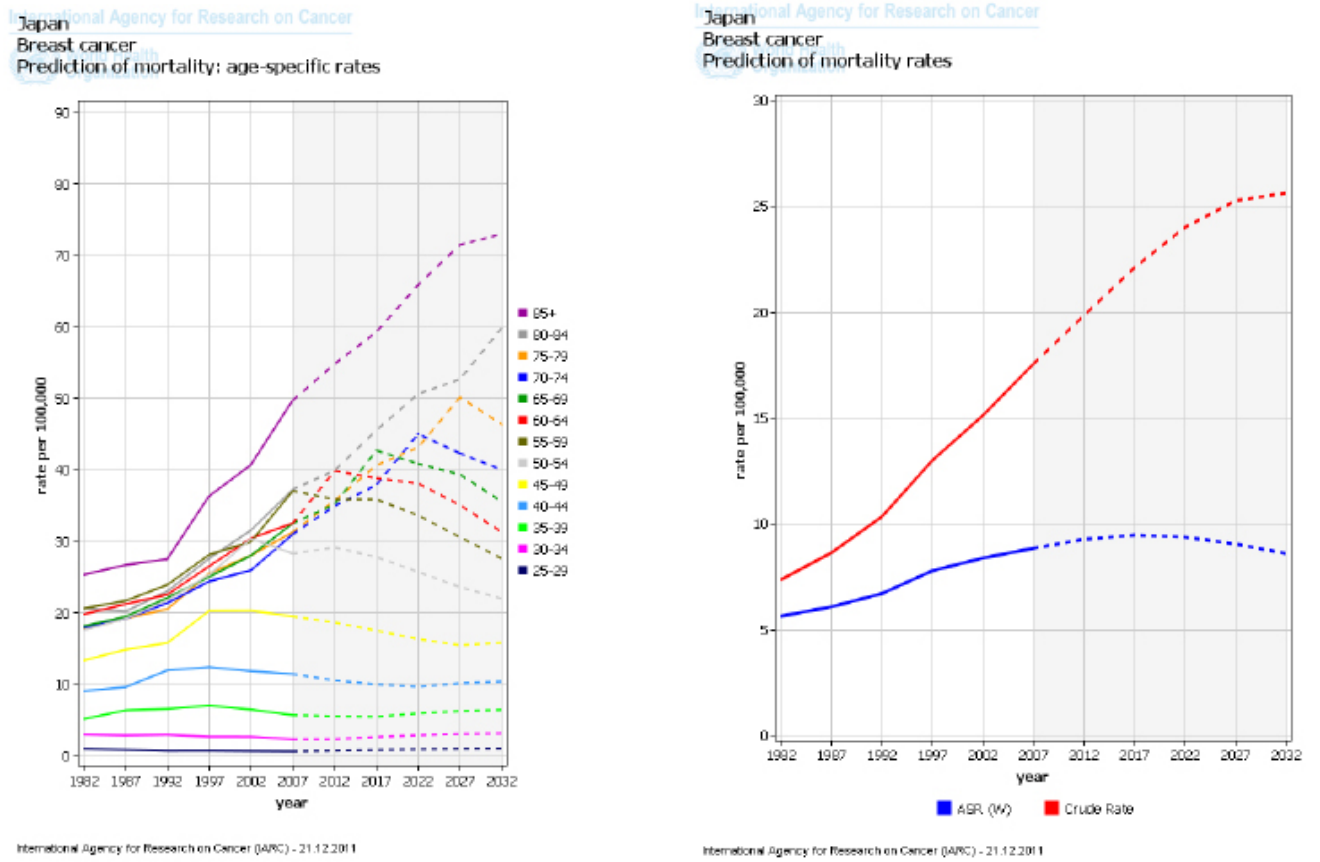


Figure 6. Prediction of breast cancer mortality in Japan using the WHO mortality database online application

International Incidence of Childhood Cancer

International Incidence of Childhood Cancer (IICC) is a collaborative project between IARC and IACR (http://iicc.iarc.fr). The objective is to provide data on cancer incidence in children and adolescents through a worldwide collaboration with cancer registries, including specialized paediatric registries. Currently, Volume 3 of IICC is under preparation. Data are being collected and validated using semi-automated procedures developed over the reporting period. An online questionnaire is administered to the participating cancer registries to aid interpretation of the collected data. Publication of results is expected by the end of 2012.

CANCER*Mondial*

In response to the ever-growing demand for descriptive epidemiological data on the global cancer burden, the CIN website, CANCER*Mondial* (http://www-dep.iarc.fr), has been completely redesigned. Information is now accessible through several applications developed within the Section (see above). Also included is the WHO mortality database, which provides easy access to the most recent information on cancer mortality recorded in selected countries around the world. Within this application is the ability to predict cancer mortality up to 2030 (Figure 6). A new option designed for the analysis of trends is being developed. It will detect one breakpoint in a time series of data and enable users to test whether or not an apparent change in trend is statistically significant (Figure 7). CANCER*Mondial* also provides links to external databases of cancer statistics and to CIN collaborative projects.

Cancer in Europe

European Network of Cancer Registries and Europe against cancer: optimization of the use of registries for scientific excellence in research

CIN has provided a Secretariat to the European Network of Cancer Registries (ENCR) for over two decades (Steliarova and Parkin, 2011). Recently, CIN has supported a major project of the ENCR, Europe against Cancer: Optimization of the Use of Registries for Scientific Excellence in Research (EUROCOURSE), an 'ERA-NET' project funded by the Seventh Framework Programme of the European Commission. This project aims to improve the operation and use of cancer registry data in scientific research and involves five partners and some 200 contributors from Europe. CIN staff have contributed to various EUROCOURSE working groups devoted to the topics of accessibility, standardization and dissemination of data collected in European cancer registries and issues of data protection and confidentiality. The project runs from April 2009 until March 2012 (http://www.eurocourse.org/).

Within EUROCOURSE, the *Registries Portal* was developed (https://cinportal.iarc.fr). The Portal considerably improves communication and data exchange with over 600 collaborators within and outside Europe and greatly increases the automation of data processing.

Software for automatic verification of received data sets (DepEdits-2) was completely redesigned from an earlier version and rewritten using JAVA. The new version contains numerous customization options and produces a standard output dataset, ready to be incorporated into a common database. DepEdits-2 has been tested on multiple datasets and will be available for use by registries at the end of 2011.

A 'common database' was developed and is stored on a SQL server. The common database contains some 60 million cancer records and will be used for multiple studies, including those with a worldwide scope.

European cancer observatory

The European part of the common database has been analysed and results will be disseminated through the European Cancer Observatory website through three channels:

EUCAN to provide national estimates of incidence, mortality and prevalence for 40 European countries for 2012 (as an IARC-based continuation of the ECO website currently hosted at http://eu-cancer.iarc.fr/); EUROCAN to allow the analysis of incidence and mortality rates and time trends (Figure 8); and EUROCIM to enable research access to the underlying database (according to the requirements of the individual cancer registries. The β version of the website will be released by the end of 2011 (http://eco.iarc.fr)).

NORDCAN

The NORDCAN project is a joint activity of the Association of Nordic Cancer Registries (ANCR) and IARC, supported by the Nordic Cancer Union (NCU). The NORDCAN database includes information about cancer incidence, mortality and prevalence recorded by the five Nordic countries from the first (earliest 1943) to the most recent (up to 2009) year available. The latest version (4.0) of NORDCAN (Engholm *et al*., 2010) now includes 1-, 5- and 10-year standardized relative survival by country, covering the years 1964–2003. The website, which presents these data together with advanced graphical and analysis options, is available in English and five Nordic languages (http://www-dep.iarc.fr/nordcan.htm). It is hosted at IARC and is maintained and developed by CIN. The NORDCAN application was delivered to the Italian Association of Cancer Registries (AIRTUM) to present similar data from the Italian cancer registries. A worldwide-based version of NORDCAN is in preparation and will contain time series of incidence data from either national cancer registries or groupings of regional registries within the same country and national mortality data extracted from the WHO database.

European Partnership for Action Against Cancer (EPAAC)

CIN is involved in the European Partnership for Action Against Cancer (EPAAC) as a 'collaborating' partner in support of the 'Health Information' work package lead by the National Cancer Institute in Italy. This 'joint action' is funded by the European Commission DG SANCO for a three year period beginning March 2011. IARC will contribute statistics on incidence and mortality in the EU Member States and possibly work on survivorship and the cost of cancer registration. Implementation of this plan is subject to identification of appropriate funding for this activity.

Figure 7. Joinpoint analysis of breast cancer mortality trends in the UK, women (aged 20-84), using the WHO mortality database online application

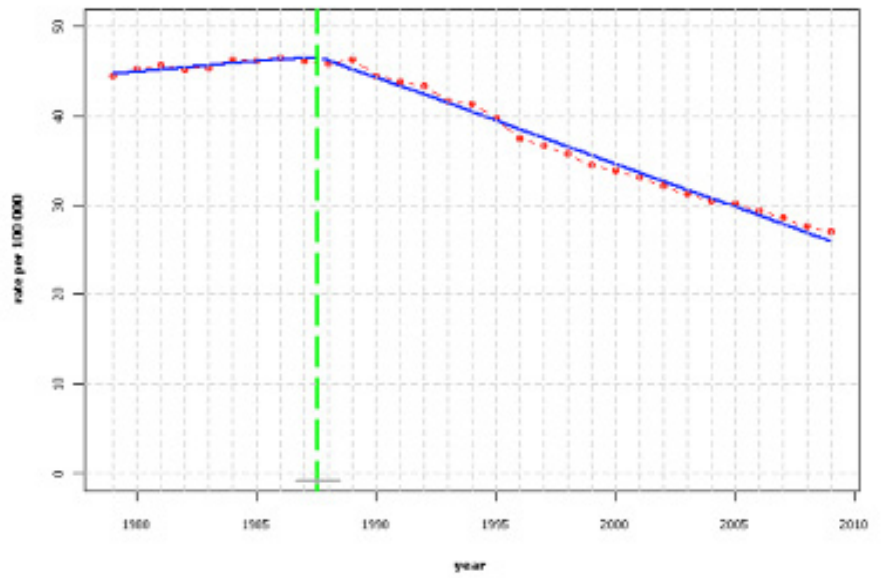


Figure 8. European Cancer Observatory: the new EUROCAN website

Automated Childhood Cancer Information System

The Automated Childhood Cancer Information System (ACCIS) is a European project, co-funded by the Ministry of Health of the Federal Government of Germany. The aim of this project is to collect, analyse, interpret and disseminate data on incidence and survival of children and adolescents with cancer in Europe using automated procedures. Over the current reporting period, the database was updated to include some 170 000 cancers in children and adolescents arising from 1500 million person-years in the period 1970–2007 (Figure 9).

Two papers on childhood cancer are in preparation: one to update the report of increasing incidence trends and another on incidence and survival of germ cell tumours in children and adolescents.

Cancer registry development

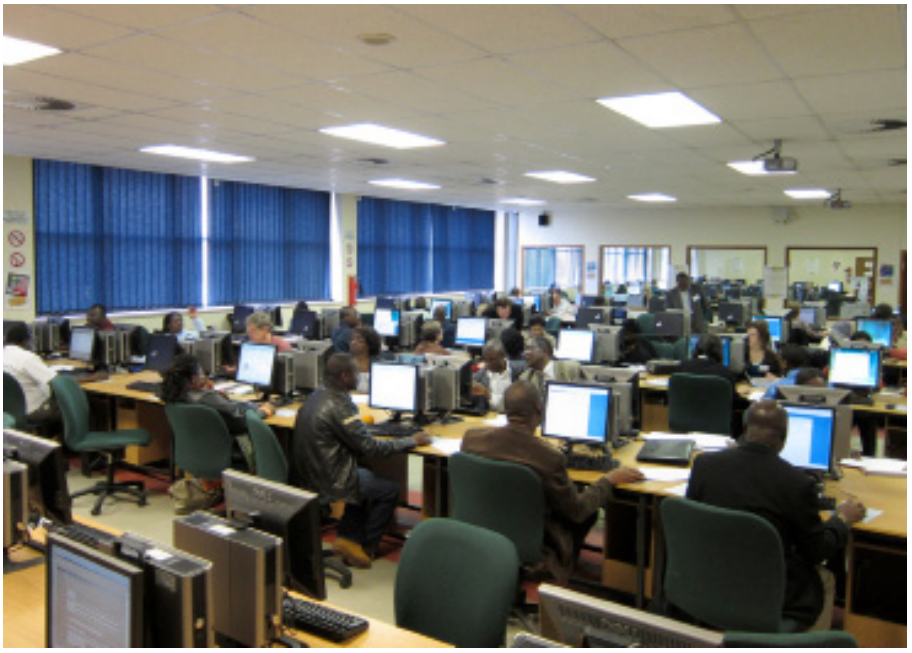
CIN undertakes several activities to support the development of population-based cancer registries throughout the world. It also provides a Secretariat to the IACR (www.iacr.com.fr) and, together with the local hosts, is responsible for organizing the annual meeting of the IACR (held in Yokohama, Japan in 2010 and in Mauritius in 2011). CIN interacts with cancer registries and their associated networks around the world and has developmental projects of relevance to all registries (e.g. updating and dissemination of the International Classification of Diseases for Oncology (ICD-O) for which a revision to the 3rd edition was published in 2011). In collaboration with IACR, CIN is also engaging in a revision to the textbook *Cancer Registration, Principles and Methods* due for publication in 2012.

CIN's priority in developmental work is to support cancer registration in LMICs. This incorporates several activities including:

- Collaborative Research Agreements (CRAs) with cancer registries in Guinea, Mali, Mozambique, Niger, Nigeria, Zimbabwe (2008–2010/11) and India (2010–2012). Several new CRAs with cancer registries in Africa and Asia will be established for the next biennium.
- Training: CIN is responsible for module 1 of the annual IARC Summer School, which provides training in cancer registration and its application to epidemiology. Regional cancer registration training courses took place in Cape Town in 2010 (Figure 10) and in Mumbai and Cairo in 2011; further courses are being planned for 2012 in South America, Asia and Africa.
- Expert site visits: CIN staff are involved in conducting site visits to assess the feasibility of establishing new cancer registries and to provide developmental advice to existing registries, particularly in low- and middle-income countries. Recent site visits took place in Nigeria, Kenya, Indonesia and Oman; expert visits to Sri Lanka and Mongolia are foreseen in 2012.

Figure 9. Automated Childhood Cancer Information System (ACCIS) re-launched on the new website

Figure 10. Cancer registration training course, Stellenbosch University, Cape Town, South Africa, September 2010



• CanReg: The registration software package has been developed by IARC and is currently used in over 50 countries. The open source version of CanReg5, version 5.00, was officially launched at the 2010 IACR conference in Japan. One of the major changes from previous versions of CanReg is the focus on user autonomy – a user can download and set up the program with no interaction with IARC, but still follow the most important standard coding and quality control systems. Other improvements are stronger multi user support, more modern database, multi platform support, increased security and improved analytical capabilities. The software is available to download for free in several languages (English, French, Russian, Portuguese and Spanish – with a Chinese version shortly). A handbook is also available. Training courses and workshops were held in India (Regional), Kenya (Regional), Japan (International), Mauritius (International), Egypt (Regional), South Africa (Regional), IARC Summer School (International), Ecuador (Regional), Trinidad & Tobago (Regional), Morocco (National) and Turkey (Regional). Continuous technical support has been given to registries using CanReg on aspects ranging from installation and tailoring to data entry and analysis.

The global initiative for cancer registry development in low- and middle-income countries

Subsequent to an IARC Governing Council resolution (May 2009) calling for a special project to improve the coverage and quality of data from cancer registries in LMIC, IARC launched the Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries (GICR), together with several other international partner organizations. This was unveiled at the UICC World Cancer Leaders Summit in November 2011. CIN was responsible for organizing a partners' meeting, held at IARC in July 2011 (Figure 11), which confirmed cancer registration as a priority area across all the organizations represented.

The GICR proposes the establishment and development of several regional registry resource centres (or hubs). IARC's role will be to coordinate and support the operation of these regional hubs, which will in turn provide local support, training and infrastructure to networks of cancer registries in their region. Regional hubs will be established as the focal contact points for technical support queries for cancer registries in the region, including the provision of technical support for CanReg5, the development of a programme of regular site visits to monitor and support improvements in the operation of cancer registries and the establishment of a regional training programme. Hubs will also help cancer registries make full use of the data they produce and participate in research programmes.

A pilot hub for the Asian region has been established at the Tata Memorial Centre in Mumbai (India) at the end of 2011. Further hubs are planned to be established over the next years depending on the success of the pilot and the availability of external funds.

Figure 11. Partners' meeting, IARC, Lyon, July 2011

Progress of the GICR may be followed on http://gicr.iarc.fr.

Childhood cancer

CIN's expertise in childhood cancer has contributed to the international programme "My Child Matters," coordinated by UICC (http://www.uicc.org/programmes/my-child-matters). This programme is devoted to improving the conditions and management of childhood cancer in selected low-resource countries. Dr Steliarova-Foucher, as a member of UICC Childhood Cancer Task Force, mentors three projects involving registration and follow-up of childhood cancer patients, in Cali (Colombia), Karachi (Pakistan) and Quito (Ecuador). Ad hoc collaborations are also being developed with the South African National Paediatric Cancer Registry, the National Cancer Registry of Trinidad and Tobago, the Chennai Cancer Registry in India and the National Paediatric Cancer Registry of Belarus.

Descriptive epidemiology

A research programme in the descriptive epidemiology of cancer has been a major component of IARC's activities since its inception. Current and planned research within CIN is characterized by developing a systematized approach to studying the global descriptive epidemiology of cancer that embraces innovative concepts and methodologies. Accordingly, the portfolio of descriptive epidemiology includes global overviews of the key indicators of cancer burden (and their interpretation) by place and time, cancer-specific or region/country-specific reports, and also includes novel use of indicators of burden (e.g. disability-adjusted life-years), of levels of development (e.g. the Human Development Index) and methodology (e.g. trends-based predictions).

Global cancer burden

With the launch of GLOBOCAN 2008 and online versions of CI5, accompanying papers have outlined the estimation procedures of GLOBOCAN (Ferlay *et al.*, 2010), presented key variations of the global burden (Ferlay *et al.*, 2010; Jemal *et al.*, 2011) and described 50 years of CI5 (Parkin *et al.*, 2010). Two additional indicators of cancer burden have been added to GLOBOCAN 2008:

Prevalence

Estimates of global cancer prevalence in 2008 for 27 sites in the adult population have been completed for 184 countries (Bray *et al.*, submitted). The five year global cancer prevalence is estimated to be almost 29 million in 2008, with prevalent cancers of the prostate and breast dominating in men and women respectively. A validation exercise based on a comparison of the observed prevalence in the Nordic countries, Italy and the United Kingdom, suggests the methods provide reasonably robust estimates of prevalence.

Disability-adjusted life-years

A set of estimates of disability-adjusted life-years (DALYs) from cancer for

184 countries have been assembled, and papers describing the methods (Soerjomataram *et al.*, submitted) and global results (Soerjomataram *et al.*, submitted) published. The DALYs link data on disease occurrence to health outcomes. The estimation process yields two key components of the burden of cancer: one related to premature mortality, the other to the loss of 'healthy' life-years related to the morbidity that follows a diagnosis of cancer. Such indicators provide valuable additional information in establishing country-specific agendas regarding cancer control.

Global burden and the human development index

A first global overview has been conducted (Bray *et al.*, submitted) investigating patterns of cancer incidence and mortality in relation to levels of the Human Development Index (HDI), a reference statistic that serves as a frame of reference for social and economic development. The study examines the patterns and trends globally and additionally estimates the future burden of cancer in relation to HDI levels, considering both relatively well characterized demographic effects as well as predicted changes in the risk of cancer.

Geographic studies

Papers have been published (or are in press) on cancer as an emerging public health problem in Africa. They review the current patterns of disease and the opportunities for reducing the burden through the application of resource-level interventions (Jemal *et al.*, submitted). Other work estimates cancer mortality in India based on verbal autopsy survey methods, including a description of cancer patterns by region and urban/rural status (Dikshit *et al.*, submitted). Also examined is the worldwide burden of cervical cancer in relation to prevention (Arbyn *et al.*, 2011; Arbyn *et al.*, submitted).

Time trends and predictions

Ongoing collaborations include those with colleagues in India on studies examining 30 year incidence trends in Mumbai. A collaboration with Dr Dhillon (SANCD, Delhi) examines the three most common cancers in women (Dhillon *et al.*, 2011), while a study with Dr Dikshit (Tata Memorial Centre, Mumbai) looks at breast cancer by menopausal status, and includes predictions of the disease up to 2025 (Dikshit *et al.*, submitted). A further paper, developed in collaboration with the Chennai Cancer Institute, examines trends in overall cancer incidence in Chennai city (1982–2006) and predicts the future burden in Tamil Nadu (2007–2016) (Swaminathan *et al.*, 2011). Collaborations with colleagues in Shanghai at the Cancer Institute examine the declining incidence rates of hepatocellular carcinoma in the city between 1976–2005 (Gao *et al.*, in press).

Collaborative efforts

Research with the National Cancer Institute includes: ongoing analyses of international HPV-related and unrelated head & neck cancer incidence trends, using a novel age-period-cohort model; long-term trends in gastric cancer by age and subsite; and an international overview of male breast cancer rates. There is also continuing work with the American Cancer Society to examine international patterns and trends in urological cancers. European collaborations have resulted in papers comparing European incidence and mortality trends in prostate cancer (Bray *et al.*, 2010) and mortality trends in testicular cancer (Znaor and Bray, submitted), while another reports the large increases in testicular cancer based on data from the Croatian Cancer Registry (Sincic *et al.*, in press). Collaborations with the Karolinska Institute, Stockholm, Sweden include an age-period-cohort collaborative analysis of lung cancer incidence trends in 11 countries according to the main histological groupings (Bray *et al.*, in press) and analyses of oesophageal cancer by histological sub-type.

There are also ongoing collaborative studies with colleagues in other IARC Sections: the analyses of trends of cervix cancer (with ICE), and global trends in melanoma of the skin (Erdmann *et al.*, submitted) and testicular cancer (with ENV).

Global population attributable fractions

As a collaboration between ICE and CIN, global and regional assessments are being prepared of the overall burden of cancer attributable to infectious causes. GLOBOCAN 2008 data are being used as a source for the total burden of cancer, while IARC Monograph 100B has been used to provide information on those infectious agents that have been classified as definite (Group I) causes of human cancer.

Method development

Jian Song Ren, an IARC fellow, has compared methods to estimate the incidence burden in China (Chen *et al.*, 2010) in collaboration with the National Central Cancer Registry in Beijing. There has also been a complete revision of the chapter entitled "Descriptive Studies" for inclusion in the Second Edition of the Springer book *Handbook of Epidemiology* (Bray and Parkin, submitted). There is ongoing work examining the comparability of the cancer registries in India. Previous studies have found a high level of consistency between the registries with respect to variables routinely collected, however differences in procedures in retrieving information, checking for duplicates and handling missing information were apparent. This study is ongoing and in collaboration with IACR and the Tata Memorial Hospital.

Childhood cancer

CIN is also contributing to two new large-scale international studies funded by the Seventh Framework Programme of the European Commission. The European Network for Cancer Research in Children and Adolescents (ENCCA) is a 'Network of Excellence' with 38 participating institutes and is coordinated by the President of SIOP Europe (Dr Ladenstein, Austria). IARC's role is to evaluate the feasibility of, and resources required by, population-based cancer registries to undertake enhanced prospective data collection to include information on diagnosis, initial risk group, tumour response and events. As a first step, a questionnaire has been developed and administered to all registries with a potential to collect the relevant data. Results of this survey will inform further research directions.

PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup) is a five year collaborative project of 16 participating institutes, coordinated by the chairman of the PanCare network (Dr Hjorth, Sweden), and aims to predict long-term side-effects to cancer therapy (http://www.pancaresurfup.eu/). IARC will ensure participation of population-based cancer registries which are not involved through the other partner institutions. A baseline status report will also be prepared to estimate the prevalence of long-term survivors of cancer in childhood and adolescence, incidence of second primary tumours and mortality after five year survival.

Courses

CIN is responsible for organizing the Cancer Registration module for the annual IARC Summer School. In addition, the following regional courses were organized on Cancer Registration and Descriptive Epidemiology:

Guayaquil, Ecuador, April, 2010
Trinidad & Tobago, April, 2010
Cape Town, South Africa, September, 2010
Mumbai, India, Feb/March, 2011
Cairo, Egypt, November, 2011

Specific training in CanReg was conducted in:

Antalya, Turkey, Feb, 2010
Casablanca, Morocco, March, 2010
Yokohama, Japan, Oct, 2010
Nairobi, Kenya, May, 2011
Mauritius, Oct, 2011

Meetings

CIN organized meetings of the Cancer Incidence in Five Continents Editorial Board (March, 2011) and the Global Initiative for Cancer Registration in Low- and Middle-Income Countries (July, 2011). Because of its provision for an ENCR Secretariat, CIN hosted Steering Group meetings (Nov, 2010 and March, 2011), a meeting of the EUROCOURSE Steering Group (March, 2011) and meetings associated with EUROCOURSE Work Packages.

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European Commission FP7-HEALTH (PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies – Collaborative Project)
GAVI (Provision of support to countries monitoring cervical cancer burden in relation to the introduction the HPV vaccine – activities using cancer registries)
Nordic Cancer Union for the NORDCAN project

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The first step in cancer prevention is to identify the causes of human cancer. The *IARC Monographs Programme* is an international, interdisciplinary approach to carcinogenic hazard identification. Its principal product is the serial publication, the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, which began in 1971 in accordance with one of the fundamental missions of the Agency: to prepare and disseminate authoritative information on human cancer, especially on its causes and prevention. Reviews and evaluations of nominated agents and exposures are carried out by Working Groups of scientific experts who are invited to participate on the basis of their contributions to the relevant areas of science. The IARC Monographs are a worldwide endeavour that has involved more than 1200 scientists from 53 countries.

Each *Monograph* consists of a comprehensive, critical summary and review of the published scientific literature. Since 1987, each has concluded with an evaluation of the overall evidence of carcinogenicity to humans. In general, three volumes of the *Monographs* are prepared annually. Since 1971, nearly 950 chemicals, complex mixtures, occupational exposures, physical agents, biological agents, personal habits and household exposures have been reviewed, some of them several times as

new information became available in the published scientific literature. About 100 of these agents have been identified as carcinogenic, and about 300 as probably carcinogenic, or *possibly carcinogenic to humans* (Groups 1, 2A and 2B). The *Monographs* have evolved into the WHO's encyclopaedia on the roles of environmental agents in human cancer causation. 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 also 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.

Volume 100 of the IARC Monographs

Volume 100 of the *IARC Monographs* comprises a reassessment and update of the more than 100 agents classified by the IARC as *carcinogenic to humans* (Group 1) in Volumes 1–99. During the period October 2008–November 2009, the *IARC Monographs Programme* organized six international Working Group meetings of experts in carcinogenesis and public health. It was agreed that no *IARC Monographs* Working Groups would convene during 2010, so as to consolidate the results of the Volume 100 project and to finalize several earlier volumes (see below). The latter included the checking for scientific accuracy and clarity of over 5000 pages of text and tables, editing of the text, and processing of the books for dispatch to the printers.

Overview of activities during the biennium 2010–2011

Publication of Monographs in print

The 2010–2011 biennium saw the publication in print of seven volumes of *IARC Monographs* as listed below (key evaluations and scientific highlights mentioned for each):

Volume 92 (853 pp)
Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures

Benzo[*a*]pyrene is *carcinogenic to humans* (Group 1). The Working Group made this evaluation in the absence of agent-specific epidemiological information, taking into account the *sufficient evidence* of carcinogenicity of benzo[*a*]pyrene in numerous animal species. Also, the fact that the complete sequence of steps in the metabolic activation pathway of benzo[*a*]pyrene to mutagenic and carcinogenic metabolites (diol-epoxides) has been demonstrated in experimental animals, in human tissues *in vitro* and in exposed humans added to this appraisal.

Volume 93 (452 pp)
Carbon black, titanium dioxide, and talc

The Working Group found evidence of an association between the use of talc for feminine hygiene and ovarian cancer, and decided that there is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder. It was evaluated as *possibly carcinogenic to humans* (Group 2B).

Volume 94 (450 pp)
Ingested nitrate and nitrite, and cyanobacterial peptide toxins

Ingested nitrate or nitrite under conditions that result in endogenous nitrosation is *probably carcinogenic to humans* (Group 2A).

Although the epidemiological evidence was *inadequate* (for nitrate in food) or *limited* (for nitrite in food), the Working Group reached this evaluation considering the following:

There is an active endogenous nitrogen cycle in humans that involves nitrate and nitrite, which are inter-convertible *in vivo*. Nitrosating agents that arise from nitrite under acidic conditions in the stomach react readily with nitrosatable compounds, especially secondary amines and amides, to generate *N*-nitroso compounds. These nitrosating conditions are enhanced following ingestion of additional nitrate, nitrite or nitrosatable compounds. Some of the *N*-nitroso compounds that could be formed in humans under these conditions are known carcinogens in experimental animals.

Volume 95 (430 pp)
Household use of solid fuels and high temperature frying

About half of the world's population uses solid fuels for cooking or heating, often in poorly ventilated spaces. Many studies show an association between household use of coal and an increased risk for lung cancer. The Working Group made the following evaluations: indoor emissions from combustion of coal are *carcinogenic to humans* (Group 1), those from combustion of biomass fuel (primarily wood) are *probably carcinogenic to humans* (Group 2A). Likewise, emissions from high temperature frying are *probably carcinogenic to humans* (Group 2A).

Volume 96 (1428 pp)
Alcohol consumption and ethyl carbamate

The Working Group confirmed the carcinogenicity to humans of alcoholic beverage consumption. On the basis of *sufficient evidence* in experimental animals for the carcinogenicity of ethanol, and in view of the epidemiological evidence showing little indication that the carcinogenic effects depend on the type of alcoholic beverage, the Working Group also concluded that "Ethanol in alcoholic beverages is *carcinogenic to humans* (Group 1)."

Volume 97 was published during the previous biennium.

Volume 98 (804 pp)
Painting, firefighting, and shiftwork

Occupational exposure as a painter is *carcinogenic to humans* (Group 1). It causes cancers of the lung and the urinary bladder, as well as mesothelioma. There is *limited evidence* in humans, based primarily on studies of maternal exposure, that painting is associated with childhood leukaemia.

There is limited evidence in humans for the carcinogenicity of occupational exposure as a firefighter and the Working Group reached an overall evaluation that occupational exposure as a firefighter is possibly carcinogenic to humans (Group 2B).

There is *limited evidence* in humans for the carcinogenicity of shiftwork that involves night work (e.g. nurses engaged in working the night shift). The notion that disturbance of the internal clock plays a role here comes from studies in experimental animals, where *sufficient evidence* was found for the carcinogenicity of light during the daily dark period (biological night). The Working Group then reached the following overall evaluation: shiftwork that involves circadian disruption is *probably carcinogenic to humans* (Group 2A).

Volume 99 (692 pp)
Some aromatic amines, organic dyes and related exposures

The Working Group confirmed the carcinogenicity of several agents that had not been reviewed in detail since *Monograph* Volume 1 (1972). On the basis of the carcinogenicity of benzidine, the Working Group concluded that "dyes metabolized to benzidine" should also be considered *carcinogenic to humans* (Group 1). "Occupational exposures of hairdressers and barbers" were evaluated as *probably carcinogenic to humans* (Group 2A), while "personal use of hair colourants" was considered as *not classifiable as to its carcinogenicity to humans* (Group 3).

With the publication of these volumes, all *Monographs* up to and including Volume 99 are now available in print.

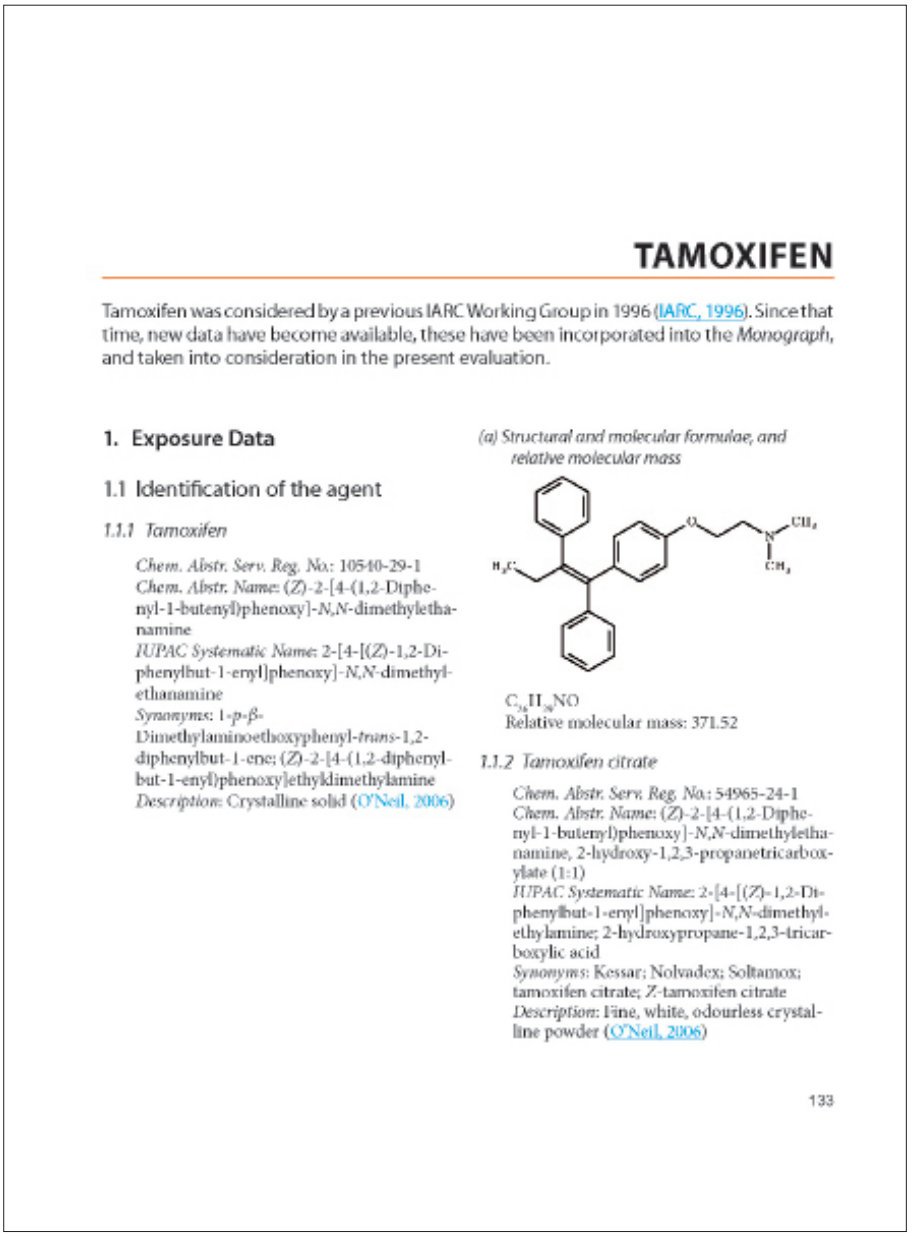
Publication of Monographs in electronic form

The complete Volumes 48–99 are now freely accessible on the *Monographs*' website as pdf files. Earlier volumes are being scanned and added regularly. In addition, the first parts of Volume 100 have been posted; subsequent parts will follow. The complete Volume 100 (A–F) will be printed as a six book series in the first half of 2012.

Improvement of format and layout of IARC Monographs

During this biennium, the *Monographs Programme* has invested in state-of-the-art publishing software and technologies to accelerate publication of delayed volumes (see above) and to bring the *Monographs* series into the 21st century. This was achieved by first integrating the use of an XML-based editorial software that – at the click of a button – copy-edits manuscripts to adhere to the WHO Style guidelines, and, more importantly, checks and corrects references automatically against both PubMed and CrossRef databases. This software also creates valid XML to be used for pagination purposes. Here, the *Programme* invested in another computer programme, built on industry-standard software that automatically lays out XML content. This was first tested with Volume 96 (> 1400 pp) and took 2.5 hours to paginate automatically, as opposed to the six weeks it would have taken doing it manually.

The *IARC Monographs Programme* also worked on changing the page size and design for Volume 100 (see example below) and subsequent volumes, introducing changes to adhere to the World Health Assembly resolutions on accessibility of WHO publications to all. The development of the e-book format is currently ongoing. When complete it will be readable on e-book readers, tablets, and smart phones. These



TAMOXIFEN

Tamoxifen was considered by a previous IARC Working Group in 1996 (IARC, 1996). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 Tamoxifen

Chem. Abstr. Serv. Reg. No.: 10540-29-1
Chem. Abstr. Name: (*Z*)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethanamine
IUPAC Systematic Name: 2-[4-[(*Z*)-1,2-Diphenylbut-1-enyl]phenoxy]-*N*,*N*-dimethylethanamine
Synonyms: 1-*p*-β-Dimethylaminoethoxyphenyl-*trans*-1,2-diphenylbut-1-ene; (*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]ethyldimethylamine
Description: Crystalline solid (O'Neil, 2006)

(a) Structural and molecular formulae, and relative molecular mass

$C_{26}H_{29}NO$
Relative molecular mass: 371.52

1.1.2 Tamoxifen citrate

Chem. Abstr. Serv. Reg. No.: 54965-24-1
Chem. Abstr. Name: (*Z*)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethanamine, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)
IUPAC Systematic Name: 2-[4-[(*Z*)-1,2-Diphenylbut-1-enyl]phenoxy]-*N*,*N*-dimethylethylamine; 2-hydroxypropane-1,2,3-tricarboxylic acid
Synonyms: Kessar; Nolvadex; Soltamox; tamoxifen citrate; *Z*-tamoxifen citrate
Description: Fine, white, odourless crystalline powder (O'Neil, 2006)

133

improvements have been realized by the *IARC Monographs* Production Team (Ms Russell, Ms Elbers, Mr L Galichet).

IARC Monographs Volumes 101, 102 and 103

During the second year of the biennium, the *IARC Monographs Programme* resumed its regular schedule of preparing three *Monographs* per year as follows:

Volume 101
Some chemicals in industrial and consumer products, food contaminants, and water chlorination byproducts (Working Group meeting, 15–22 February 2011)

In this *Monograph*, 18 chemical agents were evaluated. A common feature of these chemicals is that they have all been tested recently in two year bioassays in rodents and found to be carcinogenic. On the other hand, although humans are exposed to these substances, there are so far very few or – for some of the agents – no epidemiological studies available. The list comprised chemicals that are found in industrial and consumer products, some food contaminants, and several byproducts of water chlorination.

For all 18 agents, the Working Group concluded that there was *"sufficient evidence* of carcinogenicity in experimental animals," leading to an overall evaluation – in the absence of adequate epidemiological information – of *possibly carcinogenic to humans* (Group 2B). The only exception was 2-nitrotoluene, which was placed in Group 2A *(probably carcinogenic to humans)* on the basis of mechanistic considerations, and in view of the extraordinarily early onset and high tumour incidence in experimental animals treated with this compound.

Some of the other agents evaluated by this Working Group are:
4-Methylimidazole - to which the general population is exposed through its presence in class-III and class-IV caramels, which are widely used colourants, particularly in beverages.
Di(2-ethylhexyl)phthalate (DEHP) - a widely used plasticiser. The general population is exposed to DEHP through leaching from plastic medical devices, such as blood bags and medical tubing, and as a contaminant of food packaged in DEHP-containing materials.

Bromochloroacetic acid, dibromoacetic acid and dibromoacetonitrile - which are three of the many chlorination byproducts present in drinking water and in swimming pools.

Volume 102
Radiofrequency electromagnetic fields, including microwaves, mobile telephones and radar (Working Group meeting, 24–31 May 2011)

The rapid expansion of wireless telecommunication and other emerging technologies has resulted in widespread exposure of the general public and many workers to the electromagnetic radiation emitted by mobile telephones and other devices.

Uncertainties in the science and its interpretation in relation to possible adverse effects on health have led to different conclusions among the scientific community and to public and media concerns, particularly about a possible risk for cancer.

The Working Group considered the radiofrequency segment of the electromagnetic spectrum (30 kHz-300 GHz) with respect to its possible carcinogenic hazard, and reviewed the following exposure categories:

(a) occupational exposures to radar and microwaves, (b) environmental exposures associated with transmission of signals for radio, television and wireless telecommunication and (c) personal exposures associated with use of mobile telephones (cell phones). The most important information came from studies on cell phone use, discussed in some detail below.

The INTERPHONE study, a multicentre case-control study, is the largest investigation so far of mobile phone use and brain tumours, including glioma, acoustic neuroma and meningioma. Comparing those who ever used mobile phones with those who never did yielded an odds ratio (OR) of 0.81 (95% CI: 0.70–0.94). In terms of cumulative call time, ORs were uniformly below or close to unity for all deciles of exposure except the highest decile (> 1640 hours of use), for which the OR for glioma was 1.40 (95% CI: 1.03–1.89).

A pooled analysis from Sweden comprised two very similar studies of associations between mobile and cordless phone use and glioma, acoustic neuroma and meningioma. Participants who had used a mobile phone for more than one year had an OR for glioma of 1.3 (95% CI: 1.1–1.6). The OR increased with increasing time since first use and with total call time, reaching 3.2 (95% CI: 2.0–5.1) for more than 2000 hours of use. Ipsilateral use of the mobile phone was associated with higher risk for glioma. Similar findings were reported for use of cordless phones. Comparable results were reported in these two studies for acoustic neuroma, although the case numbers were substantially smaller than for glioma. A study from Japan also found some evidence of an increased risk for acoustic neuroma associated with ipsilateral mobile phone use.

The Working Group considered the epidemiological evidence limited and classified Radiofrequency Electromagnetic Fields as *possibly carcinogenic to humans* (Group 2B).

Volume 103

Bitumen and bitumen fumes, and some heterocyclic polycyclic aromatic hydrocarbons (Working Group meeting, 11–18 October 2011)

Bitumens are produced by distillation of crude oil during petroleum refining, and also occur naturally. Bitumens can be divided into broad classes according to their physical properties and specifications required for the different uses. The major use of bitumens is in asphalt for road paving; other uses include roofing, waterproofing, and sealing and painting. Application of bitumens may generate hazardous emissions. The Working Group re-evaluated various occupations that entail exposures to bitumens and bitumen emissions, including road paving, roofing, and application of mastic asphalt and concluded that:

==> occupational exposures to oxidized bitumens and their emissions during roofing are 'probably carcinogenic to humans'1 (Group 2A);

==> occupational exposures to hard bitumens and their emissions during mastic asphalt work are 'possibly carcinogenic to humans' (Group 2B);

==> occupational exposures to straight-run bitumens and their emissions during road paving are 'possibly carcinogenic to humans' (Group 2B).

Preparation for Volume 100 follow-up meetings in 2012

In the future, cancer assessments will increasingly rely on molecular epidemiology and information about mechanisms of carcinogenesis. To this end, Volume 100 has summarized the 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 two year bioassays and epidemiological studies of cancer are unlikely to be available.

The *Monographs* developed for Volume 100 contain information that will be synthesized in two future IARC Scientific Publications: *Tumour Concordance between Animals and Humans and Mechanisms Involved in Human Carcinogenesis.* Two workshops will be organized in 2012 to compile these publications, which will develop analyses that address important hazard- and risk-assessment questions and will cut across individual agents to discern more general principles. Because the database for each agent that is classified as *carcinogenic to humans* is generally detailed and highly informative, these analyses should have a high degree of validity. The main topics in these publications are:

Tumour concordance between experimental animals and humans. This part will compare the tumour sites observed in humans with those in experimental animals. It will explore the circumstances under which it is reasonable to expect analogous tumour sites to occur in different species. It should be noted that specific target sites for tumour formation have been identified for experimental animals since the Volume 100 *Monographs*, and more systematically for humans since *Monograph* Volume 83.

Other questions include whether there are good animal models for particular human tumour sites, whether particular tumours in experimental animals have predictive value for human cancer – either at an analogous site or at other sites – and whether different tumour sites tend to occur together. The analyses in this part may be restricted to subsets of carcinogenic agents (e.g. metals, physical agents, hormonal agents, biological agents) or they may be more general in nature.

Mechanisms involved in human carcinogenesis. This part will compile the mechanisms of carcinogenesis that are identified in Volume 100. It will be organized by mechanism, not by agent. Joint consideration of multiple agents that act through a similar mechanism could facilitate a more detailed description of that mechanism and its common mechanistic steps. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This part may also identify biomarkers that could be included in future study designs to provide more reliable information about whether a particular mechanism is operating in either humans or experimental animals.

Preparations to organize these two workshops have been initiated in 2011, in consultation with a small group of experts. The development of the database with the Volume 100 information on the two main topics (concordance/mechanisms) is ongoing. The workshops are scheduled to take place in April and November 2012 at IARC.

Topics for future Monographs (2012)

Volume 104
Polyomaviruses (SV40, BK, JC, and Merkel cell viruses) and malaria (Working Group meeting, 7–14 Feb 2012)

Volume 105
Diesel and gasoline engine exhausts and some nitroarenes (Working Group meeting, 5–12 June 2012)

Volume 106, to be decided

Priorities for future IARC Monographs

In June 2008, IARC convened an Advisory Group to identify high priorities for new *IARC Monographs* during the next five years. Most of the Advisory Group's recommendations (Table 1) were new topics that had 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 suspected cancer hazards. Topics that meanwhile have been reviewed are indicated in red.

Acknowledgements

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Table 1. High priorities for future IARC Monographs

Most pressing priorities from the Advisory Group
*Radiofrequency electromagnetic fields and radar (includes mobile telephones)
Motor vehicle emissions (includes diesel, gasoline, biofuel exhausts)
*Polyomaviruses (SV40, BK, JC, Merkel cell virus)
Asphalt/bitumen
Acrylamide, furan
Other high priorities from the Advisory Group
Acetaldehyde
*Carbon-based nanoparticles
*Crystalline fibres other than asbestos
*Growth hormone
*Iron and iron oxides
*Malaria
Nucleoside-analogue antiviral drugs
*Outdoor air pollution (includes sulfur oxides, nitrogen oxides, ozone, dusts)
*Perfluorooctanoic acid (PFOA) and other perfluorinated compounds
*Sedentary work
*Statins
*Stress
Testosterone and other androgenic steroids
*Ultrafine particles
Welding
Some agents recently tested in experimental animals
Additional high priorities arising from Volume 100
Benzene
Nickel metal
Polyhalogenated dibenzo-*para*-dioxins, dibenzofurans and biphenyls
*Never before reviewed by IARC;
In red: evaluated or soon to be reviewed (see text)

Publications

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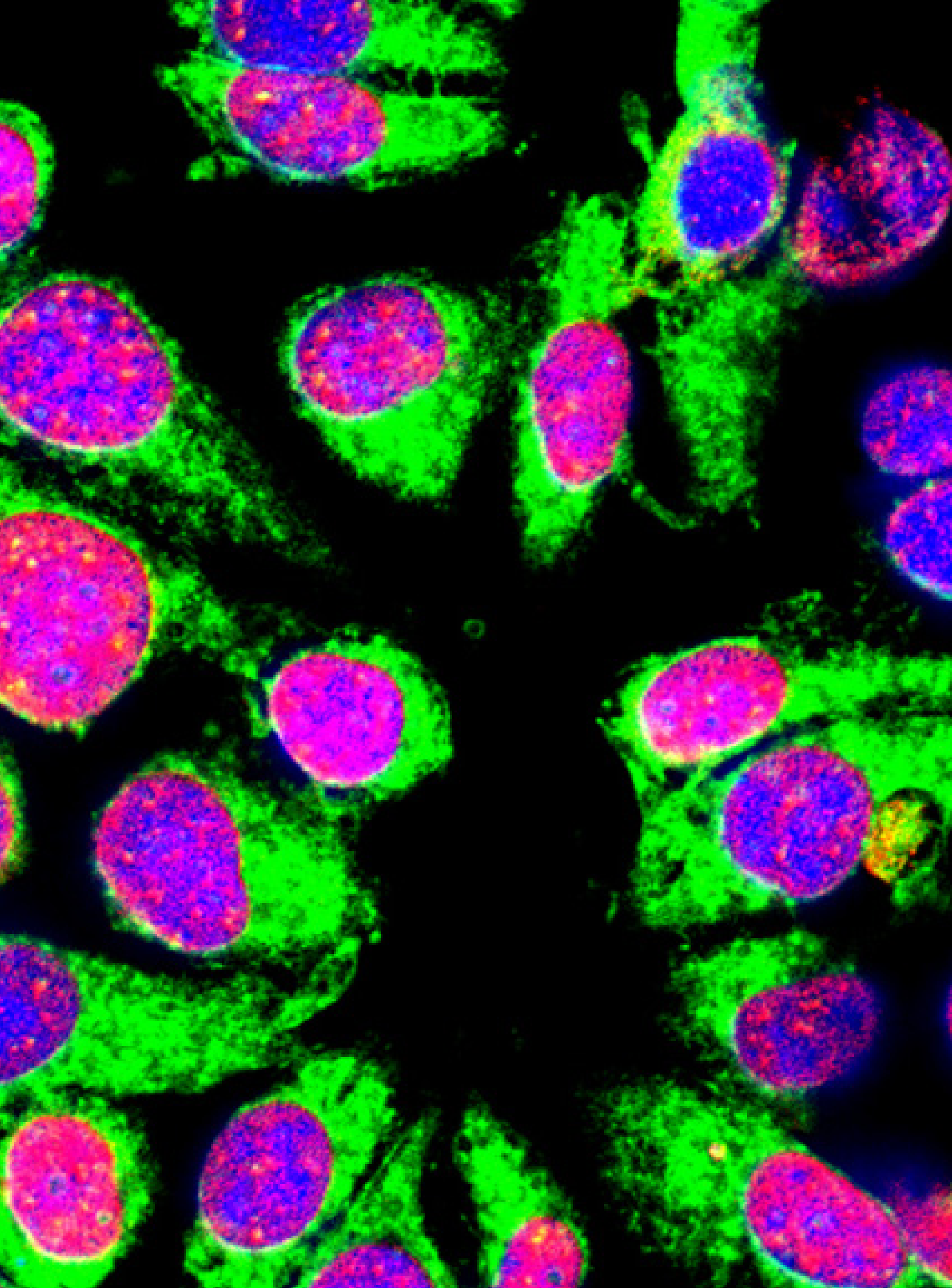
Section of Mechanisms of Carcinogenesis (MCA)

Section head
Dr Pierre Hainaut

The main objective of this section is to develop and conduct studies aimed at identifying the molecular basis of the biological processes involved in cancer causation. This implies addressing the basic mechanisms of carcinogenesis through experimental studies using cultured cells and animal models. The most direct outcome of this type of research is to identify, develop and validate innovative biomarkers, which may be applicable in large-scale studies on molecular epidemiology or pathology. The section's skills cover two broad classes of molecular alterations that underpin the cancer process: mutations and epigenetic modifications. The main targets include hepatocellular carcinoma (search for new markers and understanding of the molecular mechanisms of the synergistic effects between distinct etiological risk factors), lung cancers (understanding the molecular mechanisms of genetic predisposition and of carcinogenesis in never-smokers), oesophageal cancers (identifying causal factors through molecular studies in high-risk populations in specific geographic areas), breast cancers (unravelling interactions between mutations and epigenetic changes in maintaining cancer stem cell status) and highly cancer predisposing inherited mutations (Li-Fraumeni Syndrome). The section's work is integrated, with similar themes and sample collections being studied in both the Molecular Carcinogenesis Group (MOC) and the Epigenetics Group (EGE), thus fostering a pattern of technical and scientific interactions within the section and also with other research groups. Highlights of 2011 include important advances in identifying new biomarkers of liver carcinogenesis, defining the mechanisms by which polymorphisms in N-acetylcholine receptor genes contribute to the predisposition to lung cancer, understanding the role of the tumour suppressor p53 in breast cancer cells' response to estrogens and new studies on the effects of diet on epigenetic DNA methylation patterns.



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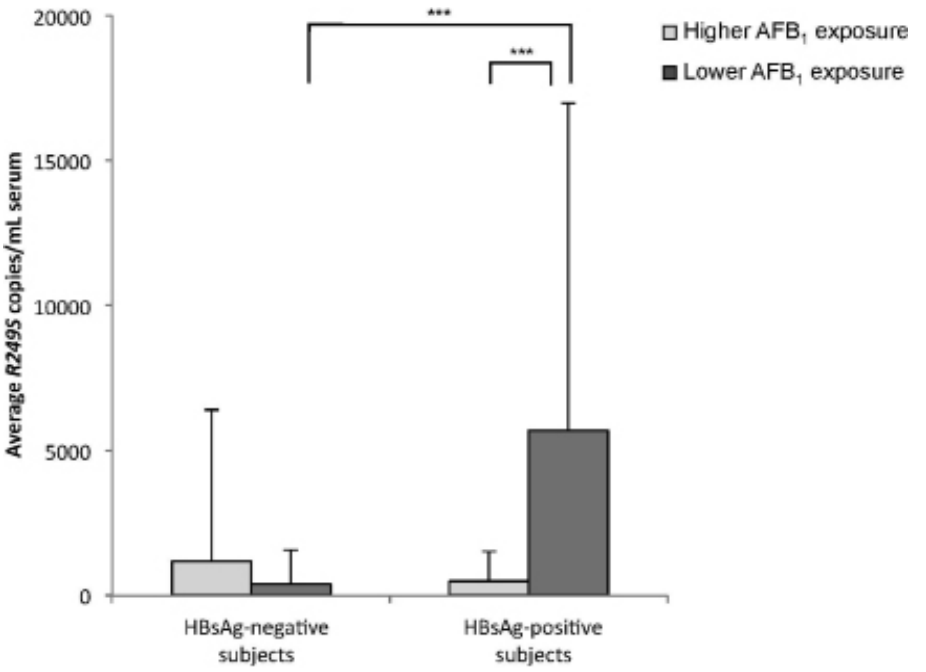
The Molecular Carcinogenesis Group (MOC) carries out projects in functional genomics aimed at better understanding the mechanisms of cancer and at identifying biomarkers for early detection. Studies focus on *TP53*, a major tumour suppressor in which the group has acquired a strong international position. This is due in part to the maintenance and dissemination of the IARC *TP53* database, the most cited international resource in the field (http://www-p53.iarc.fr). Projects by MOC include: (1) mechanisms of liver carcinogenesis focusing on interactions between p53 and viral oncoproteins on regulating liver cell metabolism and differentiation; (2) role of *TP53* mutations as prognosis and a predictive marker in breast cancer; (3) role of germline *TP53* mutations in a large cohort of carriers from Brazil, where we have discovered a founder mutation which is present in 0.3% of the population; (4) regulation of stem cell status by p53 isoforms; and (5) discovery of new early detection markers for liver cancer. This section highlights some of the significant results in 2011, while our work on the functional significance of polymorphisms in nicotinic acetylcholine receptors (NAChR) for the genetic susceptibility to lung cancer is described in the Section of Genetics.

Cancer in Africa: from descriptive epidemiology to environmental carcinogenesis

Over the past 10 years, MOC has built a network of collaborations in Western and Eastern Africa involving local cancer registries, pathology services, clinical centres and local laboratories handling specimen collections and baseline biological analyses. Highlights of this work include the analysis of trends of incidence of liver cancer in West Africa, investigation on mutations induced by aflatoxin in HBV chronic carriers from rural Gambia and the first study on molecular markers in squamous cell carcinoma of the oesophagus in Kenya, West Africa. The current collaborative network includes projects in Mali (liver cancer, breast cancer, gastric cancer), in Kenya (oesophageal cancer) and in Sudan (oesophageal and liver cancers).

Our studies on recent trends in the incidence of liver cancer in West Africa have identified a significant increase in women only. We have proposed that this increase might be correlated with the documented increase in female obesity and metabolic disease. Using registration data from Mali and The Gambia, we have investigated the variations in breast cancer incidence and have shown that premenopausal breast cancer remains by far the most common form of the disease. Over the past 10 years, we have developed approaches and detection methods to measure aflatoxin-related mutations in DNA extracted from the plasma of patients with chronic liver disease or liver cancer. To analyse the relationship between detection of aflatoxin-induced TP53 mutations (R249S) in plasma DNA and consumption of aflatoxin-contaminated food, we have used short oligonucleotide mass analysis to detect R249S levels in plasma DNA in a cross-sectional survey of 473 asymptomatic subjects (237 HBV carriers and 236 non-carriers) recruited in three rural villages in The Gambia over a 10 month period. A seasonal variation was detected with significantly higher levels of mutation in HBsAg-positive subjects surveyed during April–July than in October–March (Figure 1). HBeAg positivity (a marker of HBV replication) and viral DNA load also varied seasonally with 15–30% of subjects surveyed between April and June being HBeAg-positive, compared with < 10% surveyed during other months. These results suggest that levels of R249S in plasma DNA of asymptomatic subjects are strongly influenced by HB chronic infection status. Moreover, levels of R249S show a seasonal variation that does not match the variations in exposure to AFB1: the peak of R249S in the plasma occurs 3–6 months later than the previously reported peak of exposure to AFB1. This difference may be the consequence of a chain of molecular events determined by the turnover of hepatocytes. These results demonstrate that mutagenesis of *TP53* by AFB1 is a common event in subjects exposed to the toxin, not restricted to pre-cancer or cancer conditions. Thus, it has to be expected that additional genetic and epigenetic changes, subsequent to *TP53* mutation and HBV chronic infection, play essential roles as drivers of hepatocarcinogenesis.

Figure 1. Levels of mutant TP53 DNA with mutation at third base of codon 249 (R249S, aflatoxin-related mutation) in the plasma of subjects from 3 rural villages in The Gambia, comparing between periods of higher exposure to AFB1 (December-March) and lower exposure (April to-July). The seasonality of R249S release in HBsAg-positive subjects is shown and contrasts with the seasonality of exposure to AFB1.
In Villar *et al.*, 2011.

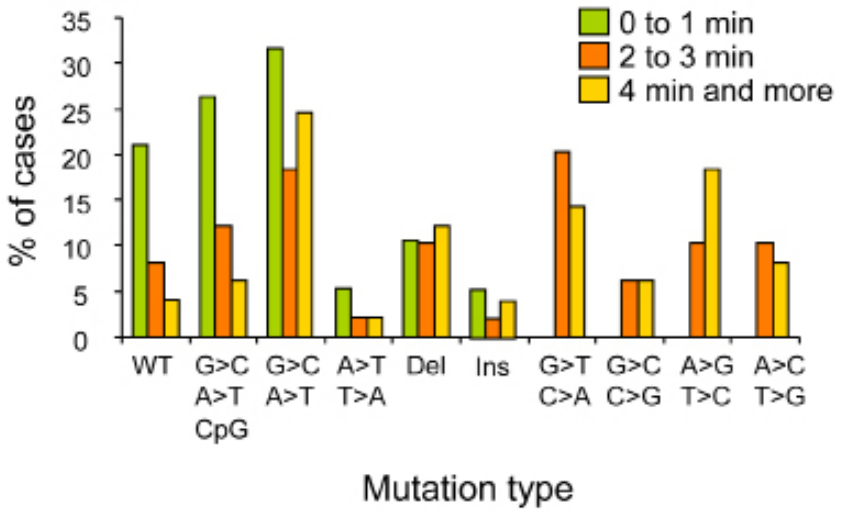


In Kenya we have developed a pilot study on retrospective cases of oesophageal squamous cell carcinoma (OSCC) in the region of Eldoret, which is documented as having a high prevalence of this cancer (detailed incidence data are not available). Studies on *TP53* mutations and HPV prevalence revealed that both biomarkers were infrequent. In contrast with many high OSCC incidence areas, mutations in *TP53* were detected in only about 25% of the cases, whereas HPV was not detected in any of the cases analysed. A similar, low proportion of cases with mutant *TP53* have been previously reported in South Africa (Transkei). Overall, these preliminary data suggest that OSCC from eastern Africa may share common epidemiological and molecular patterns with those detected in South Africa.

Oesophageal cancer in the Islamic Republic of Iran

We have pursued our long-term effort in analysing patterns of genetic alterations in OSCC from Golestan, Iran, one of the regions of the world with the highest incidence rates for this cancer. Following the detection of a significant association between the immunological detection of PAH-adducts in oesophageal mucosa and risk of OSCC, we have completed an exhaustive analysis of *TP53* mutations in 140 patients recruited in a case-control study. We detected mutations in over 90% of the cases, representing the highest rate of *TP53* mutations ever identified in any form of cancer. The mutations were diverse, suggesting that multiple distinct mutagens and mutagenic mechanisms may contribute to the overall mutation load. Nevertheless, when compared to previously published data on OSCC from other parts of Iran, OSCC from Golestan showed a significantly higher proportion of mutations at bases known as sites of adduction by metabolites of PAH. This is consistent with our previous results that this class of mutagens represents one of the main risk factors in the etiology of OSCC in the region. In addition, we identified significant variations in mutation patterns in relation with hot tea drinking habits, further supporting the notion that thermal injury has a critical impact on mucosal regeneration and DNA repair capacity (Figure 2). These results support the view that OSCC in

Figure 2. Distribution of TP53 mutation types according to tea temperature, in ESCC cases from Golestan Province, Northern Iran, a very high incidence area of this cancer. Tea temperature was estimated by the time interval between pouring and drinking tea (from 0-1 min to 4 min or more). Our study revealed different mutation patterns related to tea drinking habits. Wild-type TP53 and G:C to A:T transitions (in particular at CpG sites) were most often seen in subjects who reported drinking tea within 1 minute of pouring. Conversely, transversion mutations (including G:C to T:A mutations which often occur as the result of mutagenesis by PAH adducts) were observed only in subjects who reported a preference for drinking tea with a longer delay (at least 2 minutes after pouring). In Abedi *et al.*, in press



Northern Islamic Republic of Iran is not associated with exposure to a single class of mutagens, but develops in the context of combined effects of thermal stress and exposure to environmental mutagens on a background of susceptibility influenced by genetic and deprivation factors.

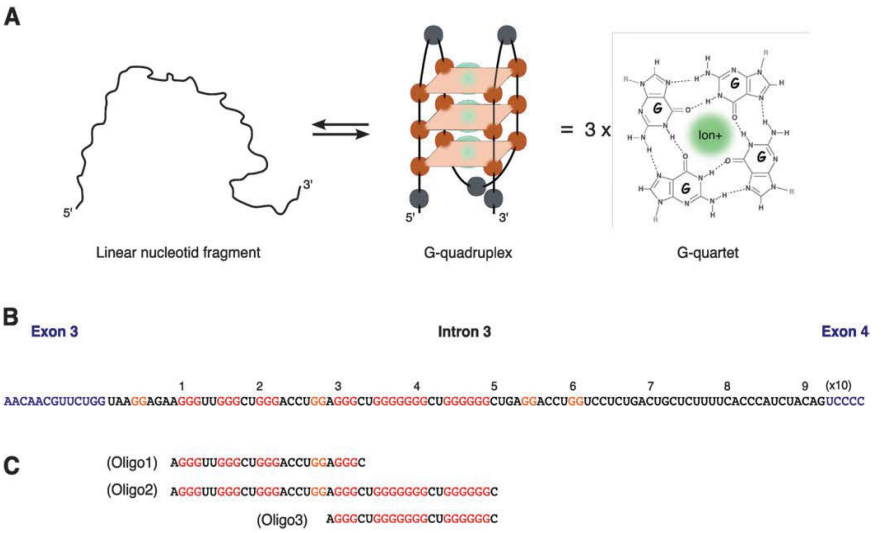
p53 isoforms and cancer susceptibility

Following our initial identification of the Delta40 (deltaN) isoform of the p53 protein, we have extended our work on the mechanisms regulating the expression of this isoform. Convergent results from our group and others show that this isoform, which lacks the first 40 amino acid residues of p53 that contains the transactivation domain, is expressed at significant levels in many normal cells and tissues where it may play a critical role in controlling the basal functions of p53 in regulation of stem cell status, proliferation, metabolism and senescence. In collaboration with the groups of JL Mergny and J Hall, we have found that a critical regulatory motif for the control of Delta40p53 expression lies in the intron 3 of *TP53*. This motif consists of a stretch of guanines which was shown to be able to fold into specific secondary structures in p53 pre-mRNA, called G-quadruplexes (G4) (Figure 3). These structures are common in genes involved in growth control, such as the MYC1 oncogene or HTERT encoding the human telomerase. Mutation of guanines in the G4 affects the splicing of p53 mRNA, leading to the retention of intron 2 and formation of an alternative splicing product that encodes Delta40p53. Significantly, the G4 structure in intron 3 overlaps with a common polymorphism in *TP53*, a 16bp repeat, which has been shown by us and others to have a strong impact on *TP53*-dependent genetic susceptibility. We have previously shown that this polymorphism is a strong modifier of age at cancer diagnosis in carriers of germline *TP53* mutations who are at high risk for familial cancer. Studies in sporadic cancer have shown that the intron 3 polymorphism is associated with an increased risk for many common cancer forms. Therefore, it is possible that genetic susceptibility associated with intron 3 polymorphism may be due to differences caused by this polymorphism in the expression levels of Delat40p53 and in the basal activity of the p53 protein.

Discovery of novel plasma protein markers for early detection of hepatocellular carcinoma

In 2007, we launched a long-term effort to discover plasma proteins that could be used for the routine detection and

Figure 3. G-Quadruplex structures in intron 3 of p53 pre-mRNA. A: schematic representation of a G-quadruplex structure. B: position of stretches of guanines involved in forming G-quadruplexes in p53 pre-mRNA. C: synthetic RNA sequences used for biophysical studies demontrating G-quadruplex formation.
(In Marcel *et al.*, 2011)



diagnosis of hepatocellular carcinoma (HCC) in regions of the world where this cancer is common and where diagnostic resources are limited. The current standard for blood-based detection is alpha-fetoprotein (AFP), a marker which is highly specific only at high levels where its sensitivity is limited. We implemented two mini case-control studies in The Gambia and Thailand, in which plasma has been collected in selected subjects with HCC (with or without cirrhosis), chronic liver disease and in controls (HBV chronic carriers or not). This collection was carried out using an optimized protocol for maintaining the integrity of plasma proteome. The two countries were chosen because they represent an etiological context dominated by HBV chronic infection with or without exposure to aflatoxin, which corresponds to the majority of HCC in low-resource countries. Our study is the first one to address the discovery of proteomics markers in this major etiological context. Thanks to a long-term collaboration with Dr Laura Berretta (FHCRC, Seattle), a proteomics pipe-line was used to extensively fractionate these plasmas and profile their content in low-abundance proteins. A total of over 3000 protein tags were identified. Comparison between cases and controls and between cases from Thailand and The Gambia has identified a set of 41 candidate markers, which contains all the protein markers already known to date. To validate these hits, we have developed a case-control study (n = 800) in Thailand and are currently developing a similar strategy in Mali. Other cohorts (developed by Dr Beretta) were also used. One of these candidate markers, osteopontin (OPN), has just emerged from this validation pipe-line. OPN levels were measured in 312 plasma samples collected from 131 HCC patients, 76 cirrhosis patients, 52 chronic hepatitis C (CHC) and B (CHB) patients and 53 healthy controls, in two independent cohorts. OPN plasma levels were significantly elevated in HCC patients compared to cirrhosis, CHC, CHB or healthy controls, in both cohorts. OPN alone or in combination with AFP had significantly better area under the receiver operating characteristic curve compared to AFP in comparing cirrhosis and HCC in both cohorts. OPN's overall performance remained higher than AFP in comparing cirrhosis and the following HCC groups: HCV-related HCC, HBV-associated HCC and early HCC. OPN also had a good sensitivity in AFP negative HCC. In a pilot prospective study including 22 patients who developed HCC during follow-up, OPN was already elevated a year before diagnosis. In conclusion, OPN was more sensitive than AFP for the diagnosis of HCC in all studied HCC groups. These findings are the first published outcome of our long-term proteomics initiative. A group of three further markers are currently in the final stages of validation. We expect that these findings will have a direct impact on early detection and diagnosis of HCC in low-resource settings.

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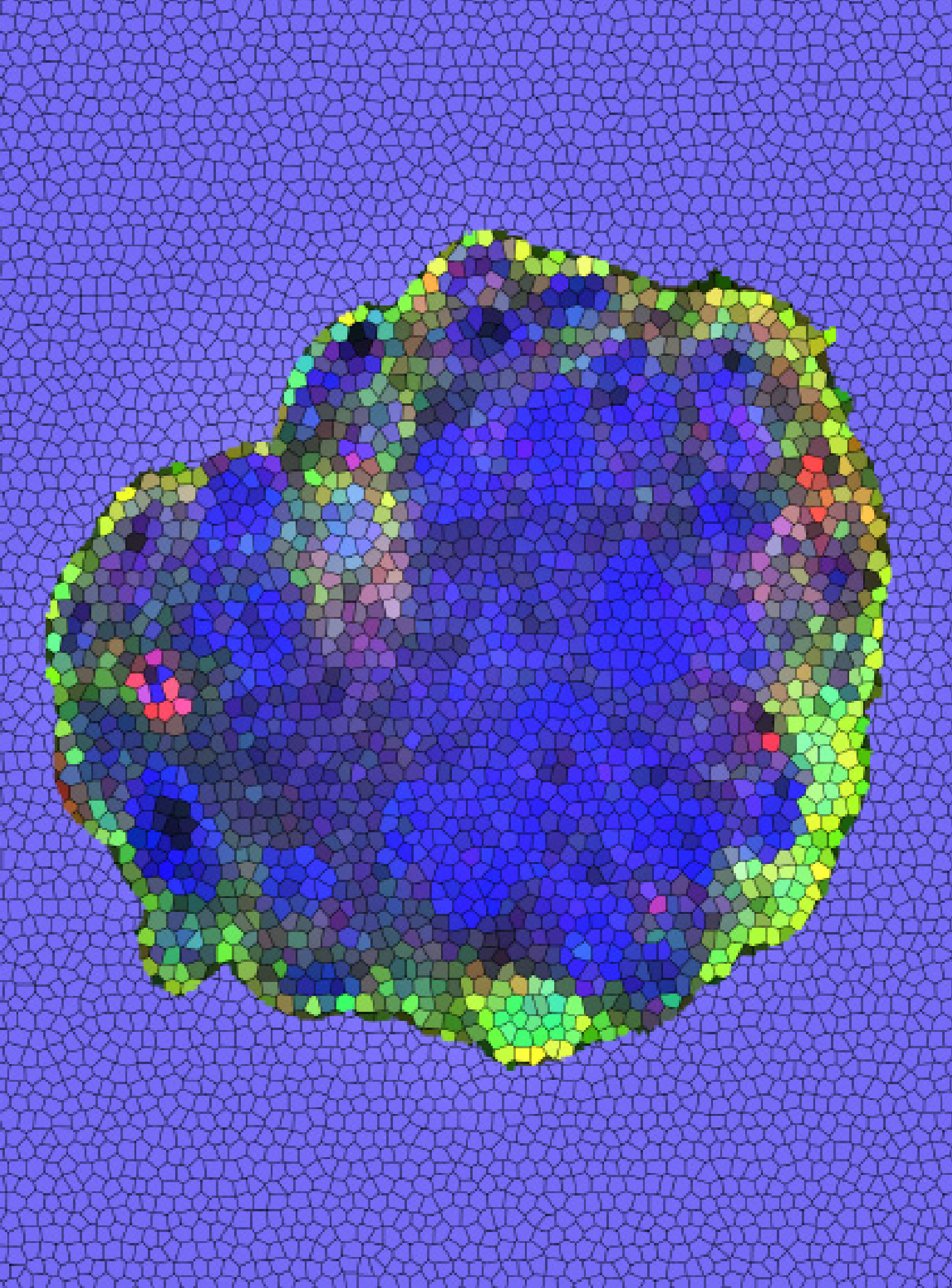

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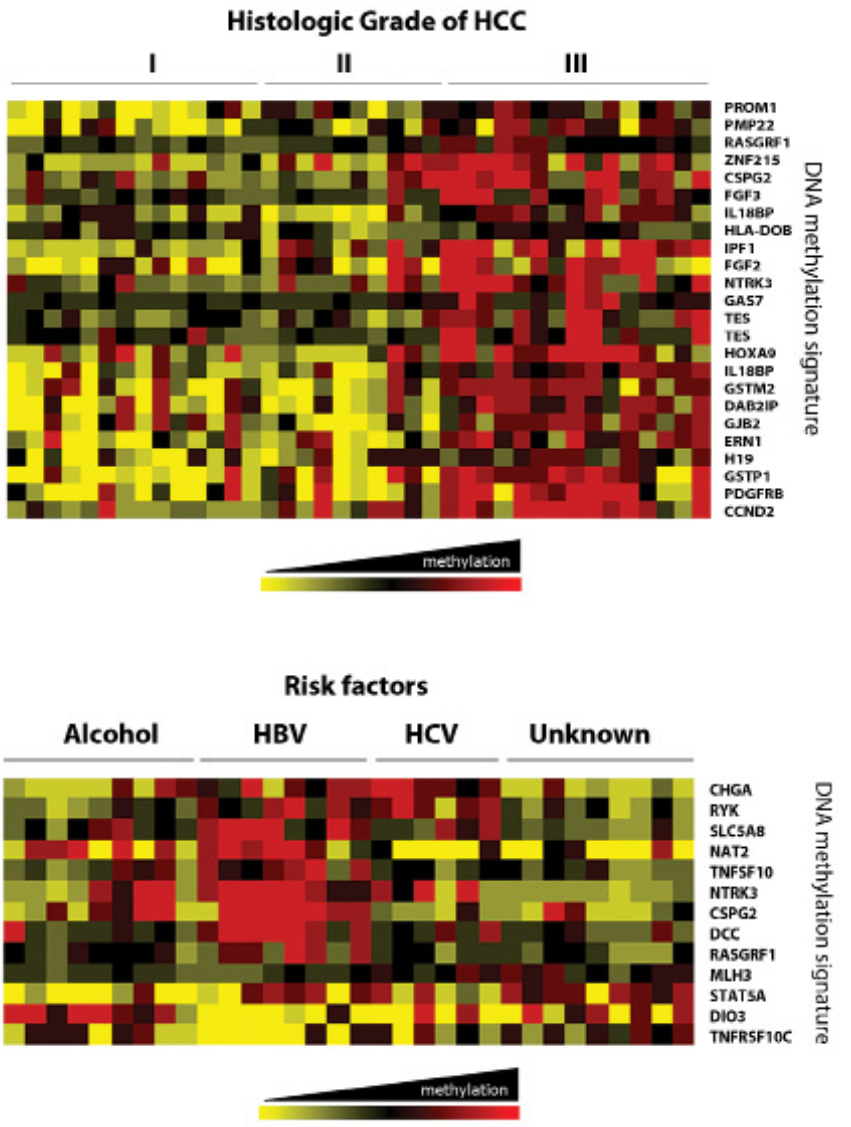
Epigenetics: an emerging field in molecular carcinogenesis

Over the past decade epigenetics research has become more mainstream, owing to the fact that epigenetic changes have emerged as key mechanisms in cancer development and progression. Although the implication of epigenetic events in cancer is supported by both epidemiological and experimental studies, the precise contribution of epigenetic mechanisms and cellular targets of epigenetic alterations in human cancers are largely unknown. 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 (Lima *et al.*, 2010; Krutovskikh and Herceg, 2010; Sincic and Herceg, 2010; Rodríguez-Paredes and Esteller, 2011). The Epigenetics Group (EGE) conducts both mechanistic studies and epigenetic profiling, so as to gain a better mechanistic understanding of tumorigenesis, and to discover and validate new epigenetic biomarkers.

Analysis of DNA methylome in hepatocellular carcinoma reveals epigenetic signature associated with risk factors and potential cancer biomarkers

Hepatocellular carcinoma (HCC) is characterized by late detection and fast progression, and it is believed that epigenetic disruption may contribute to its development and progression. A better understanding of the global deregulation of epigenetic profiles (such as DNA methylation states) and how they correlate with disease progression, will aid in the design of strategies for earlier detection and cancer prevention. We characterized the changes in promoter DNA methylation in a series of HCCs, and their respective surrounding tissue, and identified methylation signatures associated with major risk factors and clinical correlates. A wide panel of cancer-related gene promoters was analysed using Illumina bead array technology, and CpG sites were then selected according to their ability to classify clinicopathological parameters. An independent series of HCC tumours and matched surrounding tissue was used to validate the signatures (Hernandez Vargas *et al.*, 2010). While aberrant methylation of a subset of promoters was associated with tumour progression and etiological risk factors, such as HBV or HCV infection and alcohol consumption (Lambert *et al.*, 2010), hypermethylation of an independent panel of genes was strongly correlated with survival after cancer therapy. We have further investigated methylation profiles of the HBV genome in liver samples of different stages of HCC development and in in vitro infected human hepatocytes. We found discrete CpG sites in the HBV genome that are recurrently hypermethylated in cancer but not in chronic hepatitis tissue (Kaur *et al.*, 2010). Our findings suggest that hypermethylation of the HBV genome itself, resulting from deregulated DNA methylation in malignant cells, may contribute to the occult status of the disease (Kaur *et al.*, 2010). Together, our studies identified specific DNA methylation signatures associated with clinical correlates, as well as the major risk factors, providing information that could be exploited for biomarker discovery in clinics and molecular epidemiology (Hernandez Vargas *et al.*, 2010; Lambert *et al.*, 2010; Herceg and Paliwal, 2011).

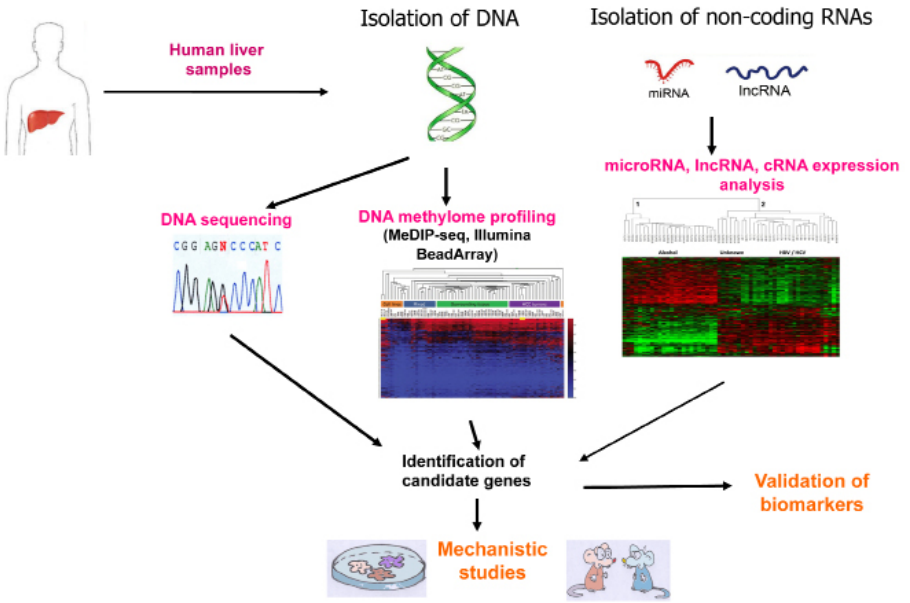
DNA Methylome changes associated with tumour grade and risk factors in hepatocellular carcinoma



Aberrant DNA methylation links cancer susceptibility locus 15q25.1 to apoptotic regulation and lung cancer

Nicotinic acetylcholine receptor (nAChR) genes form a highly conserved gene cluster at the lung cancer susceptibility

Experimental strategy for identification of molecular changes associated with hepatocellular carcinoma and risk factors



locus 15q25.1. We found that the CHRNα3 gene encoding nAChRA3 subunit is a frequent target of aberrant DNA hypermethylation and silencing in lung cancer (Paliwal *et al.*, 2010). Treatment of cancer cells exhibiting CHRNα3 hypermethylation with DNA methylation inhibitors caused demethylation of the CHRNα3 promoter and gene reactivation, whereas restoration of CHRNα3 levels through ectopic expression induced apoptotic cell death. shRNA-mediated depletion of CHRNα3 in CHRNα3-expressing lung cancer cells, elicited a dramatic Ca2+ influx response in the presence of nicotine, followed by activation of the Akt survival pathway. CHRNα3-depleted cells were resistant to apoptosis-inducing agents, underscoring the importance of epigenetic silencing of the CHRNα3 gene in human cancer (Paliwal *et al.*, 2010). In defining a mechanism of epigenetic control of nAChR expression in non-neuronal tissues, our findings offer a functional link between susceptibility locus 15q25.1 and lung cancer, and suggest nAChRs as theranostic targets for cancer detection and chemoprevention (Paliwal *et al.*, 2010; Krais *et al.*, 2011; Herceg and Vaissière, 2011).

Identification of epigenetic changes in peripheral blood as biomarkers of exposure and cancer risk

The goal of this study is to investigate whether epigenetic changes in peripheral blood (such as WBC and circulating nucleic acids) can be used as intermediate biomarkers for risk factor exposures and different health outcomes.

DNA methylation changes associated with cancer risk factors and blood levels of vitamin metabolites in a prospective study. We tested whether genomic DNA from surrogate tissues, such as blood cells, may be exploited in the discovery of biomarkers of exposure and cancer risk. DNA methylation levels in a panel of candidate genes in blood cells of cases and controls from the European Prospective Investigation into Cancer and Nutrition (EPIC) study were quantitatively determined and the association between lung cancer risk and DNA methylation patterns was examined. We also investigated whether blood levels of vitamin metabolites modify DNA methylation levels in blood cells (Vineis *et al.*, 2011). Our results revealed that DNA methylation patterns in specific genes are associated with the case/control status and that methylation levels are influenced by serum levels of 1-carbon metabolites and vitamin B. Interestingly, these associations were modulated by smoking status, consistent with the notion that blood levels of 1-carbon metabolism markers and dietary/lifestyle factors may modify DNA methylation levels in blood cells, and that blood cells can be exploited for the discovery of epigenetic biomarkers of exposures, providing proof-of-principle on the use of blood samples in the context of prospective studies (Vineis *et al.*, 2011).

Impact of dietary regime on methylation patterns in peripheral blood in an intervention study. We conducted a randomized four week intervention trial to test the impact of three dietary regimens on DNA methylation patterns in peripheral white blood cells of heavy smokers (Scoccianti *et al.*, 2011). We found that dietary intervention may induce small but significant modifications in the methylation patterns of long interspersed DNA elements (LINE1), a marker for global genome methylation, whereas several other loci analysed showed low basal levels of methylation with no substantial change after intervention. These results are consistent with the notion that balanced or supplemented diet may contribute to stabilizing normal, endogenous DNA methylation patterns, but does not provide evidence for methylation changes in specific genes associated with this short-term dietary intervention (Scoccianti *et al.*, 2011; Herceg and Vaissière, 2011).

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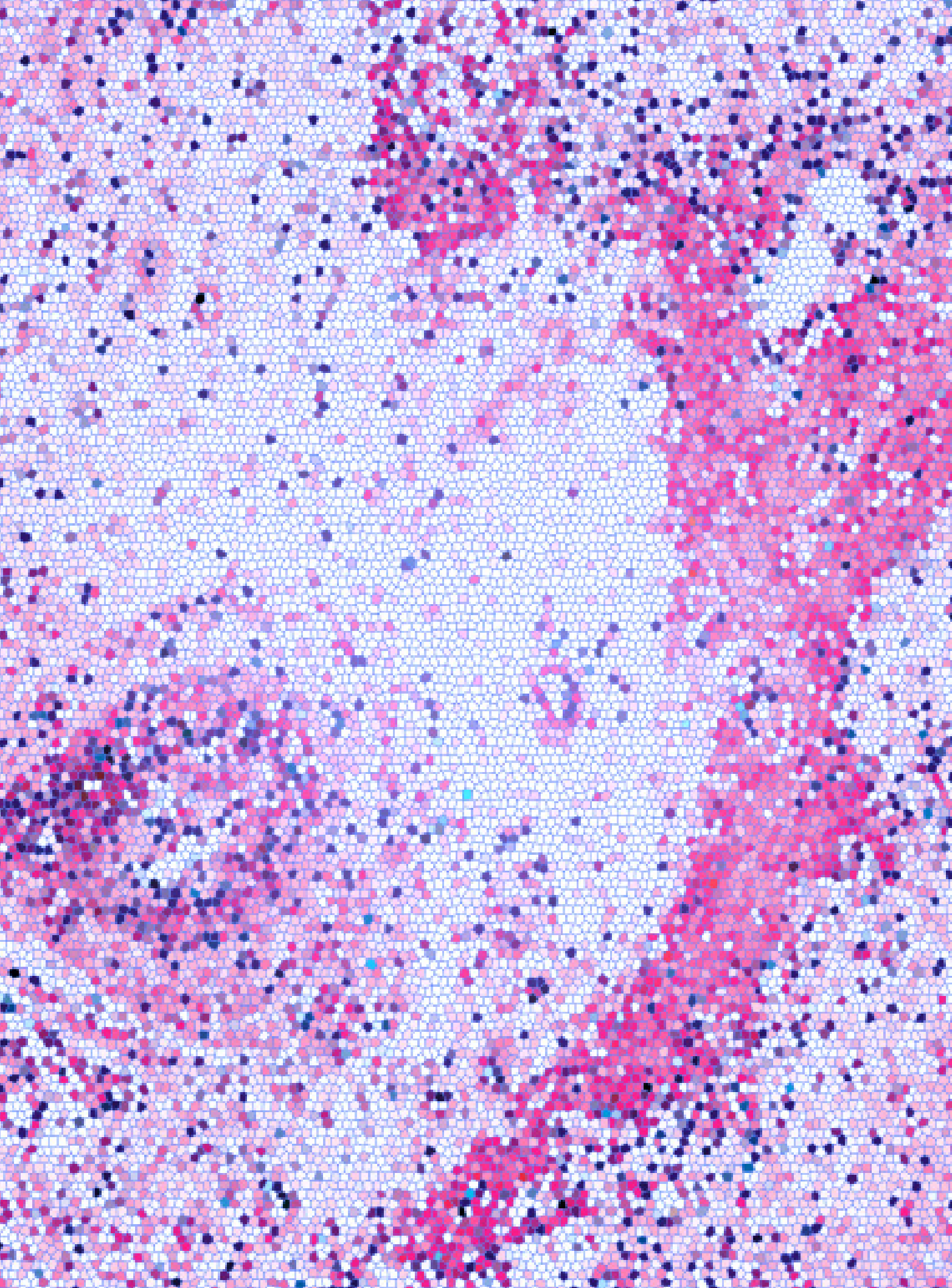

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The Section of Molecular Pathology (MPA) studies the molecular basis of human neoplasms in particular brain tumours using tumour samples from patients with excellent clinical data and follow-up. We correlate histologically recognized phenotypes with genotypes and expression profiles to elucidate the molecular basis and genetic pathways that are operative in human neoplasms; identify molecular markers for improvement of tumour diagnoses and classification; identify genetic factors that predict sensitivity to treatment, tumour progression and patient outcome; and use genetic data to identify the etiology of human cancers. Since 2006, MPA has also been responsible for the 4th edition of the World Health Organization (WHO) Classification of Tumours Series (WHO Blue Books). The third volume, WHO Classification of Tumours of the Digestive System, was published in 2010; the fourth (WHO Classification of Tumours of the Breast) and fifth (WHO Classification of Tumours of Soft Tissues and Bone) volumes are in the editing stage.

A few of MPA's more important projects over the Biennium are detailed below.

Intratumoral patterns of genomic imbalance in glioblastoma

Glioblastomas are morphologically and genetically heterogeneous, but little is known about the regional patterns of genomic imbalance within glioblastomas. Using a reliable whole genome amplification (WGA) method, recently established in our laboratory to randomly amplify DNA from paraffin-embedded histological sections with minimum amplification bias, we assessed genome wide chromosomal imbalance by array CGH (Agilant 105K) in DNA from 2–5 separate tumour areas of 14 primary glioblastomas (total, 41 tumour areas). Chromosomal imbalances significantly differed among glioblastomas; the only alterations that were observed in ≥ 6 cases were loss of chromosome 10q, gain at 7p, and loss of 10p. Genetic alterations common to all areas analysed within a single tumour included gains at 1q32.1 *(PIK3C2B, MDM4)*, 4q11-q12 *(KIT, PDGFRA)*, 7p12.1–11.2 *(EGFR)*, 12q13.3–12q14.1 *(GLI1, CDK4)* and 12q15 *(MDM2)*, and loss at 9p21.1–24.3 *(p16INK4a/p14ARF)*, 10p15.3-q26.3 *(PTEN, etc)* and 13q12.11-q34 *(SPRY2, RB1)*. These are likely to be causative in the pathogenesis of glioblastomas (driver mutations). In addition, there were numerous tumour area-specific genomic imbalances which may be either non-functional (passenger mutations) or functional, but constitute secondary events reflecting progressive genomic instability, a hallmark of glioblastomas.

Genetic pathways to diffuse gliomas

Low-grade diffuse gliomas WHO grade II (diffuse astrocytoma, oligoastrocytoma, oligodendroglioma) are characterized by

frequent *IDH1/2* mutations (> 80%) that occur at a very early stage. In addition, the majority of diffuse astrocytomas (about 60%) carry *TP53* mutations, which constitute a prognostic marker for shorter survival. Oligodendrogliomas show frequent loss at 1p/19q (about 70% of cases), which is associated with longer survival. *IDH1/2* mutations are frequent (> 80%) in secondary glioblastomas that have progressed from low-grade or anaplastic astrocytomas. Primary *(de novo)* glioblastomas with *IDH1/2* mutations are very rare (< 5%); they show an age distribution and genetic profile similar to secondary glioblastomas and are probably misclassified. Using the presence of *IDH1/2* mutations as a diagnostic criterion, secondary glioblastomas account for approximately 10% of all glioblastomas. *IDH1/2* mutations are the most significant predictor of favourable outcome of glioblastoma patients. The high frequency of *IDH1/2* mutations in oligodendrogliomas, astrocytomas and in secondary glioblastomas derived thereof suggests that these tumours share a common progenitor cell population. The absence of this molecular marker in primary glioblastomas suggests a different cell of origin; both glioblastoma subtypes acquire a similar histological phenotype due to common genetic alterations, including the loss of tumour suppressor genes on chromosome 10q.

Particularly for oligoastrocytoma, the diagnostic criteria of low-grade diffuse gliomas are highly subjective. To establish genetic profiles for diffuse gliomas and to estimate their predictive impact, we screened 360 WHO grade II gliomas for mutations in the *IDH1, IDH2,* and *TP53* genes and for 1p/19q loss and correlated these with clinical outcome. Most tumours (86%) were characterized genetically by *TP53* mutation + *IDH1/2* mutation (32%), 1p/19q loss + *IDH1/2* mutation (37%), or *IDH1/2* mutation only (17%). *TP53* mutations only or 1p/19q loss only was rare (2% and 3%). The survival of patients with *TP53* mutation ± *IDH1/2* mutation was significantly shorter than that of patients with 1p/19q loss ± *IDH1/2* in both univariate and multivariate analyses. Thus, the molecular classification on the basis of *IDH1/2* mutation, *TP53* mutation and 1p/19q loss has power similar to histological classification and avoids the ambiguity inherent to the diagnosis of oligoastrocytoma.

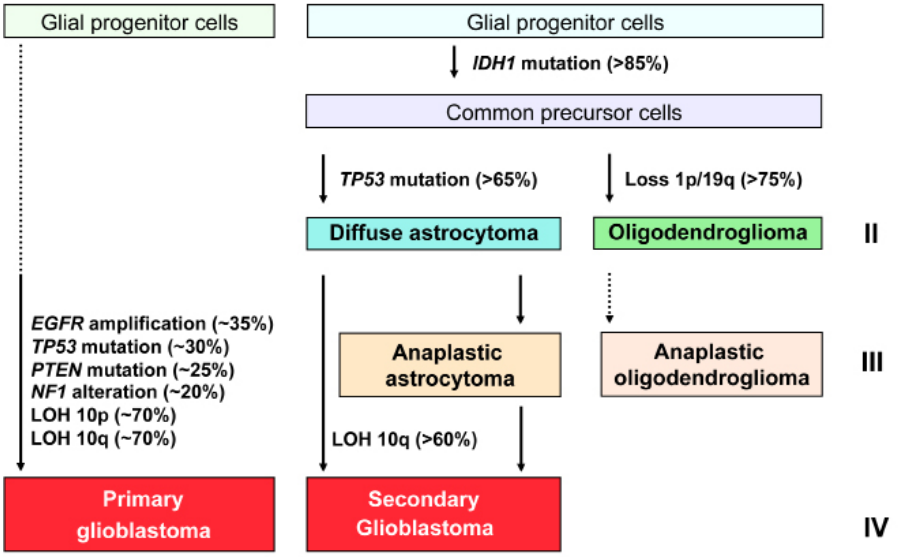

Figure 1. Genetic pathway to gliomas

Alterations in the RB1 pathway in low-grade diffuse gliomas lacking common genetic alterations

Most (> 90%) low-grade diffuse gliomas carry at least one of the following genetic alterations: *IDH1/2* mutation, *TP53* mutation or 1p/19q loss. Only 7% of cases were triple-negative (i.e. lacking any of these alterations). We carried out array CGH in 15 triple-negative WHO grade II gliomas (8 diffuse astrocytomas and 7 oligodendrogliomas), and showed loss at 9p21 ($p14^{ARF}$, $p15^{INK4b}$ and $p16^{INK4a}$ loci) and 13q14–13q32 (containing the *RB1* locus) in 3 cases and 2 cases, respectively. Further analyses in 31 triple-negative cases, as well as a total of 160 non-triple-negative cases, revealed that alterations in the RB1 pathway (homozygous deletion and promoter methylation of the $p15^{INK4b}$, $p16^{INK4a}$ and *RB1* genes) were significantly more frequent in triple-negative (26%) than in non-triple-negative cases (11%; P = 0.0371). These results suggest that a fraction of low-grade diffuse gliomas lacking common genetic alterations may develop through a distinct genetic pathway, which may include loss of cell-cycle control regulated by the RB1 pathway.

TET2 promoter methylation in low-grade diffuse gliomas lacking *IDH1/2* mutations

The *TET2* gene encodes the α-KG-dependent enzyme that catalyses the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, thus producing DNA demethylation. Miscoding mutations of the *TET2* gene have been detected in 10–25% of acute myeloid leukemias lacking *IDH1/2* mutations. Most low-grade diffuse gliomas carry *IDH1/2* mutations (> 85%), but molecular mechanisms of pathogenesis in those lacking *IDH1/2* mutations remain to be elucidated. We screened for miscoding mutations and promoter methylation of the *TET2* gene in 29 low-grade diffuse gliomas lacking *IDH1/2* mutations. Single-strand conformational polymorphism followed by direct sequencing showed the absence of miscoding mutations in *TET2*. Methylation-specific PCR revealed methylation of the *TET2* promoter in five of 35 cases (14%). In contrast, none of 38 low-grade diffuse gliomas with *IDH1/2* mutations had *TET2* promoter methylation. These results suggest that *TET2* promoter methylation, but not *TET2* mutation, may be an alternative mechanism of pathogenesis in a small fraction of low-grade diffuse gliomas lacking *IDH1/2* mutations.

Genetic alterations in microRNAs in medulloblastomas

MicroRNAs (miRNAs) control a variety of cellular processes via the regulation

of multiple target genes. We screened 48 medulloblastomas for mutation, deletion and amplification of nine miRNA genes, which were selected on the basis of the presence of potential target sequences within the 3′-untranslated region of the MYCC mRNA. Differential PCR revealed deletions in miR-186 (15%), miR-135a-1 (33%), miR-548d-1 (42%), miR-548d-2 (21%) and miR-512–2 (33%) genes, whereas deletion or amplification was detected in miR-135b (23%) and miR-135a-2 (15%). In miR-33b, deletion, amplification or a mutation at the precursor miRNA were detected in 10% of medulloblastomas. Overall, 35 out of 48 (73%) medulloblastomas had at least one alteration. Real-time PCR revealed MYCC overexpression in 11 of 37 (30%) medulloblastomas, and there was a correlation between MYCC overexpression and miR-512–2 gene deletion (P = 0.0084). Antisense-based knockdown of miR-512–5p (mature sequence of miR-512–2) resulted in significant upregulation of MYCC expression in HeLa and A549 cells, while forced overexpression of miR-512–2 in medulloblastoma/PNET cell lines DAOY, UW-228–2 and PFSK resulted in downregulation of MYCC protein. Furthermore, the results of luciferase reporter assays suggested that miR-512–2 targets the *MYCC* gene. These results suggest that alterations in the miRNA genes may be an alternative mechanism leading to MYCC overexpression in medulloblastomas.

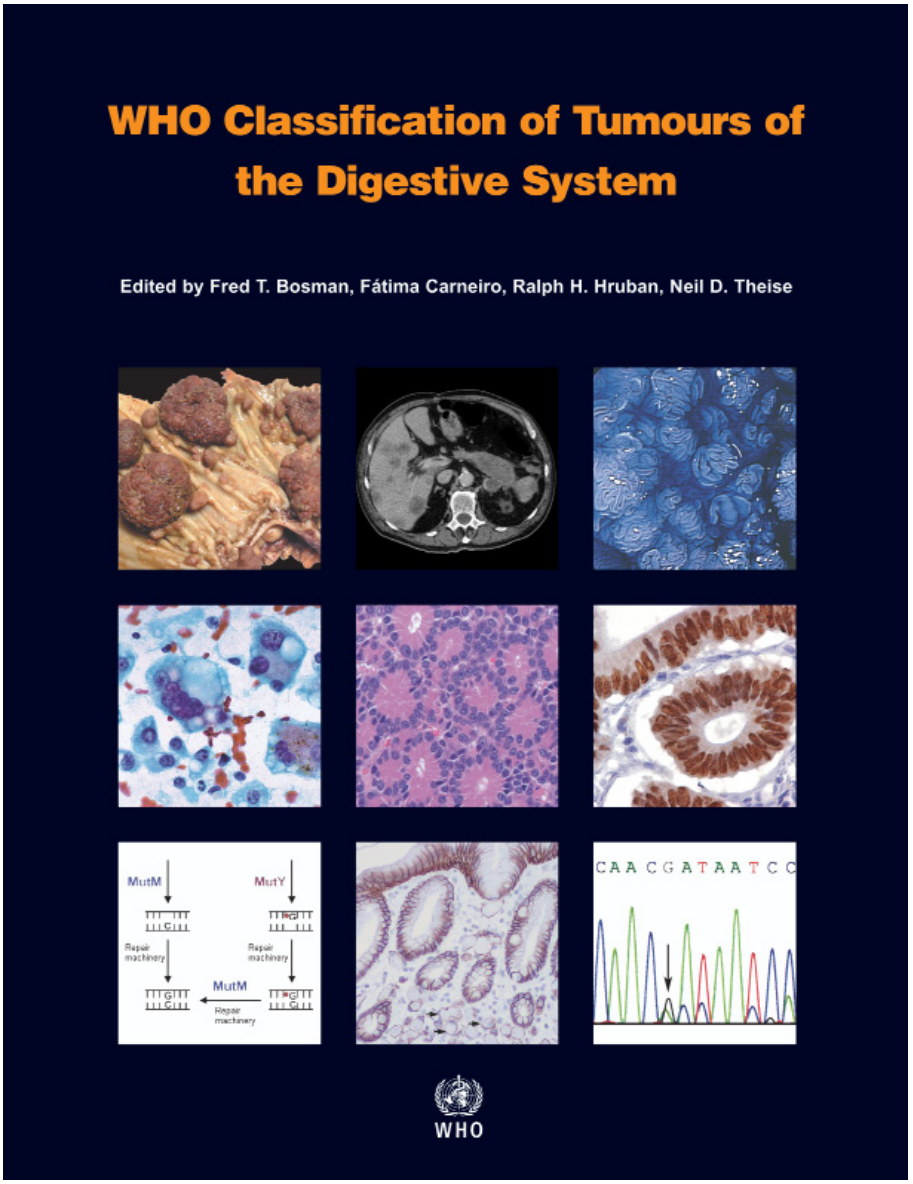

Figure 2. Cover of the book "WHO Classification of Tumours of the Digestive System"

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. Therefore, this project has high impact in not only pathology communities, but also cancer registration, epidemiology studies, clinical trials and cancer research in general.

IARC has been responsible for the WHO Blue Books since the 3rd 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 (4th 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 4th 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 > 35 000 copies have already been printed and distributed worldwide. The third volume, Tumours of the Digestive System, with four 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) was published in 2010, and > 8000 copies have been distributed. The fourth volume, Tumour of the Breast, is in preparation with five volume editors (Dr Sunil R. Lakhani, University of Queensland, Brisbane, Australia; Dr Ian Ellis, University of Nottingham, United Kingdom; Dr Stuart Schnitt, Beth Israel Deaconess Medical Center, Boston, USA; Dr Puay Hoon Tan, Singapore General Hospital, Singapore; and Dr Marc J. van de Vijver, Academic Medical Center, Amsterdam, the Netherlands). The consensus and editorial meeting was held at IARC

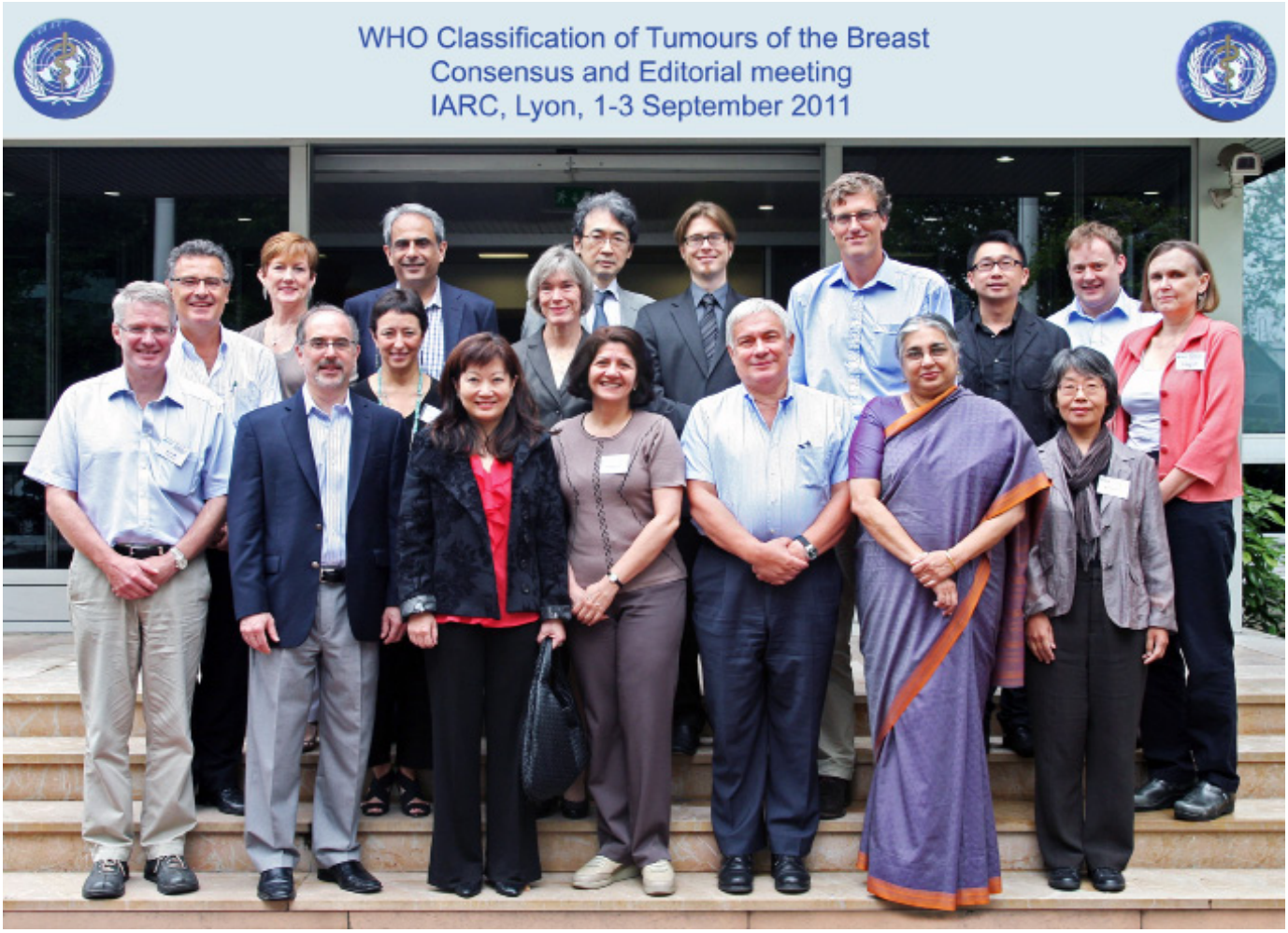

Figure 3. Photo of Working Group of Consensus and Editorial meeting of WHO Classification of Tumours of the Breast

in September 2011, and the book is scheduled to be published in summer 2012. The fifth volume of the 4th edition, Tumours of Soft Tissue and Bone, has been initiated with four volume editors (Dr Christopher D. Fletcher, Brigham and Women's Hospital, Boston, USA; Dr Pancras C.W. Hogendoorn, Leiden University Medical Center, Leiden, the Netherlands; Dr Julia A. Bridge, University of Nebraska Medical Center, Omaha, USA; and Dr Fredrik Mertens, Lund University, Sweden), and the consensus and editorial meeting is scheduled for April 2012.

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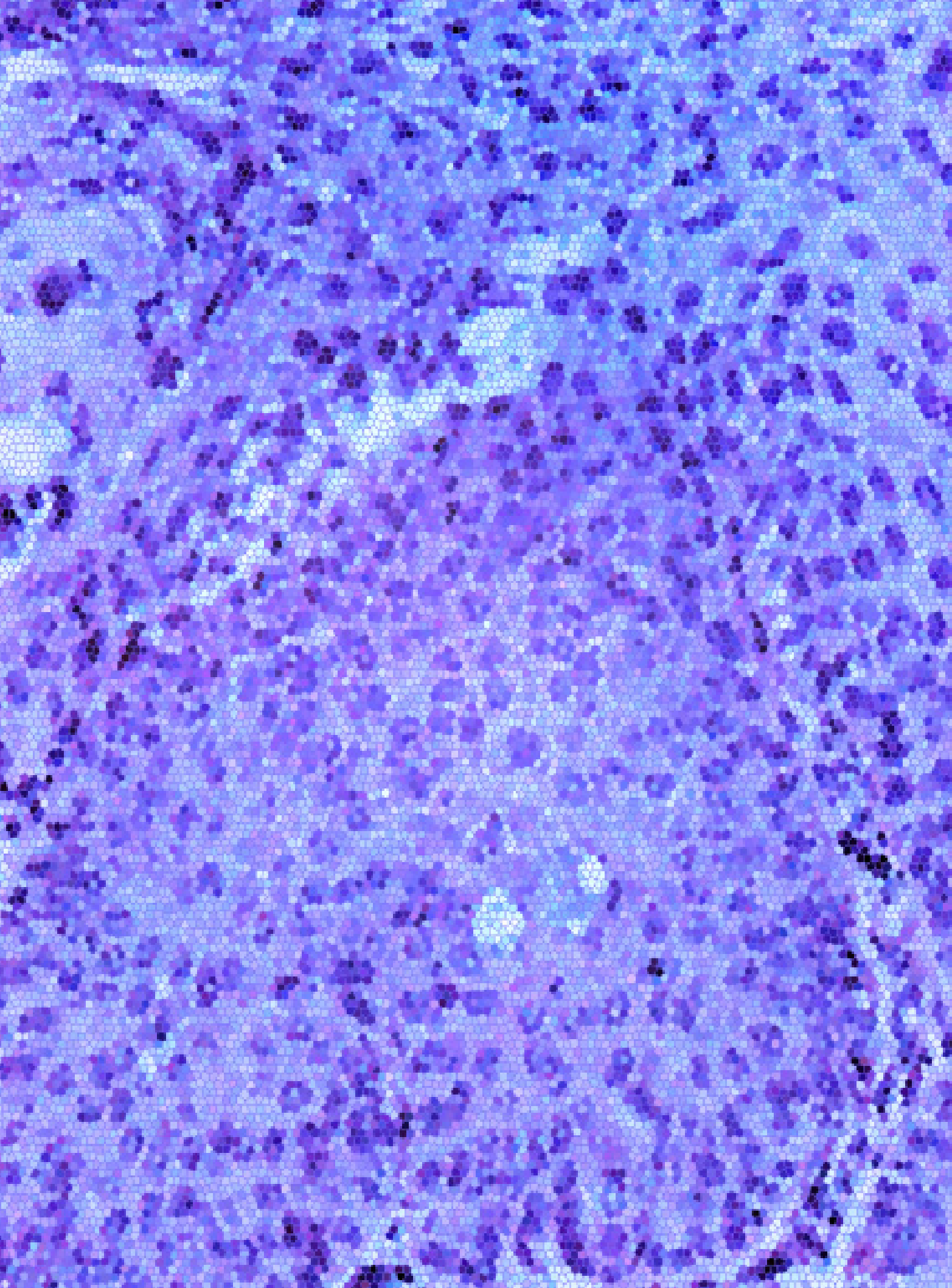


Section of Infections (INF)

Section head
Dr Silvia Franceschi

The Section of Infections (INF) is comprised of two Groups: the Infections and Cancer Epidemiology Group (ICE) and the Infections and Cancer Biology Group (ICB). ICE and ICB have worked closely together and belonged to the same Section since 2004.

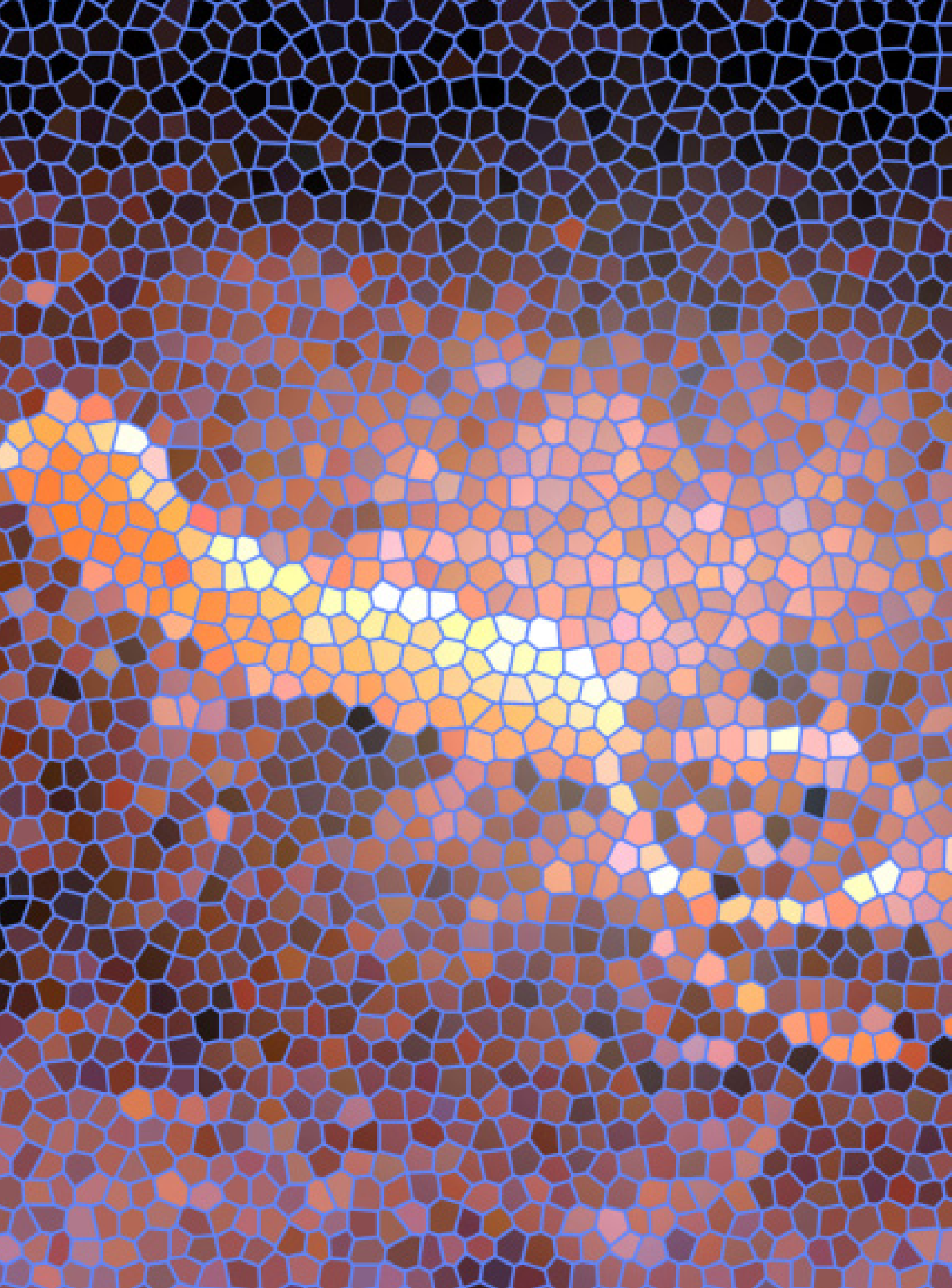
Persistent infections with viruses, bacteria and parasites account for nearly 20% of the cancer burden worldwide, with less developed countries being the hardest hit. Infections also represent, or might represent in the future, some of the most preventable cancer causes through immunization against or early detection and treatment of the infections. The infectious agents studied include 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) and Polyomaviruses although only a few of them will be described in the present Biennial Report.

The two Groups have different emphases in relation to infectious agents. ICB, for instance, is focused on cutaneous HPV to a greater extent than ICE. Conversely, ICE is more active in the study of *Helicobacter* species and HIV. Together the two Groups have initiated new projects of HPV and cancer of the head and neck. This topic is charged with greater methodological problems than HPV and anogenital cancer due to the more limited role of the virus (mainly in cancer of the oropharynx and among non-smokers). The fraction of cancer of the head and neck attributable to HPV has become, however, a crucial issue in respect to the decision to vaccinate adolescent boys against the virus in addition to adolescent girls.

With respect to areas of research, some are exclusive to ICB (e.g. transformation mechanisms) or ICE (worldwide distribution and trends of, as well as fraction of cancer attributable to, carcinogenic infections). New collaborations on other relevant aspects (the role of innate and acquired immunity, the impact of different HPV types and variants) have been initiated thanks to the increasing availability of tests suitable for large-scale application at ICB. Another great asset of INF is the complementary expertise on methodological issues. For example, ICB has expertise in relation to biological protocol issues while ICE is able to provide statistical advice.

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 Cancer Information (CIN).

The over 130 peer-reviewed articles published or accepted for publication by INF in 2010–2011 provide good evidence of the high productivity and the breadth of topics and international collaborations on by INF.



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It is well established that infections are the cause of approximately 20% of human cancers worldwide (Parkin, 2006). However, new findings indicate that additional infectious agents are involved in human carcinogenesis. A human polyomavirus, Merkel Cell polyomavirus (MCPyV), has been recently discovered and is associated with a rare tumour, Merkel cell sarcoma (Feng et al., 2008). In addition, certain HPV types that infect the skin and belong to genus ß of the HPV phylogenetic tree (Bernard et al., 2010) are suspected to be involved, together with ultraviolet radiation, in the development of non-melanoma skin cancer (NMSC) (Pfister et al., 2003).

The main goal of ICB is to establish a causal role of specific infectious agents in human cancer. Two complementary strategies are currently followed: (1) the characterization of the biological properties of proteins from potential oncogenic viruses using *in vitro* and *in vivo* model systems; and (2) the development of laboratory assays for the detection of infections in human specimens, which can be used in epidemiological studies.

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 the immune surveillance and to promote cellular transformation. Therefore, studies in the Group aim to characterize the ability of viruses to de-regulate cellular pathways involved in the immune response and cellular transformation to predict their oncogenic potential.

Regarding the development of novel diagnostic tools for infections, we have generated new detection assays with high-throughput, sensitivity and specificity for approximately 80 different viruses. The development of these novel detection assays allowed us to initiate and complete several epidemiological studies.

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

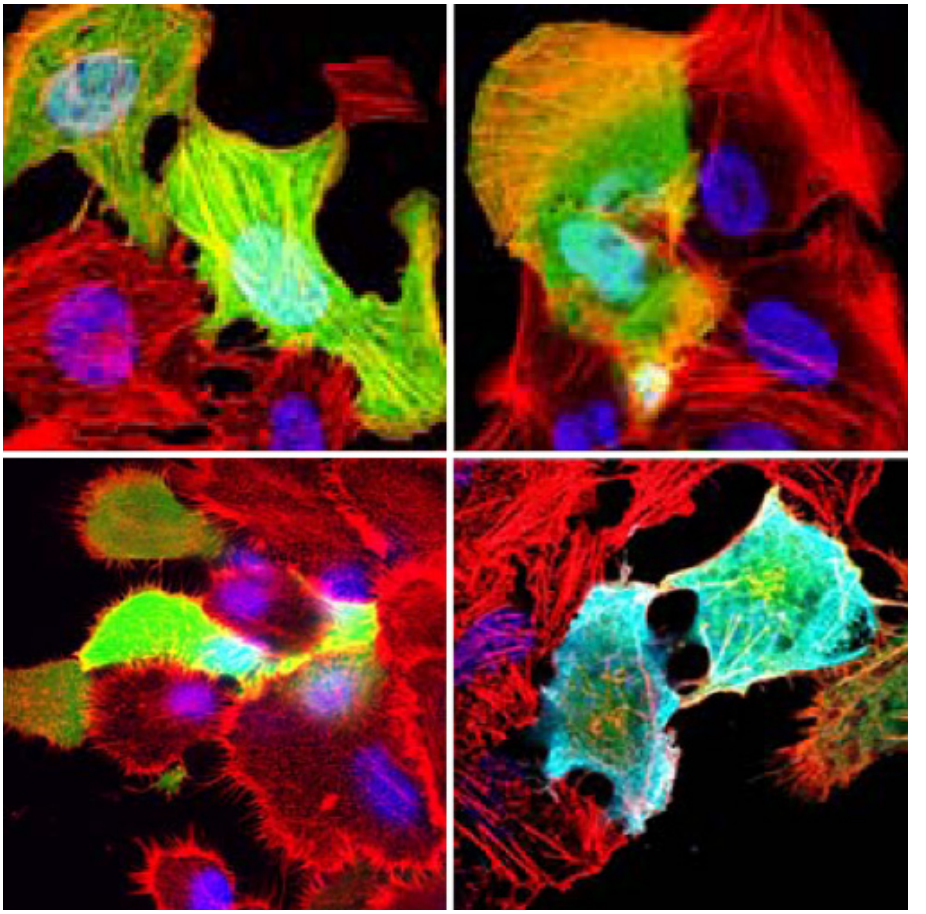

Figure 1. Primary human keratinocytes expressing E7 oncoprotein from cutaneous HPV38 with an altered cytoskeleton

Role of ß cutaneous HPV types in skin carcinogenesis

Epidemiological and biological data have shown that solar exposure and impairment of the immune system are key risk factors for the development of NMSC, which is the most common cancer in fair-skinned adult populations (Pisani *et al.*, 2002). The link with immune status strongly supports the role of an infectious agent in NMSC etiology. Several findings suggest that β HPV types are the most likely infectious agents involved in this disease (Berkhout *et al.*, 2000; de Jong-Tieben *et al.*, 1995; Harwood *et al.*, 2000; Andersson *et al.*, 2008; Waterboer *et al.*, 2008; Casabonne *et al.*, 2007; Karagas *et al.*, 2006; Bavinck *et al.*, 2010); however, their direct role is still under debate. To further evaluate the role of β HPV types in skin carcinogenesis, we have performed several studies to characterize the biological properties of their main oncoproteins, E6 and E7. Several experimental models have been used, ranging from primary keratinocytes to transgenic mice. In particular, we have focused on HPV38 E6 and E7 that were previously shown to induce immortalization of primary human keratinocytes, the natural host of the virus (Caldeira *et al.*, 2003; Gabet *et al.*, 2008). Recently our studies have demonstrated that HPV38 E6 and E7 have the ability to target several cellular pathways involved in cellular proliferation and apoptosis (Hussain *et al.*, 2011; Yue *et al.*, 2011; Accardi *et al.*, 2011). The data show that HPV38, similar to several oncogenic viruses, activates the NF-κB pathway, increasing the resistance of human keratinocytes to tumour necrosis factor α (TNF-α)- and UVB radiation-mediated apoptosis. Accordingly, inhibition of NF-κB signalling resulted in the downregulation of NF-κB-regulated antiapoptotic genes, including cIAP1, cIAP2 and xIAP genes and apoptosis (Hussain *et al.*, 2011).

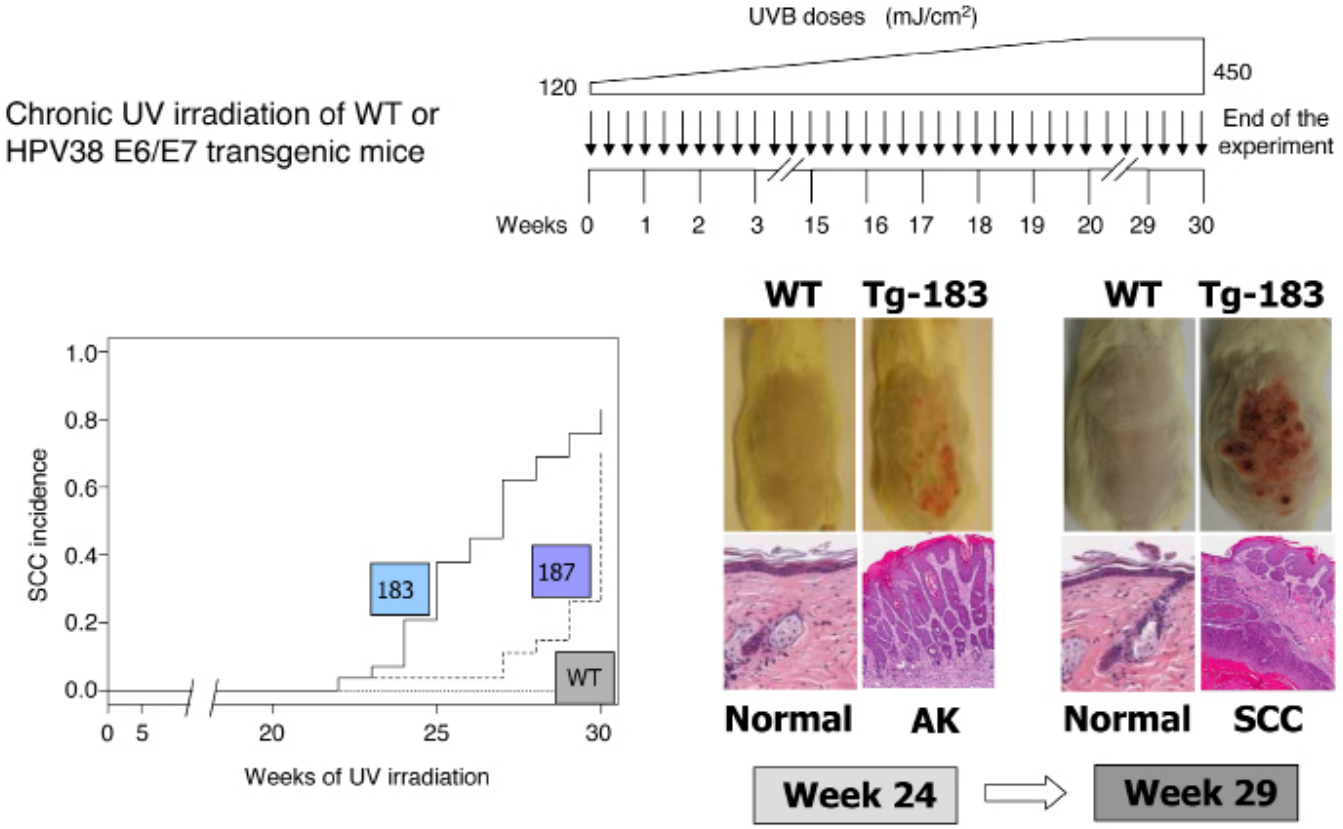

Figure 2. HPV38 cooperates with UV in the development of actinic keratosis-like lesions and squamous cell carcinoma in mice

In an additional study, we have demonstrated that HPV38 E7 induces actin stress fibre disruption and that this phenomenon correlates with its ability to downregulate Rho activity. The downregulation of Rho activity by HPV38 E7 is mediated through the activation of the CK2-MEK-extracellular signal-regulated kinase (ERK) pathway, promoting cellular proliferation. In addition, HPV38 E7 is able to induce actin fibre disruption by binding directly to eukaryotic elongation factor 1A (eEF1A) and abolishing its effects on actin fibre formation (Figure 1) (Yue *et al.*, 2011).

Findings in an animal experimental model provided additional evidence for the oncogenic potential of HPV38. We have observed that expression of HPV38 E6 and E7 in the mouse skin strongly synergizes with UV irradiation in promoting pre-malignant and malignant skin lesions. Indeed, chronic UV irradiation of HPV38 E6/E7 transgenic mice induced the development of actinic keratosis-like lesions, which in humans are considered to be precursors of squamous cell carcinomas (SCC), and subsequently of SCC in a significant proportion of the animals. In contrast, wild-type animals subjected to identical treatments did not develop any type of skin lesions (Figure 2) (Viarisio *et al.*, 2011). Thus, it is clear that the oncoproteins E6 and E7 from β HPV38 significantly contribute to SCC development in the mouse skin, rendering keratinocytes more susceptible to UV-induced carcinogenesis.

Identification of a novel mechanism of inactivation of the p53 functions

Studies on the β HPV types also led to the characterization of a novel mechanism involved in the regulation of the intracellular levels of ΔNp73α, an antagonist of the p53/p73-regulated pathways (Accardi *et al.*, 2011). We observed that HPV 38 E6 and E7 promote the accumulation of the IκB kinase β (IKKβ) in the nucleus, which in turn associate with and phosphorylate ΔNp73α at serine 422, leading to its stabilization and repression of several p53-regulated genes. Inhibition of IKKβ resulted in a rapid degradation of ΔNp73α and a rescue of the p53 functions. Interestingly, we have observed that IKKβ can stabilize ΔNp73α in some breast or head and neck cancer-derived cells. Thus, this event appeared to be important also in non-virus-induced carcinogenesis.

Prevalence of HPV infections in human specimens from different anatomical sites

We have developed novel assays based on Luminex technology 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). Due 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 and/or (ii) to promote carcinogenesis (e.g. Polesel *et al.* 2011; Rollison *et al.* 2008). 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 analyzed (Gheit *et al.* 2009; Sideri *et al.* 2009)

Role of DOK1 tumour suppressor in non-virus and virus-associated cancer

The Downstream of tyrosine kinase (DOK1) is an adaptor tyrosine kinase substrate with a tumour suppressive activity. We have previously shown that *DOK1* gene can be mutated in chronic lymphocytic leukemia (CLL). DOK1 mutated in CLL is a nuclear protein in contrast to the wild-type DOK1 which is cytoplasmic. In addition, a nuclear DOK1 with a mutated nuclear exclusion site is impaired in inhibiting cell proliferation (Lee *et al.* 2004; Lee *et al.* 2007; Niu *et al.* 2006). We also found a nuclear mislocalisation of DOK1 in HPV-immortalized keratinocytes. Thus, the subcellular localization of DOK1 correlates with its tumour suppressive activities. Further studies revealed that the expression of *DOK1* gene is repressed through hypermethylation of its promoter in the majority of healed and neck cancer (HNC) lines analyzed as well as primary human neoplasm including solid tumours (93% in HNC, 81% in lung cancer) and hematopoietic malignancy (64% in Burkitt's lymphoma) (Saulnier *et al.* 2011). In addition, an inverse correlation was observed between the level of DOK1 gene methylation and its expression in tumour and adjacent non tumour tissues. Studies are ongoing to evaluate the potential role of *DOK1* as a prognostic marker in HNC and other cancer types.

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Human papillomavirus

The study of human papillomavirus (HPV) infection, the cause of cervical cancer and target of effective vaccines and screening tests, has been the main focus of the Infections and Cancer Epidemiology Group (ICE) in 2010–2011. The IARC HPV prevalence surveys were continued to include additional populations for whom no or very limited information on the burden of HPV or cervical cancer was available (Figure 1). Evidence on the large variability in HPV prevalence was expanded and can inform the prioritization of HPV vaccine introduction in highest-risk countries in times of financial constraint.

Time since first intercourse and the risk of cervical cancer

Young age at first sexual intercourse is an important risk factor for cervical cancer (International Collaboration of Epidemiological Studies of Cervical Cancer, 2009). We envisaged, therefore, a model to elucidate the issue by interpreting the age at first sexual intercourse in terms of proxy of age at first HPV infection and, hence, duration of exposure to the virus (Plummer *et al.*, 2011). This approximation is plausible, as it is known that HPV infection is highly contagious and frequent in many world populations, and first infection with HPV often occurs in women soon after first sexual intercourse.

To reduce the confounding effect of multiple sexual partners, we investigated the relationship between risk of cervical carcinoma and time since first intercourse (TFI) using data on monogamous women only (5074 cases and 16 137 controls) from the International Collaboration of Epidemiological Studies of Cervical Cancer, 2009. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression. In addition, we used age-specific incidence rates in unscreened populations to characterize the age profile of cervical cancer incidence.

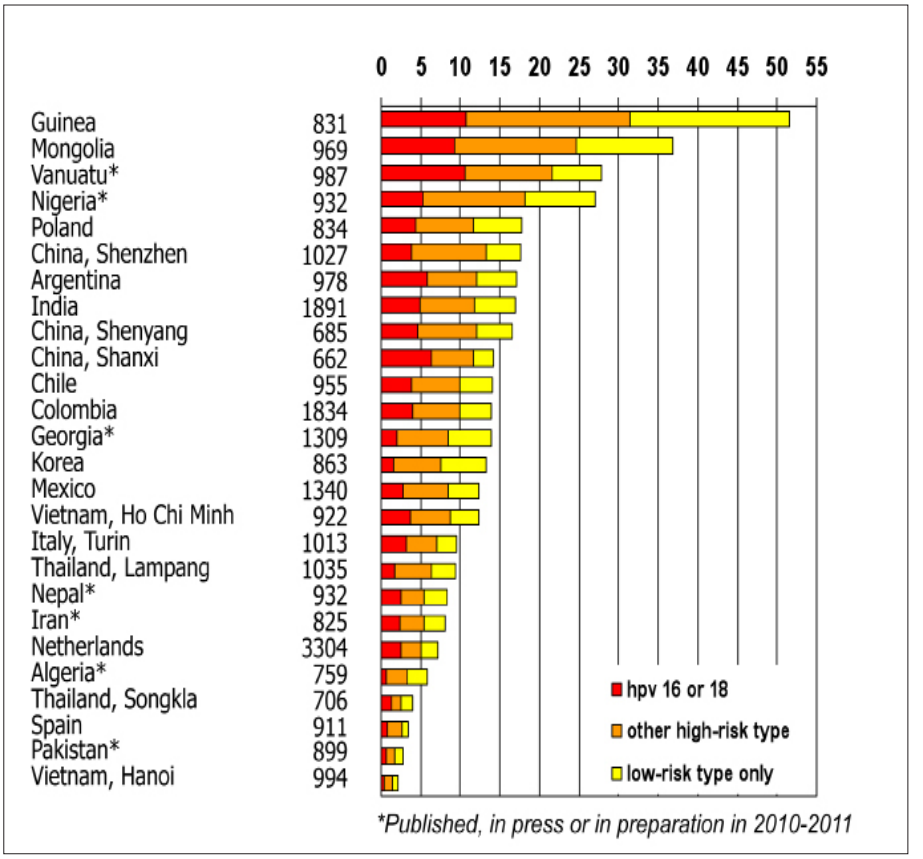


Figure 1. Prevalence (%) of cervical human papillomavirus DNA in sexually active women, IARC Prevalence Surveys, 1990–2011

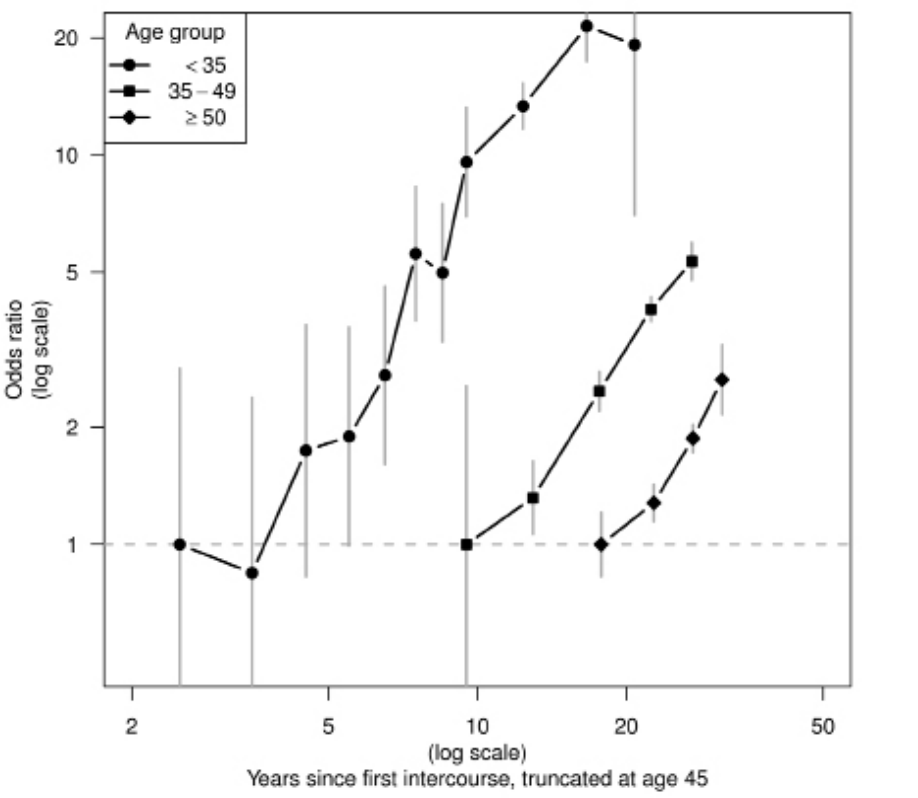


Figure 2. Odds ratios (and 95% floating confidence intervals) for cervical cancer by time since first intercourse stratified by age group (Plummer *et al.*, 2011).

There was no significant difference in slope between the three age strata (χ^2 = 2.67 with 2 degrees of freedom, P = 0.26). The data are thus consistent with a simplified model in which the OR increases as a power of truncated TFI that is constant at all ages. The OR for invasive cervical carcinoma is approximately proportional to the square of TFI (exponent 1.95, 95% CI: 1.76–2.15) up to age 45. Age-specific incidence rates of cervical cancer in unscreened populations are consistent with this model up to age 45, but remain fairly constant at older ages.

We concluded that cervical cancer resembles other cancers caused by strong early-stage carcinogens (e.g. lung cancer and tobacco smoking), with incidence rates proportional to a power of duration of exposure. But cervical cancer also resembles cancers of the breast and other hormone-dependent epithelia, where a similar flattening of age-specific incidence rates is seen at the time menopausal changes start.

Our findings have important implications for immunization strategies against HPV. HPV vaccines have been demonstrated to be highly effective in preventing HPV infection for up to eight years (McKeage and Romanowski, 2011), but the longer term protection is currently unknown. Our model suggests that delaying first exposure to HPV by vaccination would have the same lifelong effect as delaying age at first sexual intercourse. For example, a vaccine against HPV16 and 18 that lasted 15 years would prevent almost all cancers due to these HPV types below age 40 and would reduce the risk almost 5-fold above age 45 (data not shown). Assuming that the vaccine will not be effective against other HPV types, the overall effect would be to reduce all cervical cancer incidence above age 45 by more than 2-fold (Figure 3).

Conversely, our analysis suggests little advantage of vaccinating older women in the prevention of cervical cancer. Women can be infected by carcinogenic HPV at any age (Plummer *et al.*, 2011), but the lifetime cervical cancer risk caused by a new HPV infection will fall sharply with age at infection (Rodríguez *et al.*, 2010).

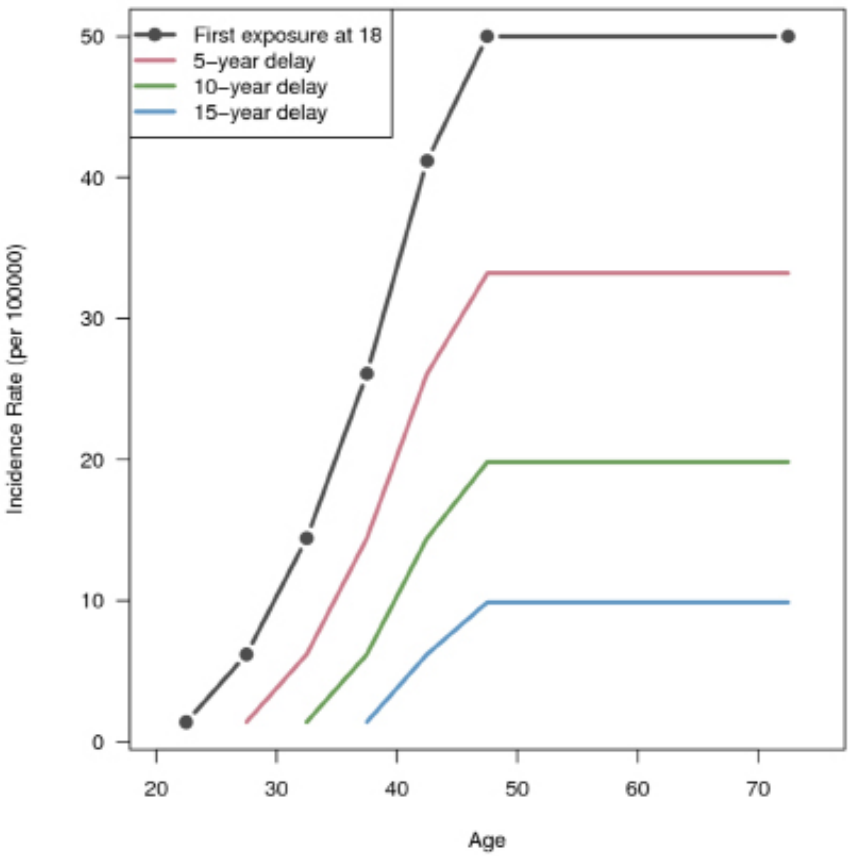


Figure 3. Predicted effect of a vaccine against HPV16 and 18 of limited duration (derived from Plummer *et al.*, 2011)

Random clustering of HPV infections

To understand viral interactions and cross-reactivity of natural or vaccine-induced immunological responses, it is important to assess whether certain combinations of HPV types are more or less likely to be found together, beyond what would be expected by shared sexual transmission and common risk factors.

The ICE has promoted international collaborations that aim to assess the pattern of HPV type clustering in a range of large-scale studies that differ by type of population included (e.g. cancer-free women or men) and HPV detection methods used. These included IARC HPV Prevalence Surveys (mainly low-resource countries) (Vaccarella *et al.*, 2010); The Guanacaste Study of HPV Natural History, Costa Rica (Vaccarella *et al.*, 2011b); The New Technologies in Cervical Cancer (NTCC) screening study, Italy (Carozzi *et al.*, 2011); and The HPV in Men study (United States, Mexico, and Brazil) (Vaccarella *et al.*, 2011a).

An appropriate statistical approach based on multilevel modelling has been developed. We used multivariate logistic regression to model type-specific HPV positivity. The presence of each HPV type was considered as a separate outcome for each woman. The model allows for the inclusion of available covariates such as age, study area and lifetime number of sexual partners. Subject-level random effects represent unobservable risk factors common to all HPV types and allow better adjustment for the complexity of sexual behaviour.

In all study populations considered (see the largest study included, the NTCC, in Figure 4) (Carozzi *et al.*, 2011), high-risk HPV coinfections seemed to occur at random in the female cervix, as well as the male external genitalia. In particular, there was no evidence that HPV16 and 18 are more or less likely to be found in combination with other oncogenic types. The few significant excesses of certain pairs of HPV types that were found could be confidently attributed to artefacts of certain HPV detection methods (e.g. cross-hybridization of similar HPV types) (Vaccarella *et al.*, 2010).

Overall, our collaborative analysis provides evidence that the removal of certain HPV types through vaccination would not result in an indirect increase or decrease in the prevalence of other untargeted types.

Distribution of HPV types in cervical cancer in women infected by HIV

Though data on the prevalence of HPV types in cervical carcinoma in women with HIV are scarce, they are essential to elucidate the influence of immunity on the carcinogenicity of different HPV types, and the potential impact of prophylactic HPV vaccines in populations with high HIV prevalence. We therefore conducted a case-case study in Kenya and South Africa (De Vuyst *et al.*, 2011). During 2007–2009, frozen tissue biopsies from women with cervical carcinoma were tested for HPV DNA using GP5+/6+-PCR assay. One hundred and six HIV-positive (mean age 40.8 years) and 129 HIV-negative women (mean age 45.7) with SCC were included. Among HIV-positive women, the mean CD4 count was 334 cells/μL and 48.1% were on combined antiretroviral therapy. HIV-infected women had many more multiple HPV infections (21.6% of HPV-positive carcinomas) compared to HIV-negative women (3.3%; P < 0.001) and the proportion of multiple infections in HIV-infected women was inversely related to CD4 level.

An excess of HPV18 of borderline statistical significance was shown in HIV-positive compared to HIV-negative cases (Prevalence ratio (PR) = 1.9, 95% CI: 1.0–3.7, adjusted for study centre, age and multiplicity of infection). HPV16 and/or 18 prevalence combined, however, was similar in HIV-positive (66.7%) and HIV-negative cases (69.1%) (PR = 1.0, 95% CI: 0.9–1.2). No significant difference emerged for other HPV types.

Our data are in agreement with a few other smaller studies on the topic. They suggest that current prophylactic HPV vaccines against HPV16 and 18 may prevent similar proportions of cervical cancers in HIV-positive, as in HIV-negative, women provided vaccine-related protection continues after HIV infection.

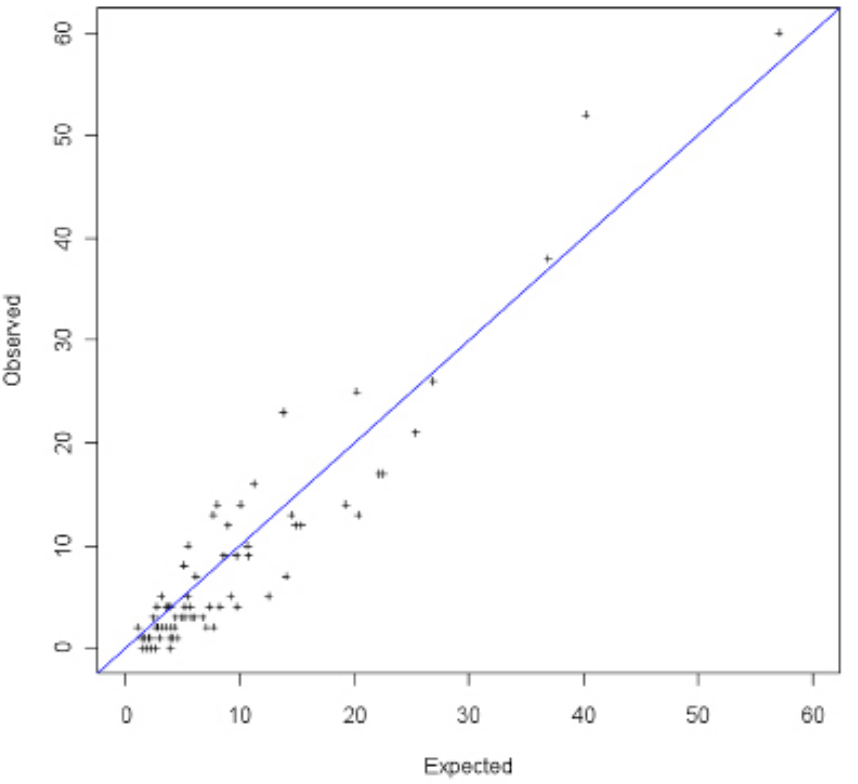
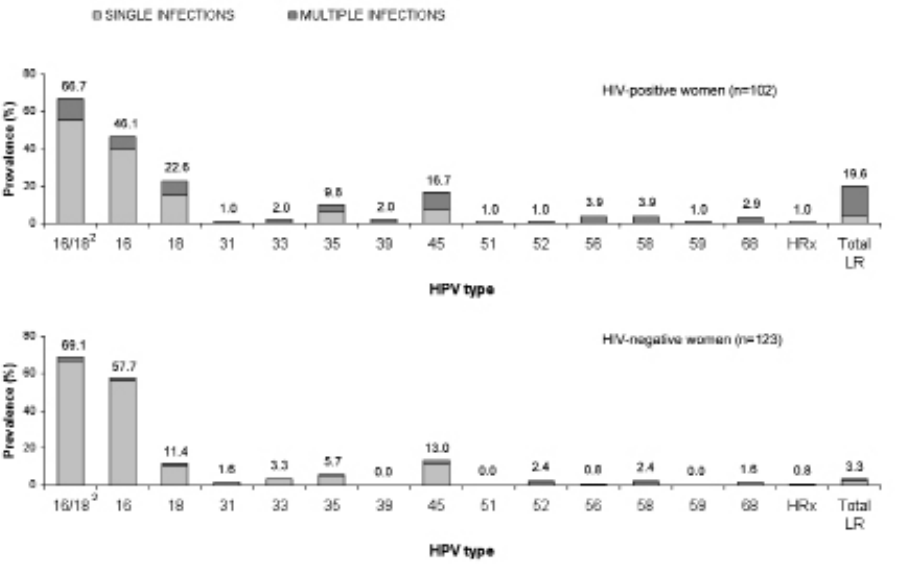


Figure 4. Observed versus Expected occurrence for 2-way combinations of 13 high-risk human papillomavirus (HPV) types. The New Technologies in Cervical Cancer study, Italy (Carozzi *et al.*, 2011)

Plus signs represent occurrences of HPV pairs. HPV pairs located in the upper triangle indicate positive clustering, while those located in the lower triangle represent negative clustering between the HPV types involved. None of the P-values for joint HPV infections were significant at the chosen significance level of 0.01.

Figure 5. Prevalence of human papillomavirus (HPV) in 225 women with cervical squamous cell carcinoma by HIV status and multiplicity of HPV infection (De Vuyst *et al.*, 2011)

10 HPV-negative women were probably false negatives and were excluded; [2]Either 16 or 18 as single infection or in combination with any type as multiple type infection;
HPV: human papillomavirus; HRX: uncharacterized high-risk type; LR: low-risk.



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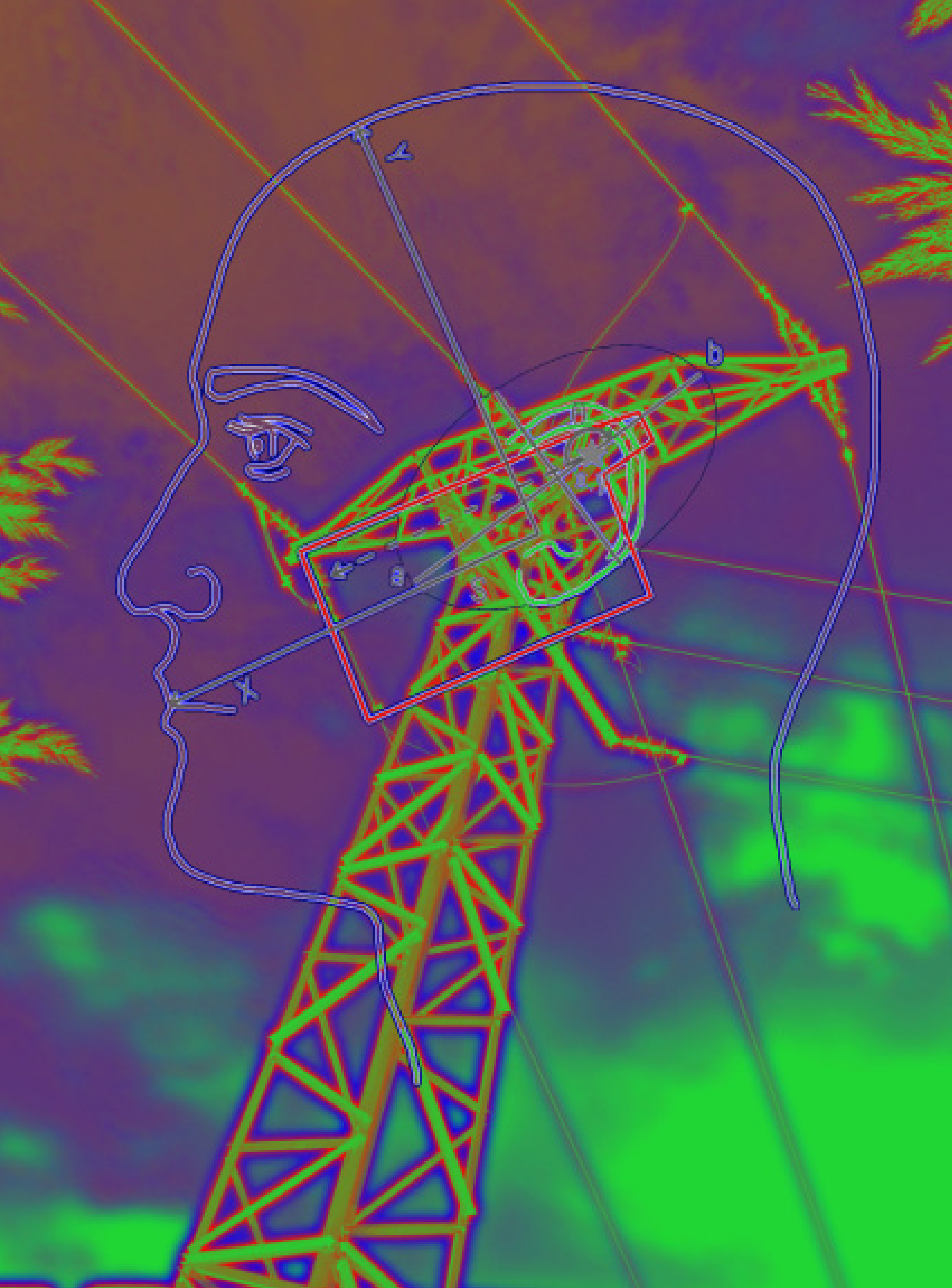
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Environment, including lifestyle, encompasses many major causes of human cancer, including tobacco use, alcohol drinking, occupational exposures, environmental pollutants and radiation. Accordingly, the research activities of the Section of Environment and Radiation (ENV) address a broad spectrum of risk factors of a variety of cancers, either by further characterizing established risk factors in terms of dose–response patterns or identifying specifically affected or vulnerable subpopulations, or by investigating possible but not established risk factors. The Section investigates those exogenous factors with the aim of contributing to the primary prevention of cancer and increasing our understanding of biological mechanisms of carcinogenesis. These objectives are achieved through collaborative, international epidemiological studies in a multidisciplinary approach, when possible, or through the initiation of single epidemiological analytical studies. Another approach used by the Section is the coordination of international consortia of epidemiological studies.

Recent results have emerged from Section projects on lifestyle, environmental, occupational and radiation-related causes of human cancer. They include investigations on tobacco use and cancer and of alcohol

consumption and cancer, a collaboration on a study in hyper-endemic areas of oesophageal cancer in Islamic Republic of Iran, studies on risk factors of head and neck cancer, and an international consortium on occupational risk factors of lung cancer. Recently launched major activities include studying adverse health effects related to pesticide use and the role of pesticides and endocrine-disrupting agents in the etiology of testicular cancer. Two pooling projects examine the impact of the parents' and children's exposure to pesticides and the subsequent risk of childhood cancer. Furthermore, the ENV is involved in projects that address cancer risks among workers in the rubber industry and those exposed to asbestos. Cancer-specific new activities include setting up an oesophageal cancer consortium in Africa, a global initiative on childhood leukaemia and further investigations into causes of brain tumours.

Projects on ionizing radiation include: the effects of protracted low doses of external ionizing radiation from medical diagnostic examinations and from occupational activities; populations exposed to Chernobyl fallout; in utero exposure of children born to workers in nuclear processing plants in the Southern Urals; and the interaction between ionizing radiation and genetic factors.

Non-ionizing radiation research activities include: a case-control study on mobile phone use and the risk of brain tumours, acoustic neuroma and salivary gland tumours; collaboration in a Danish cohort study of mobile phone subscribers; and collaboration in studies on extremely low-frequency magnetic fields and the risk of childhood cancer.

The Section is also about to finalize volume 14 of the IARC Handbooks on Cancer Prevention series on tobacco control. New activities investigate the potential carcinogenicity of another addictive plant, namely qat chewing, and its potential risk of cancer with feasibility studies carried out in East Africa.

Section of Environment and Radiation

Overview

To achieve their objectives, the ENV is involved in numerous projects that investigate exogenous factors that lead to human cancer.

Lifestyle: A recent analysis embedded in European cohort studies confirmed that cigar and pipe smoking is not a safe alternative to cigarette smoking; the lower cancer risk of cigar and pipe smokers as compared to cigarette smokers was explained by a lesser degree of inhalation and lower smoking intensity (McCormack et al., 2010). Further investigations of head and neck cancer risk revealed that quitting tobacco smoking for 1–4 years already resulted in a 30% risk reduction compared to current smokers, with the risk reduction after ≥ 20 years reaching the level of never smokers (Marron et al., 2010). For other lifestyle factors, recent meta-analyses confirmed that oral and pharyngeal, laryngeal and oesophageal cancers are strongly related to alcohol drinking. An inverse association between caffeinated coffee drinking and risk of cancer of the oral cavity and pharynx was observed, whereas tea intake was not associated with head and neck cancer risk. Findings in Golestan, Islamic Republic of Iran, a high-risk area for oesophageal cancer, suggest cigarettes and hookah smoking, nass use, opium consumption, hot tea drinking, poor oral health, low intake of fresh fruit and vegetables and low socioeconomic status to be associated with a higher risk of oesophageal cancer.

Environment and occupation: In a study of European asphalt workers, no consistent evidence of an association between indicators of either inhalation or dermal exposure to bitumen and lung cancer risk was found, while a sizable proportion of the excess mortality from lung cancer relative to the general population is likely attributable to high tobacco consumption and possibly to coal tar exposure (Olsson et al., 2010). Investigating occupational risk factors for lung cancer using eastern European multicentre datasets, showed that exposure to polycyclic aromatic hydrocarbons (PAH) did not appear to substantially contribute to the burden of lung cancer in eastern Europe. To investigate cancer risks in workers in the rubber industry, a new consortium of European cohort studies has been established. In the past two years, the Section commenced a historical cohort study of workers at Uralasbest (Russian Federation), one of the world's largest asbestos mines, to further characterize the effects on cancer of amphibole-free chrysotile, of prolonged low-levels of exposure, and the effect modification of smoking.

Mammographic density (percent fibroglandular tissue) is a strong intermediate marker of breast cancer risk. ENV is involved in several studies examining both its heritable and environmental determinants, including studies of determinants of density in young women, of within-woman changes in density and whether these in turn alter breast cancer risk, and a pooling project to examine whether worldwide variations in density underline international variations in breast cancer incidence rates.

Ionizing radiation: An international group of experts and advisors within the Agenda for Research on Chernobyl Health (ARCH) project led by IARC, reviewed the current knowledge about the health effects from the accident. They recommended international support for the long-term funding of a Chernobyl Health Effects Research Foundation, involving funding organizations and the three countries most affected by the accident (Williams et al., 2011). Pooling of nuclear workers' (NW) recently updated follow-up data from the US, United Kingdom and French cohorts, previously included in the International NW study, started in 2010. The proposed combined analysis offers the ability to derive more statistically precise risk estimates than any prior epidemiological study of cancer among NW. Evaluation of the contribution of genetic variations in candidate genes potentially relevant to thyroid tumours, and their interaction with ionizing radiation exposure to the thyroid gland, is underway using samples previously collected within the case- control study of thyroid cancer in Belarus. A study to collect and review historical literature discussing radiation dose to the breast was carried out to assess the dose likely received

by the breast during mammography examinations (Thierry- Chef et al., 2011). Cancer risks related to in utero exposure to ionizing radiation are currently being investigated by pooling the Techa River in utero exposed cohort and the Mayak workers' offspring cohort in the Southern Urals, the Russian Federation.

Non-Ionizing radiation: The rapid increase in mobile phone use has generated concern about possible health risks related to radiofrequency electromagnetic fields from this technology. In addition to a large international case-control study described below, recent results from the collaboration in a Danish nationwide cohort study of more than 400 000 mobile phone subscribers showed no increased risk of acoustic neuroma; however, heavy mobile phone users could not be studied as a separate group (Schüz et al., 2011). The Section also participates in a study on mobile phone use and risk of brain tumours in teenagers and adolescents (Cefalo) conducted jointly in Denmark, Norway, Sweden and Switzerland. Recently published results did not suggest an increased brain tumour risk in this particular age group (Aydin et al., 2011a). Given the limitations of retrospective studies when reconstructing past exposures, the Section received a grant for investigating the feasibility for running the French component of a European prospective study of mobile phone users. Current activities on extremely low-frequency magnetic fields (ELF- MF) include collaboration in a study on residential ELF-MF and survival after childhood leukaemia and participation in a European study investigating possible mechanisms.

IARC Handbook on Tobacco Prevention

Due to the large proportion of cancer caused by tobacco, the IARC Handbooks of Cancer Prevention series added tobacco control as a topic for review and evaluation. Tobacco smoking is pandemic affecting over a billion people. Tobacco use is the target of control efforts at different jurisdictional levels across nations, and the evaluation of the effectiveness of such policy interventions in the Handbooks is an important contribution for developing cancer prevention strategies. The last volume of the series, number 14, presents an evidence-based evaluation of the effects of tax and price policies for tobacco control, including the positive outcomes of reduced consumption, increased cessation and decreased initiation. Handbook volume 14 was developed by an interdisciplinary Working Group of experts from 12 countries, who critically reviewed the available evidence. The resulting working drafts were further reviewed during a meeting at IARC on 17–22 May 2010. There were several concluding statements on the effect of taxes on aggregated demand for tobacco, adult tobacco use, use among youth and among the poor, tobacco industry pricing strategies and tax related lobbying, tax avoidance and tax evasion and the economic and health impact of tobacco taxation (Chaloupka et al., 2011; Table 1).

Occupational risk factors of lung cancer (SYNERGY)

The SYNERGY project (Pooled Analysis of Case-control Studies on the Joint Effects of Occupational Carcinogens in the Development of Lung Cancer) was initiated to identify and estimate joint effects of five selected occupational carcinogens (PAH, asbestos, crystalline silica, chromium and nickel) and tobacco smoking. To date, 14 case-control studies from Europe and North America have been pooled providing lifetime occupational and smoking history from 17 705 cases and 21 813 controls. A unique feature of the SYNERGY project has been the development of SYNJEM – a country, year and job-specific job-exposure matrix with exposure estimates modelled from quantitative exposure measurements from 21 countries.

Additional analyses in the SYNERGY database have been initiated by the study group to address open research questions related to occupational lung cancer; for example diesel motor exhaust and lung cancer (Olsson et al., 2011), and organic dust exposures and lung cancer. Cumulative diesel exposure was associated with a 30% increased lung cancer risk in the highest exposure quartile and showed a significant exposure-response relationship. Those increased risks were confirmed in workers never employed in occupations with established lung cancer risk, in women and in never-smokers. Organic dust exposure was also associated with increased lung cancer risk in a dose-dependent manner, including in subjects without a history of chronic obstructive pulmonary disease or asthma. Additional analyses on painters, hairdressers, cooks, welders, miners and construction workers are underway. The SYNERGY study group collaborates with the International Lung Cancer Consortium to study alcohol and lung cancer risk, and with the Imperial College in London to develop advanced methods to study multiple interactions.

Computer tomography in children and the risk of cancer (EPI-CT)

For paediatric patients, an important innovation in diagnostic radiology has been the development of computerized tomography (CT) scans. However, the growing use of CT in children is a topic of concern in radiological protection. Considerations unique to the paediatric population include increased radio-sensitivity, particularly in infancy, a longer lifetime for radiation-related cancer to occur and a lack of size-based adjustments in technique. In light of these considerations, a project coordinated by the Section (CHILD-MED-RAD), demonstrated the feasibility of setting up in Europe a multinational cohort study to evaluate the risks associated with the low doses from CT. Following those recommendations, the EU-funded EPI-CT project started in February 2011. It is a multinational study of paediatric CT patients based on a common core protocol. The work involves pooling of cohort data from nine European countries: Belgium, Denmark, France, Germany, Spain, Sweden, the Netherlands, Norway and the United Kingdom (Figure 1). The study, which is the largest and the most statistically powerful study of paediatric CT undertaken to date, is aiming to: develop knowledge about CT use patterns; accurately quantify doses from these procedures; directly study the long-term health effects of CT, primarily cancer, on paediatric patients; and better understand the balance between risks and benefits of paediatric imaging to optimize the doses delivered from CT.

Table 1. Evidence for the effectiveness of tax and price policies in tobacco control

Concluding Statements	Sufficient Evidence	Strong Evidence	Limited Evidence
Increases in tobacco excise taxes that increase prices reduce overall tobacco use, prevalence and consumption in continuing users and induces current tobacco users to quit.	X		
Increases in tobacco excise taxes that increase prices reduce the prevalence of tobacco use and reduce the initiation and uptake of tobacco use among young people, with a greater impact on the transition to regular use.	X		
Tobacco use among young people responds more to changes in tobacco product taxes and prices than does tobacco use among adults.	X		
In high-income countries, tobacco use among lower-income populations is more responsive to tax and price increases than is tobacco use among higher-income populations.		X	
The demand for tobacco products in lower-income countries is more responsive to price than is the demand for tobacco products in higher-income countries.			X
In low- and middle-income countries, tobacco use among lower-income populations is more responsive to tax and price increases than is tobacco use among higher-income populations.			X
Changes in the relative prices of tobacco products lead to some substitution to the products for which the relative prices have fallen.		X	
Tobacco tax increases augment tobacco tax revenues and when tax increases raise prices, population health is improved. Tax avoidance and tax evasion reduce, but do not eliminate, the public health and revenue impact of tobacco tax increases.	X		
A coordinated set of interventions that includes international collaborations, strengthened tax administration, increased enforcement, and swift, severe penalties reduces illicit trade in tobacco products.		X	
Higher and more uniform specific tobacco excise taxes result in higher tobacco product prices and increase the effectiveness of taxation policies in reducing tobacco use.	X		
Tobacco industry price discounting strategies, price-reducing marketing activities, and lobbying efforts mitigate the impact of tobacco excise tax increases.	X		
Tobacco tax increases do not increase unemployment.		X	

Sufficient Evidence: An association has been observed between the intervention under consideration and a given effect in studies in which chance, bias and confounding can be ruled out with reasonable confidence. The association is highly likely to be causal.

Strong Evidence: There is consistent evidence of an association, but evidence of causality is limited by the fact that chance, bias or confounding have not been ruled out with reasonable confidence. However, explanations other than causality are unlikely.

Limited Evidence: There is some evidence of association between the intervention under consideration and a given effect, but alternative explanations are possible.

Inadequate/No Evidence: There are no available methodologically sound studies showing an association; the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between the intervention and a given effect. Alternatively, this category is used when no studies are available.

Evidence of No Effect: Methodologically sound studies consistently demonstrate the lack of an association between the intervention under consideration and a given effect.

Mobile phone use and the risk of brain tumours (INTERPHONE)

INTERPHONE is the largest case–control study to date investigating risks related to mobile phone use. Also being explored are other potential risk factors for tumours arising in the tissues most exposed to radiofrequency electromagnetic fields from mobile phones including 2765 glioma, 2425 meningioma, 1121 acoustic neuroma, 109 malignant parotid gland tumour cases and 7658 controls from 13 countries. Overall, no increase in risk of glioma or meningioma was observed with use of mobile phones (INTERPHONE Study Group, 2010). No elevated risk for glioma or meningioma was observed ≥ 10 years after first mobile phone use. There were suggestions of an increased risk of glioma at the highest exposure levels, but biases and error prevented a causal interpretation. There was no increase in risk of acoustic neuroma with ever regular use of a mobile phone or for users who began regular use 10 years or more before reference date (INTERPHONE Study Group, 2011). Elevated risks observed at the highest level of cumulative call time could be due to chance, reporting bias or a causal effect. Altogether, the possible effects of long-term heavy use of mobile phones require further investigation.

Figure 1. Estimated EPI-CT cohort size for each participating country

Upcoming activities

Several of the above described activities have started recently and are still in the phases of demonstrating feasibility, creating the infrastructure for the study, data collection or follow-up. Therefore the scientific results will appear in future years, and for some of the larger projects, perhaps over the next decade or longer. As shown, the Section will continue to be active in all areas: from lifestyle to environmental pollutants, occupational exposures and radiation (both ionizing and non-ionizing), and in areas where key questions on cancer causation are unanswered. With regard to cancer sites, it is particularly lung, oesophageal, testicular, breast and childhood cancers and brain tumours that are addressed by multiple activities and where research collaborations often go beyond environmental and radiation risk factors.

A long range goal of the Section is to launch studies on environmental-, occupational- and radiation-related risks in Africa (McCormack & Schüz, 2011). During the ongoing modernization of Africa, there are concerns that environmental exposures to carcinogens, sometimes at high levels, are likely given suboptimal attention in regards to workers' and environmental protection. The use of outdated technologies and lack of hazard awareness, among other concerns, add to the unease.

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Section of Nutrition and Metabolism (NME)

Section head
Isabelle Romieu

Diet, nutrition, metabolic/hormonal imbalances, excess energy consumption, obesity and physical inactivity are thought to be important contributors to increasing cancer incidence rates worldwide. However, the mechanisms of action of these factors remain poorly understood. In addition, the contributing influence of dietary transitions from traditional to Western-type diets, which is taking place in low- and middle-income countries (LMICs) (e.g. Latin America), and exposures in utero and during early infancy are not well studied.

The main objective of the Section of Nutrition and Metabolism (NME) is to address these issues by evaluating the association between diet (including dietary patterns), nutrition, physical activity and energy imbalance with cancer risk in high- and low-to-middle-income countries using cohort and case-control designs or human intervention studies. Among other responsibilities, this Section plays a leading role in the coordination and maintenance of the European Prospective Investigation into Cancer and Nutrition (EPIC), a large ongoing prospective cohort initiated by IARC.

Emphasis is on improving the accuracy, understanding and interpretation of dietary exposures; developing, validating and disseminating standardized dietary methodologies relevant to international study settings; applying biomarkers and metabolomics to study cellular, biochemical and physiological changes and consideration of gene–diet/nutrient/environment interactions. This approach will allow for a better understanding of the mechanisms/metabolic pathways by which diet, contaminants and hormones affect cancer and intermediate endpoints.

Ultimately, the translation of findings into public health recommendations and the development of appropriate cancer prevention strategies are of major importance to the Section.

Nutritional Epidemiology Group (NEP)

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Ms Jessica Fournera

Research in the Nutritional Epidemiology Group (NEP) complements work conducted in the Dietary Exposure Assessment Group (DEX) and the Biomarkers Group of the Section of Nutrition and Metabolism (NME). Our research focuses on the role of diet, nutrition, metabolic/hormonal imbalances, excess energy consumption, obesity and physical inactivity on the incidence of cancer, and other metabolic diseases related to cancer, with emphasis on biomarkers and gene-diet/nutrient/environment interactions. We are developing a lifespan approach by conducting epidemiological studies to evaluate risk factors that begin in pregnancy and early infancy and continue through young adulthood, midlife and older adulthood.

Our approach includes studies conducted in both high-income countries and LMICs where epidemiological transition offers a unique opportunity to study the occurrence of chronic disease and the associated risk factors related to rapid change in lifestyle.

Studies in high-resource settings (the EPIC project)

Over the last two years, NEP has ensured the cyclic endpoint and vital status update of the EPIC database, with the centralization of the most recent information on incident cancer events and on mortality from collaborating centres. Accordingly, new versions of project-specific databases were made available to the EPIC working group network, including the preparation of nested case-control datasets. The Group provided computing support to the Laboratory Information Management System (LIMS) for the retrieval of biological samples, in collaboration with the IARC Laboratory Services and Biobank Group.

NEP is active in several cancer site-specific EPIC working groups. For colorectal cancer, recent publications include: a study of blood levels of parathyroid hormone, which showed a positive risk association at very high levels, particularly among men (Fedirko *et al.*, 2011a); blood lipid and lipoprotein concentrations, which demonstrated that high concentrations of serum HDL are associated with a decreased risk of colon cancer (van Duijnhoven *et al.* 2011); metabolic syndrome (Aleksandrova *et al.*, 2011); plasma folate, B-vitamins and related genetic variants (Eussen *et al.*, 2010a; Eussen *et al.*, 2010b); C-reactive protein (Aleksandrova *et al.*, 2010) and biomarkers of oxidative stress (Leufkens *et al.*, in press). Also, research is ongoing to more fully assess the biologically plausible lifestyle, dietary, metabolic and genetic effect modifiers of the vitamin D–colorectal cancer (CRC) association. Furthermore, the Group has been collaborating on a vitamin D–CRC project within the Vitamin D Pooling Project Consortium, which is comprised of more than 15 cohort studies from around the world. Finally, NEP has extended its previous vitamin D work on colorectal cancer survival showing that higher vitamin D status before cancer diagnosis improves survival of patients with colorectal cancer, but selected genetic polymorphisms in the vitamin D pathway genes do not have an effect on survival and do not modify the inverse association with vitamin D.

In 2010, the Group received funding from the World Cancer Research Fund for a project to explore the role of advanced glycation end products, colonic barrier function and endotoxin exposure on risk of colorectal cancer. The project intends to combine biomarker measures and dietary/lifestyle data to perform pathway analyses for multiple determinants of colorectal cancer risk.

For liver cancer, biomarker and data analyses are ongoing for several studies exploring dietary, lifestyle and hormonal determinants of risk. The Group is leading the analyses on dietary factors (e.g. glycemic index, glycemic load, dietary fibre and red and processed meats) and nutritional biomarkers (e.g. total iron and ferritin) in relation to cancers of the liver, intra- and extra-hepatic bile ducts and gallbladder. They are also contributing to the ongoing analyses on causes and the burden of hepatocellular carcinoma (HCC) (Trichopoulos *et al.*, in press), the role of obesity and hormones in the development of HCC and identification of proteomic and metabolomic biomarkers of HCC.

Other recent NEP publications relate to gastric cancer (Balassiano *et al.*, 2011; Jakszyn *et al.*, 2011a; Sala *et al.*, 2011; Campa *et al.*, 2011a; Duell *et al.*, 2010; Eussen *et al.*, 2010c), prostate cancer (Campa *et al.*, 2011b; Price *et al.*, 2010), pancreatic cancer (Grote *et al.*, 2011; Chuang *et al.*, 2011; Petersen *et al.*, 2010), bladder cancer (Jakszyn *et al.*, 2011b; Büchner *et al.*, 2011), lung cancer (Johansson *et al.* 2010; Menvielle *et al.*, 2010), endometrial cancer (Dossus *et al.*, 2010; Allen *et al.*, 2010), ovarian cancer (Gram *et al.*, 2011), lymphoma (Neasham *et al.*, 2011) and all cancer sites (Elliott *et al.*, 2010; Boffetta *et al.*, 2010).

Breast cancer epidemiology in high- and low- and middle-income countries

Breast cancer is the most frequent cancer among women worldwide, with an estimated 1.38 million new cancer cases diagnosed in 2008 (10.9% of all cancers), and the most frequent cause of mortality in both developed and developing countries. Except for reproductive factors, little is known about lifestyle risk factors. In addition, few studies have focused on premenopausal breast cancer, which is associated with greater severity of disease and shorter survival.

NEP is focusing on studying breast cancer risk in both developed and developing countries. As part of the Breast Cancer Working Group of the EPIC Project, we have evaluated the role of specific nutrients in relation to breast cancer in both pre- and postmenopausal women, in particular the role of glycemic load and glycemic index (Romieu, submitted) and the role of fibre (Ferrari, submitted). Results suggest a role of the insulin pathway in the risk of breast cancer and a protective effect from fibre on breast cancer risk. We are currently evaluating the role of folate and its interaction with alcohol intake, specific gene polymorphisms and epigenetics. To provide integrated recommendations for breast cancer prevention, we are working on the development of a healthy lifestyle index using the large EPIC database (Ritte *et al.*, 2011; Key *et al.*, 2011; Campa *et al.* 2011b; Menvielle *et al.*, 2011; Campa *et al.*, 2010; Key *et al.*, 2010; Bakken *et al.*, 2011).

In LMICs, we are collaborating on the EsMaestras study, a large cohort study of Mexican teachers recruited in 12 Mexican states (close to 80 000 women), which was developed to investigate the role of lifestyle factors in relation to chronic disease in women, particularly breast and cervical cancer. In this population we observed a strong link between obesity and a diet rich in carbohydrates, sweet drinks and processed food (Romieu *et al.*, 2011a). We also observed a positive association between metabolic syndrome and breast density, a strong predictor of breast cancer among premenopausal women (Romieu *et al.*, 2011b). Further analyses are ongoing to determine the role of hormones, IGF1, IGFBP3, leptin, adiponectin, other cytokines and nutrient biomarkers in relation to breast density.

In a large, multicentre case-control study of breast cancer conducted in three states of Mexico, we explored the association of fatty acid (Chajes, submitted) and vitamin D (Fedirko, submitted), a nutrient with high prevalence of deficiency among Mexican women in relation to breast cancer. This work was developed in collaboration with the National Institute of Public Health (NISP) and the National Institute of Cancerology (INCAN) in Mexico and the Ministry of Health (Mexico).

Recently, we have initiated a multicountry study (Brazil, Chile, Colombia, Costa Rica and Mexico) of molecular subtypes of premenopausal breast cancer in Latin American women. The objective of the PRECAMA study is to evaluate the distribution of specific molecular cancer subtypes and identify the role and mechanisms of diet, physical activity, obesity and metabolic disorders in breast cancer incidence and survival. The pilot phase is ongoing. A similar project is planned in South Africa.

The role of early life exposure on later health events: Latin American Birth Cohort Consortium on Healthy Growth and Development

The role of fast nutritional transition and changes in lifestyle on children's growth and development, as observed in LMICs, is not well established. Early exposure to poor diet, a sedentary lifestyle, tobacco smoke and other environmental exposures can change infants' and children's growth pattern and may result in altered metabolism, obesity and risk of chronic disease in adulthood. The objectives of the Latin American Birth Consortium on Healthy Growth and Development are to combine Latin American birth cohorts from three major Latin American countries, Brazil, Chile and Mexico, to evaluate early life factors associated with optimal growth patterns and development and the prevention of obesity and metabolic disorders.

Obesity is a global epidemic and an increasing number of children are affected, which is often associated with co-morbidities in childhood and adulthood. Worldwide, close to 42 million preschool children (under the age of five) are overweight or obese and 35 million of them are living in developing countries. One of the first activities of the consortium will be to explore the role of maternal anthropometry with the health and growth in offspring.

Gene-nutrient interactions

Exploration of gene-nutrient interactions is of interest to the Group. Recent activities include involvement in the Micronutrient Genomics Project, an international collaboration. Investigations are currently underway on body iron status, hemochromatosis gene mutations, the variation in the vitamin D receptor gene (Hughes *et al.*, 2011) and genes involved in the vitamin D signalling (grant application pending) and risk of colorectal cancer. The interaction of folate with alcohol and folate metabolism genes, particularly for breast cancer, is also an area of active study, as well as the role of nutrients on epigenetics (Teegarden D *et al.*, submitted).

Alcohol and cancer

The Group initiated, in collaboration with the French Direction Générale de la Santé, an exhaustive evaluation of the role of alcohol and tobacco on the incidence and mortality of cancer, cardiovascular disease and diabetes, using scientific evidence produced from EPIC.

NEP is participating in a collaborative effort to perform a comprehensive review and meta-analysis of alcohol consumption and risk of cancers, particularly those cancer sites for which collective information is still unavailable or insufficient. A particular focus for this effort is the effect of low-dose intakes of alcohol. A recent publication from this project shows an increased risk of colorectal cancer for consumption of >1 drink per day (Fedirko *et al.*, 2011b). Also, the Group has contributed to the preparation of manuscripts on alcohol consumption and lung cancer in never smokers (Bagnardi *et al.*, 2011), oesophageal squamous cell carcinoma (Islami *et al.*, 2011; Rota *et al.*, 2010) and laryngeal cancer (Islami *et al.*, 2010), and on the effects of low-dose alcohol consumption (≤ 1 drink/day) on all cancer sites (Bagnardi *et al.*, submitted).

The Group was also involved in a project based on the EPIC study on the attributable burden of alcohol consumption on cancer risk. It showed that alcohol is responsible for a large proportion of cancers in Europe (Schütze *et al.*, 2011).

Determinants of healthy ageing

The Group leads the cancer-specific 'work package' as a partner in the European project entitled Consortium on Health and Ageing Network of Cohorts in Europe and the United States (CHANCES). The project brings together 13 international cohorts and aims to conduct pooled analyses of risk determinants for various diseases of aging, particularly cancer risk and survival in elderly populations.

Nutritional metabolomics

Recently, NEP suggested that metabolomics could play a key role in future assessments of novel biomarkers of dietary intake (Primrose *et al.*, 2011; Chadeau-Hyam *et al.*, 2011; Jenab *et al.*, 2009a). We are leading a collaboration to explore metabolomic profiles specific to dietary patterns and lifestyle habits. The Group is also involved in conducting nested case-control studies of NMR metabolomic analyses for pancreatic and liver cancers, in collaboration with a leading center, the European Center for High Field NMR in Lyon, France (http://www.ens-lyon.fr/crmn/crmn/index.html).

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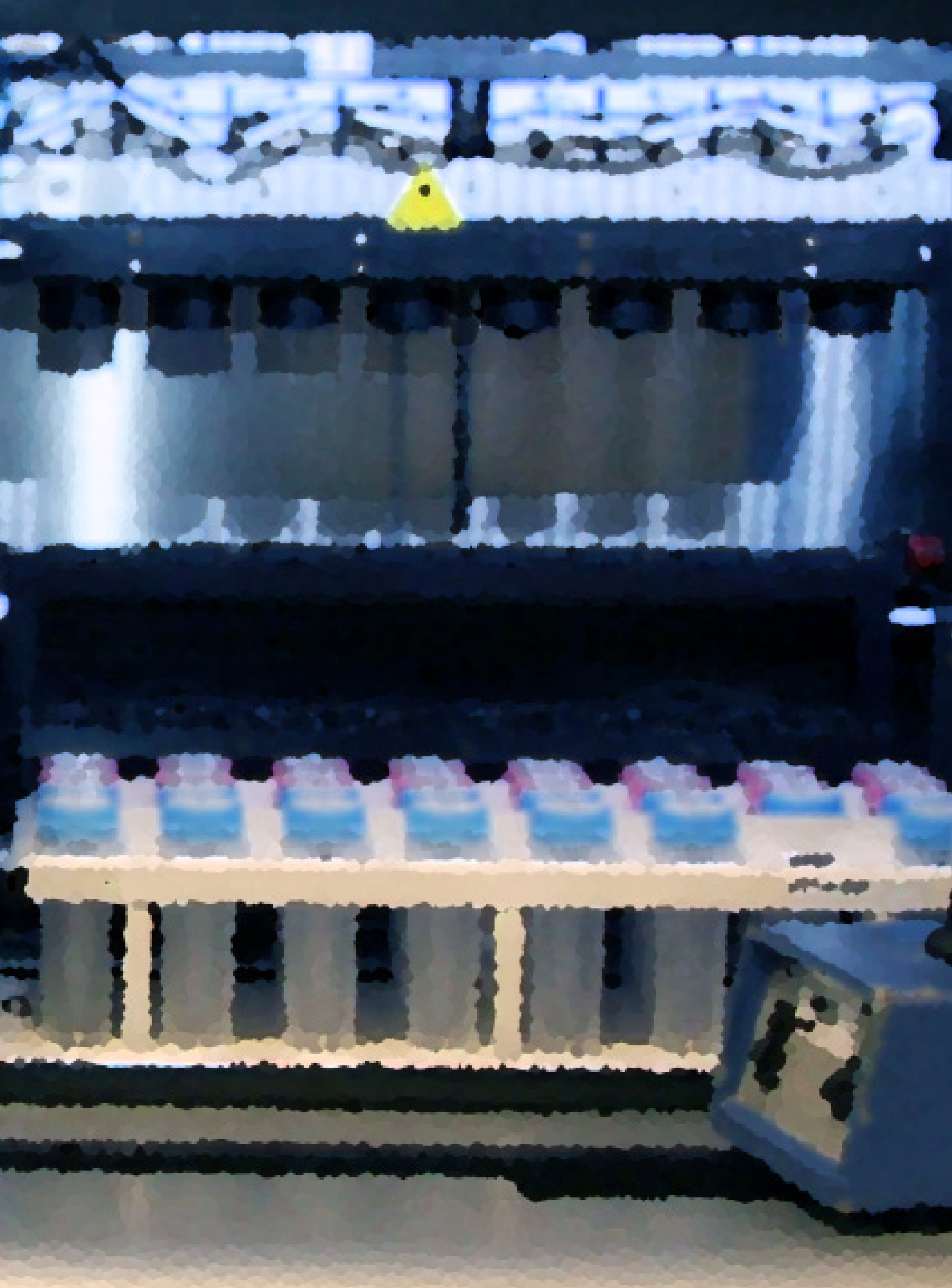

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The Biomarkers Group (BMA) was created in 2010. The major objective of the BMA is to identify new biomarkers of dietary exposure, food contaminants, environmental toxicants and hormones and metabolism, and to apply them to large cohort and case-control studies in relation to cancer risk, as well as to small-scale interventions in humans. The Group will work closely with DEX and NEP. This approach will allow a better understanding of the mechanisms/metabolic pathways by which diet, contaminants and hormones affect cancer and intermediate endpoints.

Two major approaches are in place to attain these goals:

1. Development of new analytical methods to characterize the human metabolome

The human metabolome (all small molecules contained in a biological sample) carries considerable information that reflects the physiology of an individual. Recent progress in analytical techniques allows one to capture an increasing amount of this information.

Within the Group, high-throughput and highly sensitive methods, including mass spectrometry and immunological methods, have been developed to discover, validate and implement biomarkers of dietary and environmental exposure, physical activity and physiological status. These methods can be specific for a compound. During this biennium, we have developed a reference method for the analysis of Bisphenol A, a major endocrine disruptor among food contaminants. The method has been validated on blood cord samples in collaboration with the Hôpital Neurocardiologique, Bron (Harthe *et al*, submitted).

Special emphasis is given to metabolomics, a powerful and innovative approach able to measure hundreds of metabolites in human biospecimens. Such an approach, only recently applied to molecular epidemiology in metabolome-wide association studies, will contribute to our understanding of the role of diet and lifestyle on cancer risk. A new in-house research capacity has been set up with the acquisition of two highly sensitive mass spectrometers coupled with liquid chromatography (LC-MS) and a new generation gas chromatograph (GC), which is used to characterize and quantify large sets of molecules from complex families, like fatty acids or polyphenols.

Targeted metabolomics is applied to the quantification of specific portions of the metabolome such as dietary polyphenols, major antioxidants of the diet with over 400 compounds known in various foods, or phthalates also known for their large structural diversity. Fractions of the metabolome sharing a similar functionality (e.g. phenols, carboxylic acids or amines) are labelled with deuterated or 13C-labelled reagents to form characteristic derivatives. The formation of such derivatives (metabolite coding) greatly improves sensitivity, selectivity and reduces analytical variability for quantification of compounds often present in trace amounts. These methods are developed in collaboration with the Service Central d'Analyse, Solaize, Lyon (CNRS) and the Chemistry Department of the University of Alberta. They are applied to samples of low volume (a few uL) compatible with cohort studies, where sample volume is often a limiting factor. A GC methodology has been developed and validated in collaboration with the Institut Gustave Roussy for the separation and quantification of 60 fatty acids, including 12 trans fatty acid isomers, some of them are being validated as biomarkers of industrially processed foods (Chajès *et al*, in press, 2011a).

Non-targeted metabolomics is used for biomarker discovery. Metabolic fingerprints obtained by high-resolution mass spectrometry in subjects differing in their lifestyle or diet, are compared by multivariate statistics to identify biomarkers characteristic of a specific food or diet. These methods are applied to the identification of novel biomarkers of food intake or environmental exposure in collaboration with the University of Alberta (Department of Computing Science), Imperial College London, INRA Clermont-Ferrand and University College Dublin.

2. Implementation of biomarkers in cohort studies

Biomarkers have been implemented to explore associations with cancer risk in a few particularly relevant areas:

Fatty acids and cancer. New associations between specific fatty acid profiles and the risk of gastric cancer (Chajès *et al*, 2011b) and breast cancer (Chajès *et a*l, 2011c) have been revealed. The gas chromatography has been improved and sixty fatty acids from plasma phospholipids have been identified and quantified in the EPIC study. The Group is currently undertaking a large nested case-control study (5000 breast cancer cases), in collaboration with the Lipidomic Platform from the Institut Gustave Roussy, to investigate associations between biomarkers of exposure to dietary trans fatty acids characteristic of industrially processed foods and dietary trans fatty acids characteristic of ruminant-derived foods, along with other fatty acids from the lipidome, and breast cancer risk within the EPIC cohort.

Several studies on the association between fatty acid biomarkers and cancer risk are ongoing within both the EPIC cohort and the Mexican EsMaestras and CAMA cohorts. The goal is to better understand interactions between fatty acids with specific gene and pathways in relation to gene methylation and cancer outcomes.

Hormones and cancer. The BMA has vast experience investigating hormones as risk factors for various cancers. Over the last biennium, the activities of the Group have focused on the validation of commercially available assays for measurements of hormones (growth factors, sex steroids, c-peptide, adiponectin, leptin and thyroid hormones) for large-scale epidemiological studies. We have undertaken hormone analyses for different case-control studies nested within EPIC to characterize associations between endogenous hormones and cervical cancer risk (Rinaldi *et al.*, submitted) and between thyroid hormones and thyroid cancer risk. The BMA has also undertaken analyses of estrogens on samples from the New York University Women's Health study

and the Northern Sweden Health and Disease study within the framework of a collaborative project on breast cancer, and is currently initiating the analyses of several hormones on samples from the Mexican EsMaestras cohort for a project exploring the associations between hormone levels and breast density in women. The Group has a special interest in exploring the relationship between endogenous hormones (sex steroids, growth factors, insulin and cytokines) and environmental risk factors, including physical activity, in the EPIC cohort (manuscript in preparation).

The scientists of the Group are also involved in the activities of several cancer-related EPIC working groups (breast, ovary, endometrial) in close collaboration with NEP. We are coordinating the activities of the EPIC thyroid cancer working group (in collaboration with Dr. Silvia Franceschi, ICE), and leading a study on obesity, reproductive factors, thyroid hormones and thyroid cancer risk. The Group is also collaborating on case-control studies on breast cancer risk in women in Latin America and South Africa, led by NEP. For all these projects, the collection of different biospecimens (blood, urine, tumor tissues) and measurement of different biomarkers for nutritional, hormonal and metabolic status are foreseen, to improve the understanding of the mechanisms involved.

Polyphenols and cancer. Polyphenols are the most abundant antioxidants in the diet and are thought to play a role in cancer prevention. In collaboration with the University of Alberta and the University of Barcelona, the BMA has developed a comprehensive database on polyphenols in foods and their metabolites (Phenol-Explorer 2.0; Perez-Jimenez *et al.*, 2010b,c). In collaboration with NEP, a food composition table for polyphenols for the EPIC cohort has been constructed based on this data and is being used to study associations with cancer risk. Data on polyphenol metabolism is used to identify candidate biomarkers of exposure (Perez-Jimenez *et al.*, 2010a) which will be validated in the EPIC cross-sectional study.

Food metabolome. Over 20 000 chemical constituents have been described in foods. Ingested with food intake and absorbed through the gut barrier, they are present in blood and urine and form what we have called the food metabolome. A number of these metabolites reflect consumption of foods that may influence cancer risk. Over the last year, the Group has identified a specific fatty acid profile in pre-diagnostic plasma samples as a biomarker of both dietary fatty acids and fatty acid metabolism. In close collaboration with DEX, we have investigated new biomarkers of processed foods in a cross-sectional study nested in the EPIC cohort, and have identified plasmatic trans elaidic acid as a biomarker of highly processed foods (Chajès *et al*, in press, 2011a).

We also undertook, in collaboration with DEX, the construction of a new database on the food metabolome and on biomarkers of food intake. Applying metabolomics to the EPIC cross-sectional study, we will compare groups of consumers and non-consumers of various foods and identify characteristic biomarkers of consumption for these foods. These new biomarkers will be applied to large cohort studies to look for new associations with cancer risk.

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The overall goal of the Dietary Exposure Assessment Group (DEX), within the Nutrition and Metabolism Section (NME), is to improve the accuracy, understanding and interpretation of (changes in) dietary exposure in studies on diet and cancer and other intermediate diseases. This Group has a leading role in the development of standardized dietary assessment methodologies and in improving their integration in dietary monitoring and diet-disease analyses, particularly in international study settings.

Development of standardized dietary assessment methodologies

Great interest has been expressed for using the computerized 24-hour dietary recall method EPIC-Soft, initially developed as a reference calibration method within the EPIC study, in various other national and international nutritional studies. This justified further investments in its development and validation.

In the recently completed European Food Consumption Validation (EFCOVAL) project, EPIC-Soft was successfully adapted, further developed and validated on various aspects expected to fulfil specific needs of pan-European dietary monitoring and risk assessment (Slimani *et al.*; 2011, Crispim *et al.*, 2011, Huybrechts *et al.*, 2011). Figure 1 shows a typical interview screen of the food/recipe description and quantification step using EPIC-Soft. Figure 2 illustrates distributions of usual protein intake as estimated by an EPIC-Soft 24-hour recall interview and by biomarker measurements.

To respond to the need for wide dissemination of the EPIC-Soft application, while preserving its core concepts of standardization and integrity, a centralized web-based platform (EPIC-Soft Methodological Platform (EMP)) hosted at IARC is under development (the concept has been finalized and the technical implementation is ongoing). This comprehensive platform will provide full support to conduct international nutritional studies in Europe and elsewhere, using common tools and procedures to collect, control and handle dietary interview data.

Figure 1. Typical screen of a 24-hour recall interview of the food/recipe description and quantification step using EPIC-Soft

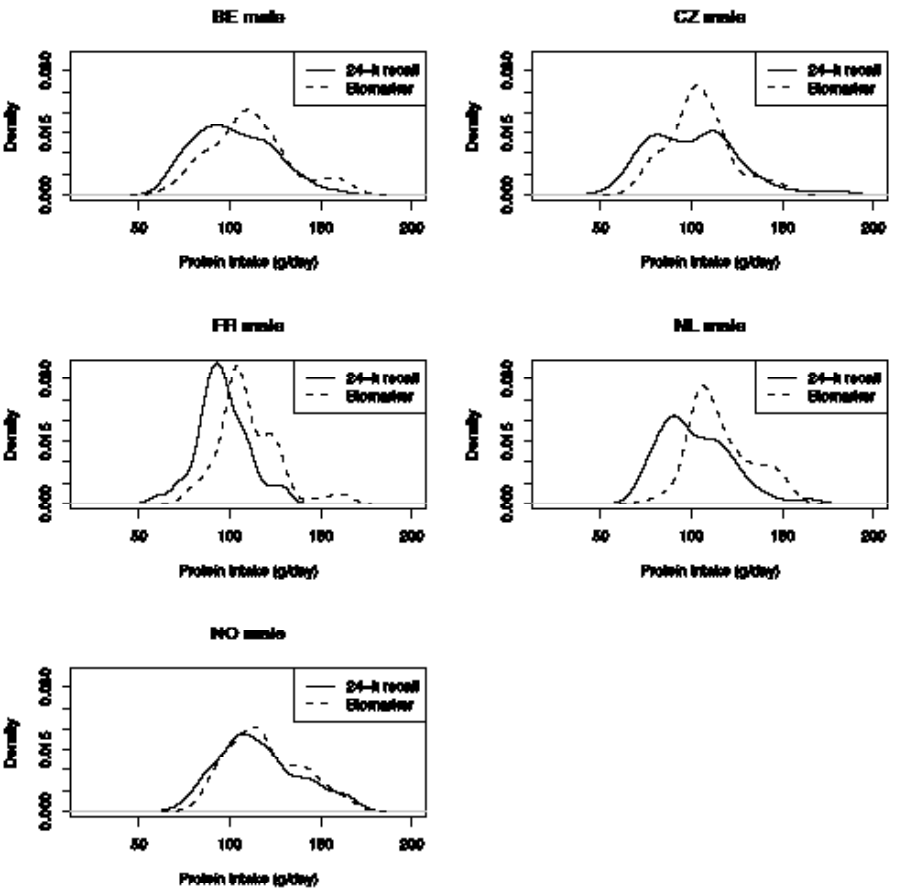

Figure 2. Estimated distribution of usual protein intake in men in the EFCOVAL study, based on two 24-hour dietary recall interviews (EPIC-Soft) and biomarkers for five European countries (BE, Belgium; CZ, the Czech Republic; FR, France; NL, the Netherlands; NO, Norway)

The decision by the European Food Safety Authority (EFSA) to launch the first pan-European monitoring survey, while recommending EPIC-Soft as the reference method to be used across the EU Member States, acknowledges the Group's methodological activities and endorses the recommendations and conclusions of the EFCOVAL project (http://www.efsa.europa.eu/en/press/news/datex100212.htm).

Additional related software has been successfully developed or is under development: (1) A data entry version of EPIC-Soft (PANCAKE project) has been created and is better suited and more user-friendly for data entry of repeated consecutive measures of food consumption collected by food diaries among children and the elderly. Currently, it is being tested in a pilot study in the Czech Republic and Belgium (manuscript in preparation); (2) The conceptual specifications of a new EMP module for matching food consumption data from EPIC-Soft with nutrient and other databases in international studies, is currently being developed by DEX within the EU-funded project EuroFIR Nexus.

DEX was also involved in the evaluation of measurement properties of dietary assessment tools (Illner *et al.*, 2011). A review paper of the applicability of new technologies in dietary assessment for large-scale epidemiological studies is in preparation.

The development of new dietary tools also includes the extension of the standardized EPIC Nutrient Databases (ENDB) developed by DEX (Slimani *et al.*, 2007). A new folate database has been compiled (manuscript in preparation) based on an in-depth inventory and evaluation of the available concentration data (Bouckaert *et al.*, 2011).

Studies on dietary exposure (including biomarkers of diet)

In collaboration with researchers within the NME, descriptive analyses have been completed or are ongoing related to dietary exposure, such as the first standardized comparison of dietary folate intake across 10 European countries (Park *et al.*, 2011) and dietary acrylamide exposure in the EPIC study (manuscript in preparation) and the related biomarkers including plasma fatty acids (Chajès *et al.*, 2011).

In the EFSA-funded EMP-PANEU project (Food Consumption Data Collection Methodology for the EU-Menu Survey), and in light of the future pan-European food consumption survey, DEX is currently implementing five country-specific versions of EPIC-Soft (Bulgaria, Finland, Hungary, Poland and Portugal). Furthermore, a new training module with e-learning components as a possible future part of the EMP platform will be tested.

Studies on diet and cancer and other (intermediate) chronic diseases

DEX is also involved in projects concerning the role of diet and biomarkers of diet in relation to cancer (EPIC) and other chronic diseases, such as obesity and diabetes (EPIC-PANACEA, INTERACT projects). A particular focus is on industrial foods (industrial trans fatty acids, acrylamide, excess energy consumption and glycemic index/glycemic load dense foods). This work is in collaboration with other researchers from the NME. Within the EPIC-PANACEA project on obesity and lifestyle factors, DEX is coordinating published findings on the relationship between diets rich in foods with high glycemic index/glycemic load and plasma fatty acids and obesity (Huybrechts *et al.*, Chajes *et al.*, both in preparation), as well as a methodological work on underreporting among obese subjects using both dietary and biomarker data (Freisling *et al.*, 2011).

Development and application of new methodologies to analyse dietary patterns

One of the Group's new research interests is dietary pattern analyses - a promising approach for better depicting the complexity of diet and improving the understanding of its association with diseases, particularly cancer. DEX, in collaboration with researchers from other Sections (BST, NEP) and external partners, initiated a project on analysing nutrient and biological patterns in international studies with applications in colorectal cancer (ongoing grant), breast cancer (ongoing grant) and diabetes (INTERACT project). As a starting point of these activities, research has been published on the diversity of nutrient patterns in the EPIC study at a population level using a multidimensional graphical representation of the patterns (*Freisling *et al.*, 2010).

Goals and future projects

Already under discussion are two European projects which will make use of the improved EPIC-Soft methodology: the first pan-European monitoring survey involving the 27 Member States (direct institutional contract between EFSA and IARC to support its implementation already in place), and a second dietary measurement on a large subsample of the EPIC cohort. Using a common standardized methodology (EPIC-Soft) will provide a unique opportunity to bridge two major areas of nutritional surveillance (EU Menu project) and epidemiology (EPIC) in Europe, open new avenues for cancer and other research, and facilitate translation of scientific evidence into public health, policy and other actions.

Discussions have been initiated about developing versions of EPIC-Soft for Brazil, Mexico (Latin America) and South Korea, which would support new NME projects and provide greater insight on dietary changes in non-European countries and those countries undergoing nutritional transition.

Finally, an ambitious project ('Nutrition and physical (in)activity as determinants of cancer risk in Africa: data for formulating new research strategies and targeted regional prevention guidelines'), funded by IARC's Fellowship Programme, will commence with the arrival of Dr Pisa (postdoctoral fellow). This project aims to perform an unprecedented inventory of the current available data related to nutritional cancer research in Africa. It will consider crucial methodological and logistical aspects (e.g. available/needed dietary and physical activity assessment methodologies, cancer prevention guidelines and cancer registries). This evaluation is expected to create opportunities to support and develop further nutritional and cancer research activities in African countries.

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Publications

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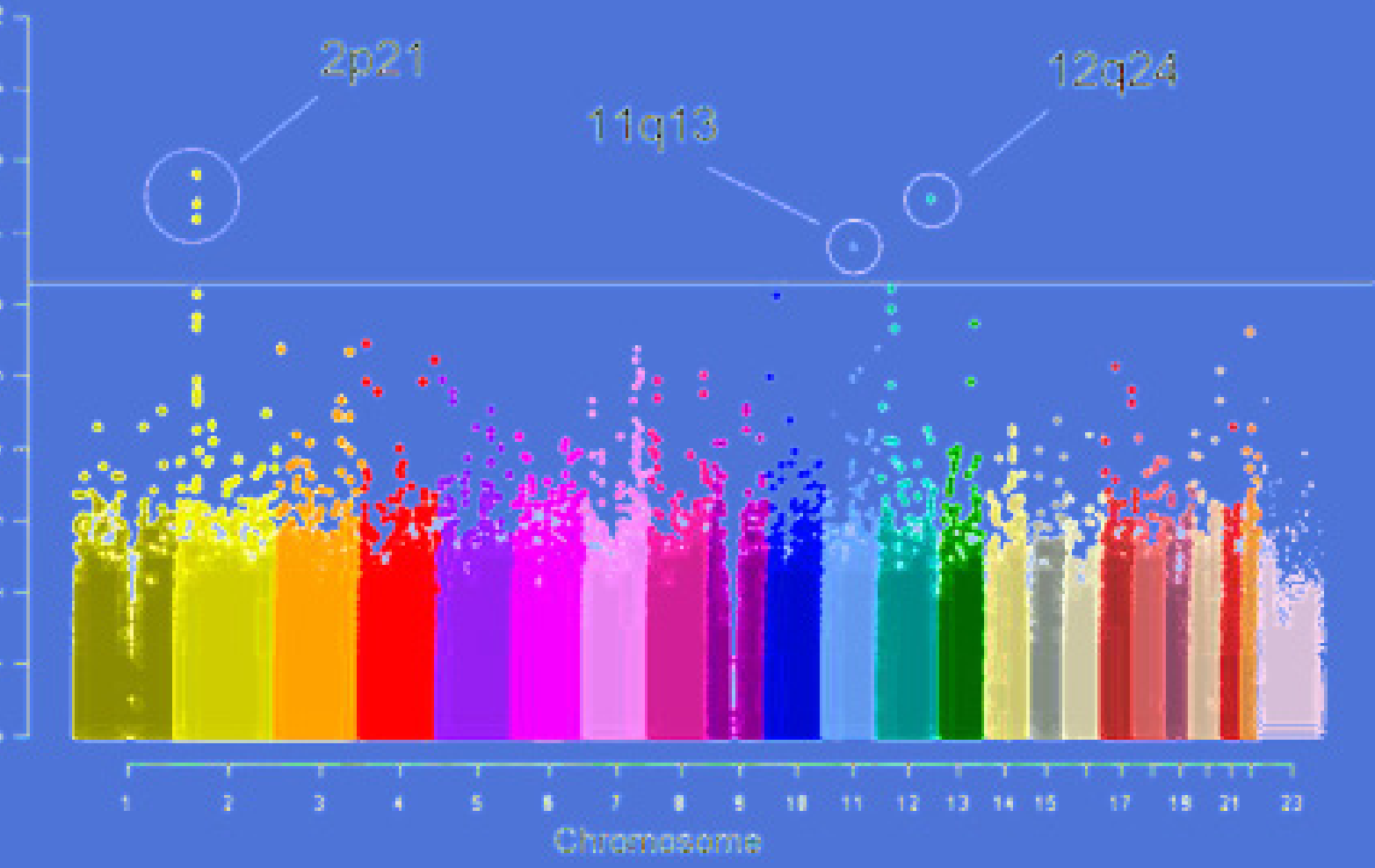
Section of Genetics

Section head
Dr Paul Brennan

Identifying specific genes and gene variants that contribute to the development of cancer will offer a greater understanding of biological pathways that lead to cancer, help elucidate how environmental factors may exert their effects in combination with genes, and aid in identifying individuals who are at high enough risk to benefit from existing risk reduction strategies. The Section of Genetics (GEN) comprises the Genetic Epidemiology Group (GEP), the Genetic Cancer Susceptibility Group (GCS) and the Biostatistics Group (BST), all with the overall mission of identifying genes involved in cancer, characterizing the spectrum of pathogenic sequence variants that they harbor, and understanding how they interact with non-genetic factors.

GEN projects usually involve extensive field work in collaboration with external investigators, so that large-scale epidemiological studies with appropriate clinical and biosample collections can be developed. The primary interest of GEN is the analysis and identification of common genetic susceptibility variants and their interaction with non-genetic risk factors. Genetic analysis comprises either candidate gene type studies (conducted in-house) or genome-wide association studies (GWAS) (currently conducted in collaboration with outside partners, although now also feasible in-house). GEP studies also assess non-genetic exposures, partly in recognition of the importance of non-genetic factors in driving cancer incidence, and also in order to facilitate accurate assessment of gene-environment interactions. By contrast, GCS has a focus on identification of uncommon or rare genetic variants that may have a larger effect than common single nucleotide polymorphisms (SNPs), but that are not sufficiently frequent to be captured by current GWAS genotyping arrays. Such DNA variants are identifiable through a case-control mutation screening approach. To this end, GCS has developed an in silico-driven strategy to stratify variants according to their probability of being pathogenic. Thus, the GCS research programme complements that of GEP, and also provides a facility for bioinformatics prediction on functionality of genetic variants, as well as a capacity to conduct in vitro experiments to validate functional hypotheses on variants of interest that are identified in both groups. In parallel to its own research activities, GCS also maintains and develops the genetic services platform (GSP) and related Laboratory Information Management System (LIMS) to support GEN large-scale molecular epidemiology projects and other IARC genomics projects. BST interacts at all stages to provide overall statistical support.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Chromosome

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The overall goal of the Genetic Epidemiology Group (GEP) is to identify genetic susceptibility variants of various cancer sites and study their interaction with environmental factors. An additional aim is to develop accurate risk prediction models that take both demographic information (e.g. age and sex) and biomarkers (genetic and non-genetic) into account. GEP focuses specifically on cancers related to tobacco and alcohol consumption, as well as rare cancers (e.g. nasopharyngeal cancer (NPC)). Many activities typically involve field work in order to recruit large numbers of cases and controls that have extensive questionnaire information and biological samples. For young onset cancers (such as NPC and childhood cancers) a trio design is also employed. Genetic analyses usually include a genome-wide approach initially, with subsequent large-scale coordinated replication studies in diverse populations. The latter is achieved by the development of international consortia in which GEP takes a leading role. Confirmed susceptibility loci are investigated in more detail with a variety of techniques, including *in silico*, expression and sequencing studies, often conducted in collaboration with other IARC groups. In addition to studies of genetic factors, GEP is conducting a wide range of investigations involving non-genetic factors, including evaluations of circulating biomarkers, such as human papillomavirus (HPV) antibodies, for head and neck cancers; cotinine for lung cancer; and dietary biomarkers for multiple cancers. GEP also performs extensive evaluations of questionnaire data, particularly data that have been collected during field work.

Genetic susceptibility of renal cell carcinoma

The primary GWAS conducted in 2010-2011 was a joint collaboration between IARC and the Centre National de Génotypage (CNG) and focused on renal cell carcinoma (RCC). Based on a series of studies, including a large case-control study from central Europe coordinated by GEP scientists (1400 cases and 2500 controls), the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study (300 cases and 400 controls), and an additional three studies, the final dataset comprised approximately 2500 cases and 5000 controls. This data was combined with a parallel study coordinated by scientists at the US National Cancer Institute (NCI) (principally Stephen Chanock and Nat Rothman) with approximately 1300 cases and 3400 controls. A combined dataset of approximately 3800 cases and 7400 controls using standardized quality control thresholds and common variable definitions was developed, with coordinated analysis at both IARC and NCI. Further IARC samples for replication, which included 3000 cases and 5000 controls, were also incorporated. This study has resulted in the identification of three novel susceptibility loci for RCC, one of which, *EPAS1* on 2p21, encodes hypoxia-inducible- factor-2 alpha, a transcription factor previously implicated in RCC development (Purdue *et al*., 2011). This finding was notable in former and current smokers but not in non-smokers, suggesting an interaction with smoking (P heterogeneity = 0.004) (Figure 1). This observation raises the possibility that the effect of EPAS1 is dependent on tobacco smoking.

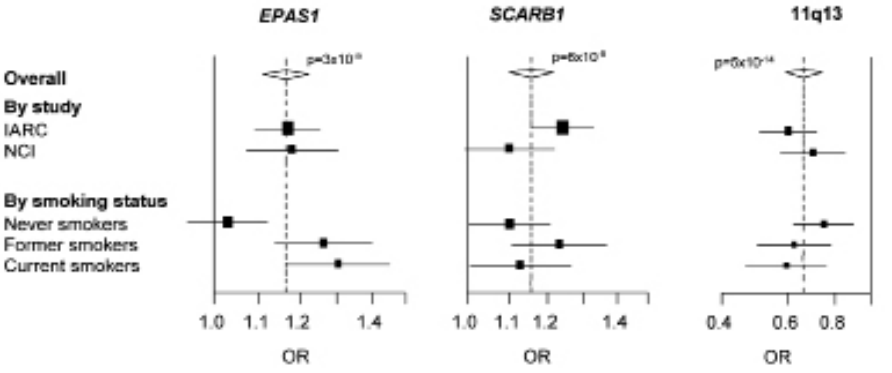

Figure 1. Forest plot shows odds ratios (OR) for three SNPs that were identified as susceptibility variants of renal cell carcinoma, overall and stratified by study and smoking status.

Genetic susceptibility for tobacco and alcohol related cancers

In 2010, we completed a GWAS of head and neck cancers, again in collaboration with the CNG. This involved an initial genome-wide analysis of over 2000 cases and a combined group of 8000 controls from IARC studies. Replication of 20 variants was conducted in a series of 13 independent studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Initial results further confirmed evidence for an important role of *ADH* genes in these cancers, as well as evidence for two additional susceptibility loci in regions 4p21 and 12q24 (McKay *et al*., 2011)

Genetic susceptibility to lymphomas

GEP is additionally investigating genetic susceptibility to lymphomas. Within our ongoing collaboration with the CNG, GEP is performing a GWAS of 1200 Hodgkin's lymphoma case-control pairs from eight European countries. Genome-wide genotyping and initial statistical analysis has been completed and multiple independent variants across 6p21 have been identified, two of which were specific for EBV status. An additional novel locus located within the IL13 gene was also identified, suggesting common genetic pathways with other immune-related phenotypes (Urayama *et al*., in press)

Lung cancer and non-genetic risk factors

Numerous studies have reported that fruits and vegetables are protective against lung cancer, and that the one-carbon metabolism pathway (i.e. folate pathway) has been suggested as a mechanism responsible for this protective effect. In order to investigate this hypothesis we analysed serum samples from 900 cases of lung cancer and 1800 matched controls that were collected prospectively within the EPIC cohort of 500 000 European subjects. Serum samples for all subjects, taken on average five years prior to diagnosis among the cases, were analysed for four B vitamins (B2, B6, folate and B12), methionine and homocysteine. After accounting for smoking, a substantial lower risk for lung cancer was seen for

elevated serum levels of B6, as well as for serum methionine. These associations were of sufficient statistical strength to exclude chance as explanation. Similar and consistent decreases in risk were observed in never, former and current smokers, indicating that results were not due to confounding by smoking. A lower risk was also seen for serum folate, although this was only apparent in former and current smokers. When participants were classified by median levels of serum methionine and B6, subjects with above median levels of both had an almost 60% lower lung cancer risk overall. Cumulative lung cancer risk calculations by smoking status and stratified by B6 and methionine levels, indicated important differences in risk associated with having above or below median levels of both vitamin B6 and methionine (Figure 2).

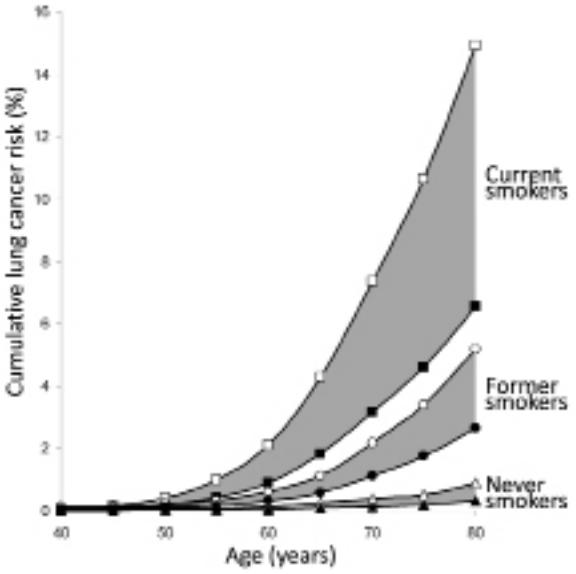

Figure 2. Cumulative risks of lung cancer up to age 79 among never, former and current smokers, stratified for men, and for having above (high/high) and below (low/low) median levels of both vitamin B6 and methionine, respectively.

International study of rare childhood embryonal tumours

Following a meeting held in IARC in 2006 of investigators with an interest in childhood cancers, a large-scale etiological study of rare childhood cancers was piloted in eight countries in 2008-2010 (France, UK, Canada, Australia, Canada, USA, Serbia, Macedonia and Czech Republic). A case-control trio design has been shown to be feasible in all countries participating in the pilot, and five additional countries (Brazil, Japan, India, the Netherlands and El Salvador) may start piloting the protocol in 2011. The aim of the International Study of Rare Childhood Embryonal Tumours (ISET) is to investigate the role of exposure to suspected factors at different key periods at the beginning of life (preconceptional, prenatal and postnatal), as well as genetic susceptibility factors, gene-environment interactions and novel molecular markers. Focusing on Wilms tumour and neuroblastoma, already more than 250 case trios and 1750 unrelated controls have been recruited, with approximately 650 and 450 case trios expected each year, respectively. The full scale study will expand to retinoblastoma, rhabdomyosarcoma and hepatoblastoma.

Priorities for 2012-2013

Genetics and genomics of renal cell carcinoma

GEP will continue to have a central role in the CAGEKID study, which is funded by the European Commission to conduct whole genome sequencing on tumour/non-tumour DNA pairs from at least 100 individuals with kidney cancer. On completion of sequencing, we will join other CAGEKID partners in a comprehensive evaluation of the germline and somatic variation that contributes to risk of RCC. This will be complemented by an examination of gene expression and epigenetic changes. GEP will ensure the availability of at least 100 RCC cases that correspond to the International Cancer Genome Consortium's criteria for full participation in the CAGEKID study, comprising whole genome sequencing and expression analysis of tumour/non-tumour pairs. Further, and in collaboration with colleagues at NCI, we will expand our GWAS of RCC to approximately 8000 cases and 16 000 controls. Funds for this expanded analysis have been provided by NCI.

Lung cancer genetics

Genome-wide data is available on over 15 000 lung cancer cases and 25 000 controls from eight different study groups (with IARC studies contributing about 25% of data). Initial meta-analysis of the majority of these studies has not identified any additional susceptibility loci beyond the three previously reported (5p15, 6p21 and 15q25), although limited subgroup analyses from individual studies has detected heterogeneity of effects for all three loci (by histology for 5p15, by smoking status for 15q25, and by geographic region for 6p21). It is therefore reasonable to expect that a coordinated analysis by subgroup may identify additional susceptibility loci in addition to those previously detected. In collaboration with others, we will carry out a stratified meta-analysis of all studies with a particular focus on identifying subgroup effects by histology, smoking status, family history, age, sex and stage of disease.

Head and neck cancers and human papillomavirus

Further analyses of the role of human papillomavirus (HPV) in head and neck cancers, and potential genetic modifiers, will include a coordinated analysis of the presence of HPV antibodies in pre-diagnostic blood samples within the EPIC cohort, with this being potentially expanded to other cohorts through the cohort consortium. This initiative is being led by GEP scientists along with scientists at NCI (Dr A Kraemer in the

Division of Cancer Epidemiology and Genetics). We will also evaluate the strong geographic differences in HPV prevalence in head and neck cancers by coordinating an analysis of HPV in a large series of samples from Europe, the US and Brazil.

A comprehensive evaluation of the one-carbon metabolism pathway in tobacco-related cancers

We plan to further evaluate the associations of B vitamins with lung cancer risk and risk prediction by initiating a consortium of prospective cohort studies within different populations from Europe, the US, Australia and Asia. The overall aims are to identify the consistency of these associations in different populations, the extent to which they are modified by measurement errors and day-to-day variations in vitamin status, and determine whether analyses of genes found to be associated with these biomarkers provide evidence of causality. In addition, we will assess the potential of using circulating biomarkers in lung cancer risk prediction models. These goals will be achieved by developing a Lung Cancer Cohort Consortium which will include biochemical analysis of at least 5000 lung cancer cases and comparable controls selected from over 20 participating cohorts, with equal proportions of never, former and current smokers. Funds to develop this consortium and to perform these analyses have been provided by the National Cancer Institute of the United States.

We will also extend this analysis to other types of cancer related to tobacco in order to test whether these associations are specific to lung cancer. Our immediate aim is to examine the role of B vitamins in head and neck cancers and RCC. This will initially be assessed within the EPIC cohort (approximately 500 case-control pairs for each cancer type) and may be extended to the cohort consortium based on initial results. These analyses within EPIC will be coordinated with our ongoing GWAS for both cancer types, thereby resulting in a large series of subjects with both genome-wide data and B vitamin measurements. Funds for this analysis have been provided by the World Cancer Research Fund.

Genetic epidemiology of nasopharyngeal cancer

In the short-term, we plan to complete the biorepository of 2000 nasopharyngeal cancer (NPC) cases and controls from the ongoing studies in Singapore, Thailand and Malaysia. Subsequently, we will initiate the evaluation of susceptibility loci that have been identified in Chinese GWAS in order to determine their repeatability in other Asian populations.

Large population cohorts

GEP will continue to coordinate two large population cohorts that were initiated by GEP and other non-IARC scientists. These include a prospective cohort of 200 000 adults from three cities of Siberia Russia (being conducted with the Cancer Research Centre, Moscow; and the Clinical Trials Services Unit, Oxford, UK). Analysis will focus on the role of alcohol on all causes of mortality. Also being investigated is the Golestan Cohort study of 50 000 individuals from Northeastern Iran, being conducted with colleagues from Tehran and NCI. GEP's analysis will focus on the effects of opium, obesity and hypertension on all causes and cause-specific mortality.

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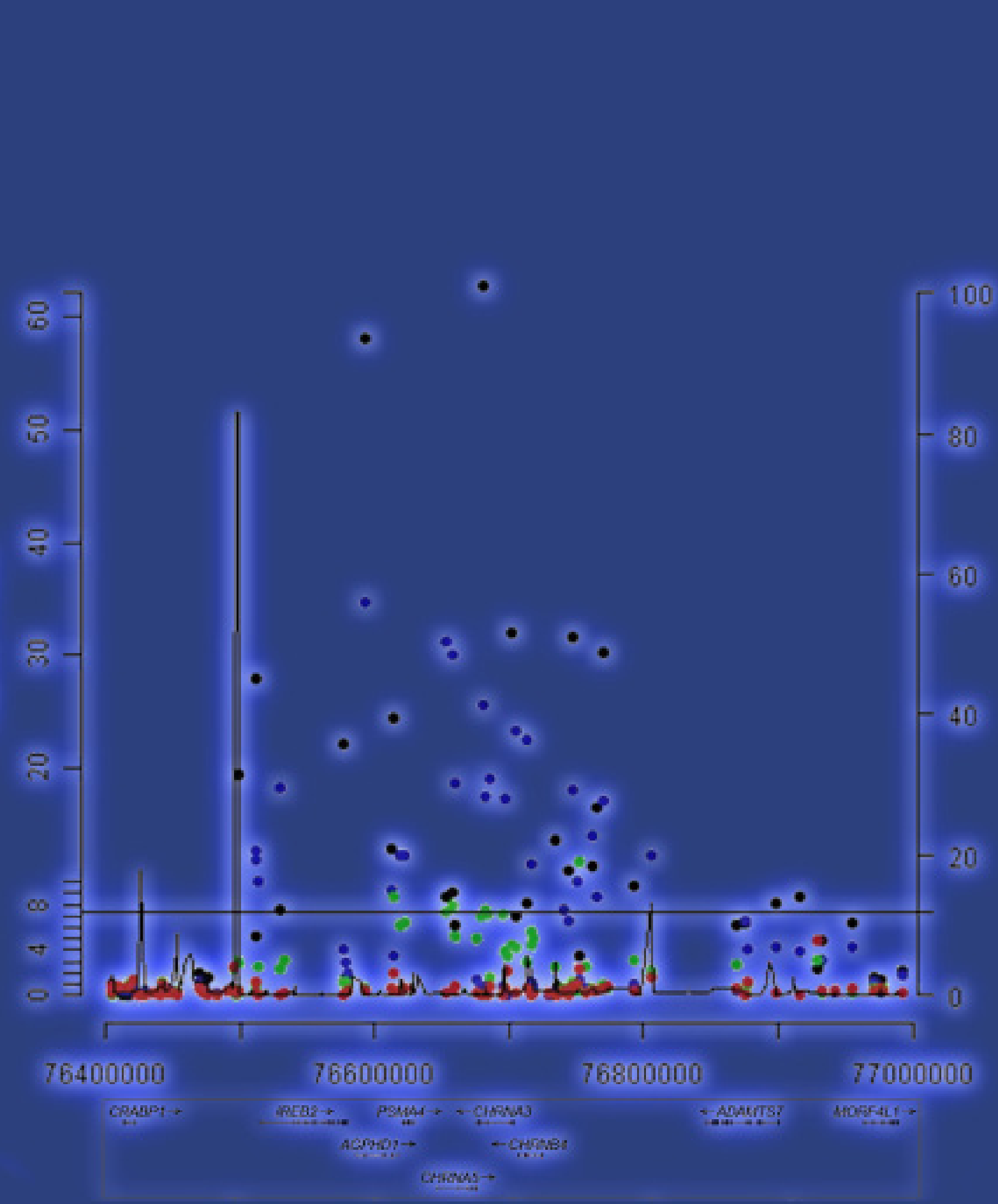
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The focus of the Genetic Cancer Susceptibility Group (GCS) is to investigate the contribution of inherited genetic factors to the etiology of cancer. An integrative approach is used, applying a variety of genomics-based techniques, including genotyping, mutation screening and expression studies, coupled with bioinformatics analysis, to both family- and case-control-based study designs. Of particular interest is the contribution of variants with a relatively rare population frequency, although we remain involved with studies of common SNPs through our collaboration with GEP. GCS also maintains and develops the Genetic Services Platform (GSP) and related Laboratory Information Management System (LIMS) to support genomics-based projects within the GEN section, as well as other IARC genomics groups.

Investigation of common and rare genetic variants in breast cancer susceptibility genes

GCS aims to measure the genetic risk attributable to the different types of genetic variation in breast cancer. These projects integrate data from case-control genotyping, case-control mutation screening, bioinformatics and allelic imbalance expression studies to identify dysfunctional variants responsible for cancer susceptibility, with a focus on breast cancer susceptibility genes and the characterization of new moderate- to high-risk susceptibility alleles.

Bioinformatics tools can quantify the functional consequence of the variants in silico using the degree of evolutionary conservation observed at this site. We have applied our case-control mutation screening approach to the breast cancer susceptibility genes *ATM* (Tavtigian *et al.*, 2008) and *CHEK2* (Le Calvez *et al.*, 2011) to demonstrate the efficiency of ranking rare missense substitutions using in silico programs before comparing the distribution and frequencies of the different types of variants in a series of early-onset breast cancer cases and controls. Although loss-of-function mutations in *ATM* and *CHEK2* have been associated with intermediate-risk of breast cancer, our strategy allowed us to demonstrate that a subset of rare missense substitutions make a comparable contribution to disease susceptibility.

Differential allelic expression in CHEK2 alleles

Differential allelic expression (DAE) occurs when two alleles of a particular gene are expressed unequally. DAE can result in quite major expression level differences between alleles, for example when a truncating mutation results in nonsense mediated mRNA decay or when more subtle differences in allele expression levels are due to a sequence variant in a regulatory element. Our initial DAE assay, based on high-resolution melting curve analysis and probes designed for a genetic marker located in the target gene's mRNA, has demonstrated DAE in lymphoblastoid cell line mRNA in heterozygote carriers of the c.1100delC truncating mutation in the *CHEK2* cancer susceptibility gene (Nguyen-Dumont *et al.*, 2010). We are now developing potentially more sensitive and higher throughput DAE tests by taking advantage of possibilities offered by the massive parallel technologies.

In collaboration with GEP, GCS has additionally provided genetic and analytical expertise for the completion of multiple genome-wide association studies (GWAS), notably, HNSCC (McKay *et al.*, 2011) and kidney cancers (Purdue *et al.*, 2011). We are actively pursuing GWAS of Hodgkin's lymphoma and cancers of the oral cavity. The Genetic Services Platform in GCS additionally plays an important role in GWAS by performing genotyping to quickly replicate and validate findings.

The Genetic Services Platform

Nested within the GCS, the Genetic Services Platform (GSP) aims to implement cutting edge genomics techniques and make them available to all IARC groups, along with relevant technical expertise and support. Genomics applications are piloted prior to implementation to ensure their suitability to IARC's large population-based studies. In 2010-2011, the GSP undertook eight pilot and 14 collaborative research projects using the set up platforms in collaboration with GEP, MOC, EGE, PAT, ICB and RAD.

In parallel, GSP has worked closely with ITS and MOC to develop a Sample Management System for IARC biobank to allow the efficient handling of the increasing number of biological samples hosted at IARC (Voegele *et al.*, 2010).

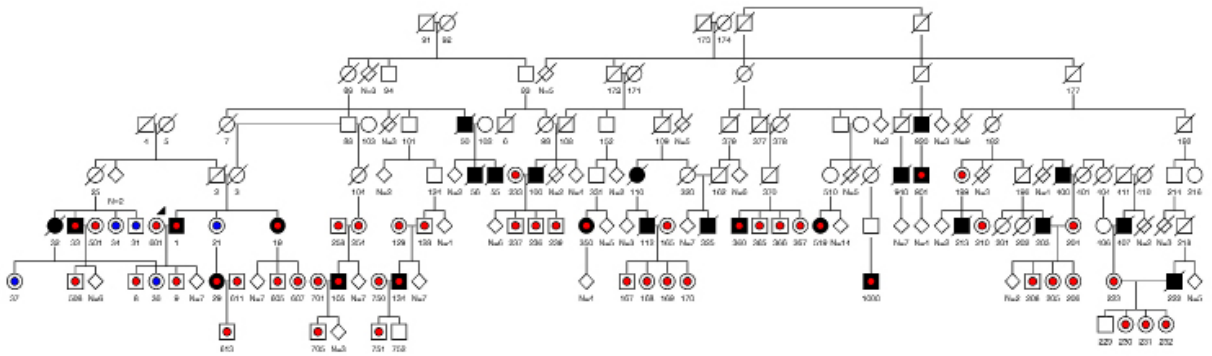
During 2011, the GSP also installed next generation sequencing (NGS) technology at IARC. A Life technologies 5500xl SOLiD next generation sequencer and a medium capacity Ion-Torrent personal genome machine have been installed and the associated workflows are currently being implemented under the umbrella of the GCS LIMS. We are now piloting a variety of NGS applications (particularly exome resequencing, RNAseq and methylation-related sequencing) with IARC scientists and technical staff. We have put in place a high-performance computing cluster and relevant software to enable analysis of large quantities of data produced by a NGS platform, as well as its long-term storage and backup. GCS bioinformaticians are developing bioinformatic workflows for the analysis of NGS data.

Projects from 2012-2013

Over the next few years, GCS will apply NGS to our projects. We will remain focused on describing genetic susceptibility, but we will also endeavor to use knowledge from the somatic events occurring during tumorigenesis, assayed using NGS and other genomics-based techniques, to inform our analysis of the germline events.

Genetic susceptibility to nasopharyngeal carcinoma

Isolated populations offer rare opportunities to investigate the genetic cause of human disease. We have identified one exceptionally large multiplex pedigree from the Bidayuh population where the incidence of nasopharyngeal carcinoma (NPC) is one of the highest in the world. Blood samples have been collected for 11 of the 26 NPC patients in this pedigree. We will use exome DNA sequencing to conduct a comprehensive genetic analysis to identify potential genes segregating in this pedigree. Through our collaboration with Dr Allan Hildesheim of the Division of Cancer Epidemiology and Genetics at NCI, who is conducting parallel efforts in Taiwanese NPC pedigrees, and further



Large extended Bidayuh pedigree from Sarawak, Borneo, Malaysia. Red dots indicate where blood samples have been collected

study in additional NPC patients at IARC, we will compare, contrast and cross validate results from this large pedigree.

Investigation of the Knudson's two-hit model in tumorigenesis

Many tumours resulting from a hereditary predisposition under Knudson's 'two-hit' genetic model contain one inherited mutant allele and the remaining allele is mutated somatically during tumorigenesis. The co-occurrence of germline and somatic mutations in the same gene in a given individual is a relatively rare event by chance alone. The observation of only a few dual mutation events will be sufficient to pinpoint a gene as noteworthy. We intend to perform whole exome sequencing of both the normal and tumour material of lung cancer patients with a positive family history, and use this data to identify genes acting along the lines of the two-hit model. Noteworthy genes can then be further investigated in broader/larger case-control studies to validate and further explore significant findings.

Investigation of common and rare genetic variants in melanoma susceptibility genes

Malignant melanoma is a rare tumour of melanocytes that, because of its aggressive nature, causes the majority of deaths related to skin cancer. The objective of this study is to identify new melanoma susceptibility genes and the characterization of the pathogenic sequence variants associated with increased risk of developing melanoma. We have set up a large-scale case-control mutation screening study nested in the EPIC cohort. Also in collaboration with Dr Françoise Clavel-Chapelon's group (INSERM U1018, Villejuif, France), we are investigating the relationship between genetic factors, pigmentary phenotype (sun exposure) and risk of cutaneous malignant melanoma (CMM) in the E3N prospective cohort. Results emerging from the association study in this cohort will complement findings from the case-control mutation screening study in EPIC, where dysfunctional variants will be sought in genes of the same pathways (pigmentation, nevi development).

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Publications

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Biostatistics Group (BST)

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(until April 2010)
Ms Marie Paturel (until July 2011)

Visiting scientist
Professor Nanny Wermuth

After moving to GEN in 2010, the Biostatistics Group (BST) has increased collaborations with the other GEN groups, while maintaining former collaborations and cross-agency activities. In particular, BST is responsible for the training and development of IARC's statistical personnel located in the various sections.

In silico functional classification

BST continues to collaborate with GCS on *in silico* functional classification, which has taken on new directions with the advent of next generation sequencing (NGS). While the now traditional genome-wide association studies (GWAS) have been successful in identifying many genetic features which predispose to various cancers, they have small individual effects and jointly explain only a small part of the familial clustering of all common cancers. It is possible that many of the remaining genetic variants are individually very rare, but occur in such variety that together they explain an important fraction of the heredity of cancer. Moreover, since the effects of individual variants are greater, they are more likely to provide insight into mechanisms of oncogenesis. However, their individual rarity precludes the use of standard genetic epidemiological techniques. It is necessary to first use other evidence, such as evolutionary variability between species, to classify these variants into categories of possibly similar effect. These categories can then reach population frequencies that allow them to be investigated by standard epidemiological methods. This approach has helped identify the importance of missense mutations in several genes for predicting the risk of breast cancer (Le Calvez-Kelm *et al.*, 2011; Southey *et al.*, 2010).

This project has two facets: supporting the adaptation of previously developed tools (AlignGVGD) to study the genetics of melanoma (with Dr Fabienne Lesueur); and investigating methods better adapted to high-throughput data generated by NGS.

Omics integration

Two key reasons BST moved to NGS are because of the extremely large number of genetic variables investigated (potentially every element of the genome), and the ability to obtain several complementary types of data (i.e. germline genotype, tissue genotype, tissue-specific RNA expression and high-density methylation data). The number of measured variables makes traditional case-control comparisons impractical because of the need for multiple comparisons correction. However, the variety of data types creates the possibility of novel approaches, such as using tissue-specific expression to localize areas of the genome likely to be active in that tissue, then examining these areas for GWAS.

Another option is the comparison of genomic and somatic modification. BST is collaborating with Dr James McKay to develop the statistical methodology to use matched comparisons within individuals to identify regions showing modification in both tumour and germline DNA, as would be expected under Knudson's two-hit hypothesis.

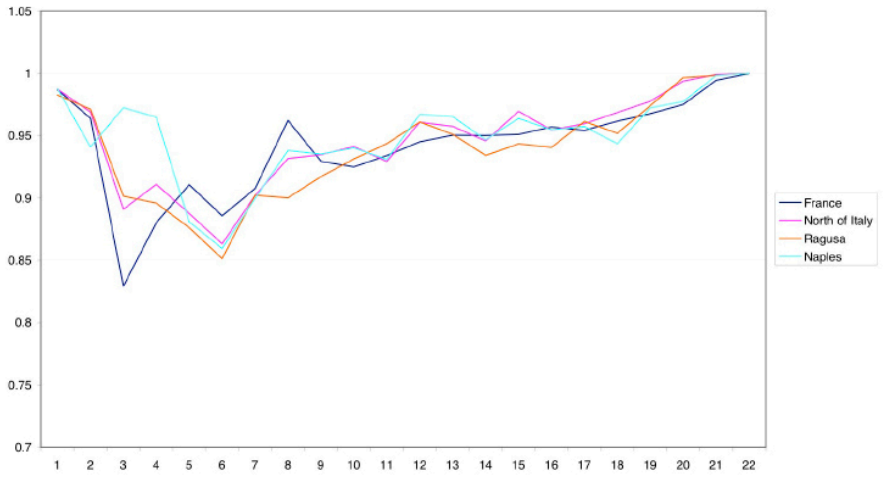

Figure 1. Cumulative explanation of variation in dietary patterns in EPIC by principal components, according to centre of recruitment

General biostatistics support

A common feature of most epidemiological research is that exposure data is approximate. This applies to questionnaires, self-reported smoking behaviour, estimated radiation exposures and imputed genotypes. In all cases, incorporating these noisy data into conventional regression analyses can result in biased estimates and inappropriate inferences. Hence, a core methodological interest is the development, evaluation and use of methods such as Markov Chain maximum likelihood and regression calibration. This underpins continued collaborations with the ENV, as well as within GEN (Timofeeva *et al.*, 2011).

BST also provides guidance on the use of traditional biostatistical tools, both within IARC and in outside collaborations (Hery *et al.*, 2010; Burgess *et al.*, 2011)

Statistical education and training

IARC has adopted a model of disseminated statistical support by dispersing individuals with differing levels of statistical training among the various sections. Encouraging development and sharing of statistical skills is therefore one of the responsibilities of BST.

Training is carried out through BST with the largest block of teaching taking place within the Introduction to Epidemiology Summer School. This course was also repeated in 2010 for IARC staff unable to attend as part of the Summer School and it was fully subscribed. In 2011, BST facilitated a course on the use of the statistical package R in epidemiology (coordinated by Dr Martyn Plummer, INF). Further courses and a seminar series are under development.

In addition, BST funding has been used to provide support for IARC staff to attend meetings specific to statistical methodology and to bring senior statisticians for short visits to give seminars and otherwise discuss advanced methodologies. Visitors in 2011 included Prof Per Kragh Andersen

from the University of Copenhagen and Dr Frank Dudbridge from the London School of Hygiene and Tropical Medicine. Other visits are planned and BST will host Prof Nanny Wermuth, a distinguished statistician, as a Senior Visiting Scientist in 2011-2012.

Priorities for 2012-13

Over the next two years, BST will continue the development and evaluation of methodological approaches both for genetic epidemiology, using the variety of data types available from IARC's recently acquired NGS capabilities, and for more general statistical issues in epidemiology. In parallel to this, it will be crucial to establish collaborations with external statisticians to complement the resources at IARC. Such collaborations will contribute to the development of a culture of cross-institutional cooperation on statistical work.

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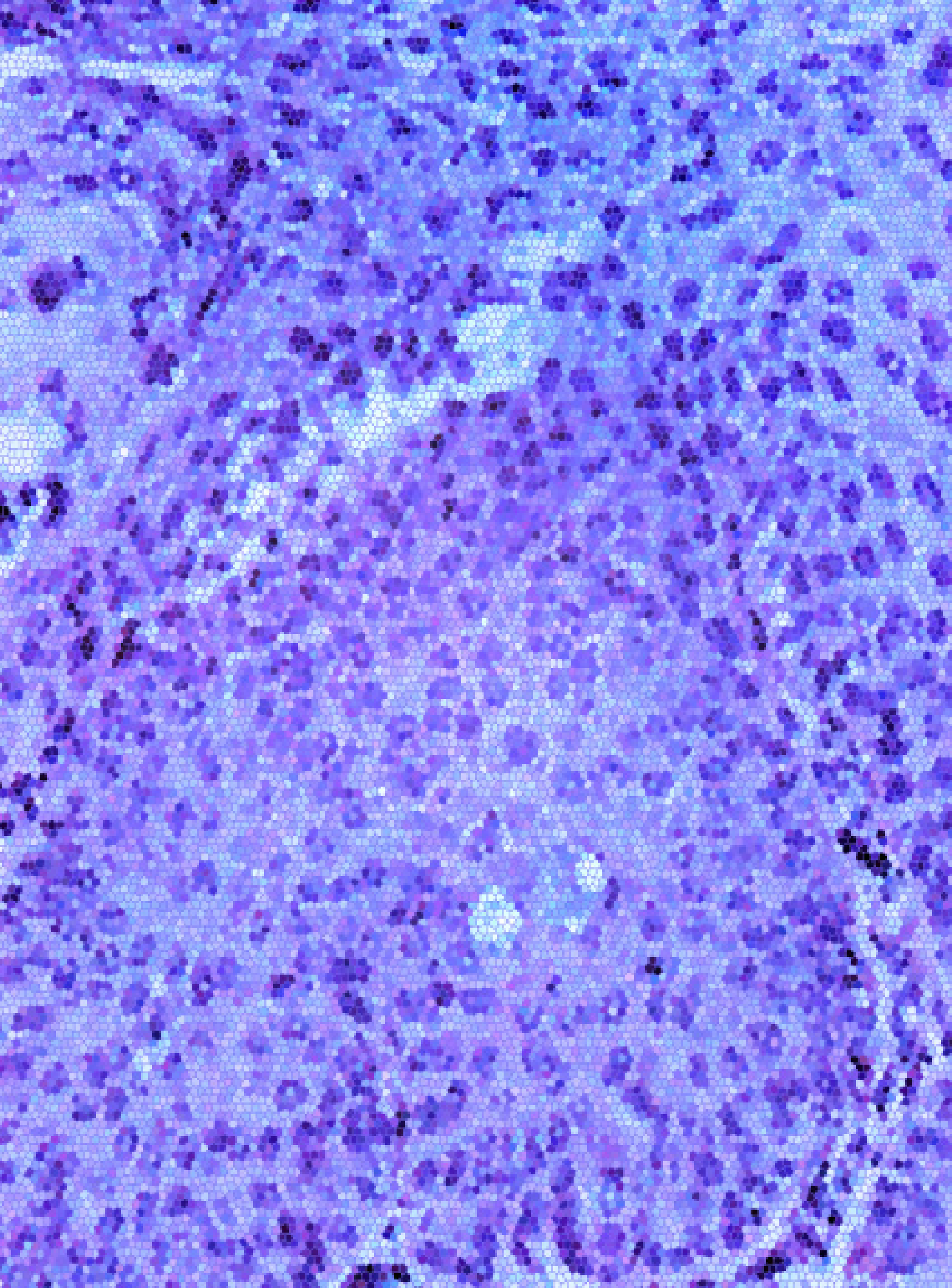
Section of Early Detection and Prevention (EDP)

Section head
Dr R. Sankaranarayanan

The Section of Early Detection and Prevention (EDP) conducts a range of studies to determine the feasibility, efficacy and cost-effectiveness of different primary and secondary prevention interventions for breast, cervical, colorectal and oral cancers in low- and middle-income countries, and to address quality assurance aspects of breast, cervical and colorectal cancer screening in national programmes conducted throughout the world. These studies aim to reduce cancer burden by prevention and screening and to reduce the wide disparities in the availability and access to affordable, quality-assured and effective early detection interventions around the world. Also addressed are the means by which the research activities can contribute to improving the capacity and infrastructure of health services to provide effective interventions.



Screening Group (SCR)

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Mr Eric Lucas

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Mr Jean-Marie Fayette
(until April 2011)
Ms Krittika Guinot
Dr Richard Muwonge

The objective of the Screening Group (SCR) is to guide the development of evidence-based public health policies for cancer screening and early diagnosis in a range of health care settings, particularly in low- and middle-income countries. This will lead to reduced burden of disease and improved quality of life and result in further development of health services and rational utilization of health care resources. To this end, our studies address the performance, efficacy, cost-effectiveness, harmful effects and quality assurance of different screening interventions for breast, cervical, oral and colorectal cancers in various health care settings, as well as the development of training resources in collaboration with national institutions in different countries.

Cervical cancer screening and prevention

Long-term follow-up of participants in the randomized trials of screening

To determine the long-term impact of a single round of human papillomavirus (HPV) screening, either by Pap smear or visual inspection with acetic acid (VIA), in preventing cervical cancer cases and deaths, around 210 000 women in the Dindigul and Osmanabad district screening trials in India have been followed-up. This has been achieved through linkage with population-based cancer registries, mortality registration systems and active follow-up by house visits. The 10-year follow-up results for the Osmanabad district cervical screening study are given in Table 1. There was a significant 35% reduction in cervical cancer mortality following a single HPV test as compared to the women receiving a single Pap smear; cervical cancer incidence following VIA was similar to that following cytology. Cervical cancer incidence in HPV-negative women was four times less than that of cytology-negative women, further indicating that HPV testing is a more effective approach than cytology in reducing cervical cancer burden (Table 2). The 11 year follow-up in the Dindigul district study indicates a 25% reduction in incidence and 27% reduction in cervical cancer mortality, documenting long-term protection following a single round of VIA screening in this cohort (Table 3 and

Table 1. Cervical cancer incidence and mortality during 2000-2009 using the cytology group as the reference in the Osmanabad District randomized controlled trial

Group	Cases	Person-yrs of follow-up (PYO)	Rate per 100 000 PYO	Hazard ratio (95% CI)
Incidence of all cervical cancer				
Cytology	162	311 480	52.0	1.00
HPV	147	332 150	44.3	0.85 (0.67 - 1.09)
VIA	181	331 360	54.6	1.05 (0.85 - 1.30)
Incidence of stage II or higher cervical cancer				
Cytology	62	311 480	19.9	1.00
HPV	46	332 150	13.8	0.70 (0.49 - 0.98)
VIA	98	331 360	29.6	1.49 (1.10 - 2.00)
Cervical cancer mortality				
Cytology	69	312 290	22.1	1.00
HPV	48	332 820	14.4	0.65 (0.47 - 0.91)
VIA	77	332 160	23.2	1.05 (0.79 - 1.39)

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

Table 2. Cervical cancer incidence during 2000-2009 among women screened HPV-negative at baseline in the Osmanabad District randomized controlled trial

Group	Cancer cases	Number of women	Incidence rate (per 100, 000 PYOs)	
			Crude	ASR
HPV	11	24 380	4.6	4.3
Cytology	27	23 762	11.6	15.0
VIA	40	23 032	17.7	20.1
Total	78	71 174	11.2	13.1

PYOs: person years of observation; ASR: age-standardized rate; HPV: human papillomavirus; VIA: visual inspection with acetic acid

Table 3. Cervical cancer incidence and mortality during 2000-2010 in the Dindigul District randomized controlled trial

Group	Cases	Person-yrs of follow-up (PYO)	Rate per 100,000 PYO	Hazard ratio (95% CI)
Incidence of all cervical cancer				
Control	205	235 031	87	1.00
VIA	217	366 563	59	0.74 (0.60 - 0.92)
Cervical cancer mortality				
Control	133	235 031	49	1.00
VIA	139	366 563	32	0.73 (0.56 - 0.95)

CI: confidence interval; VIA: visual inspection with acetic acid

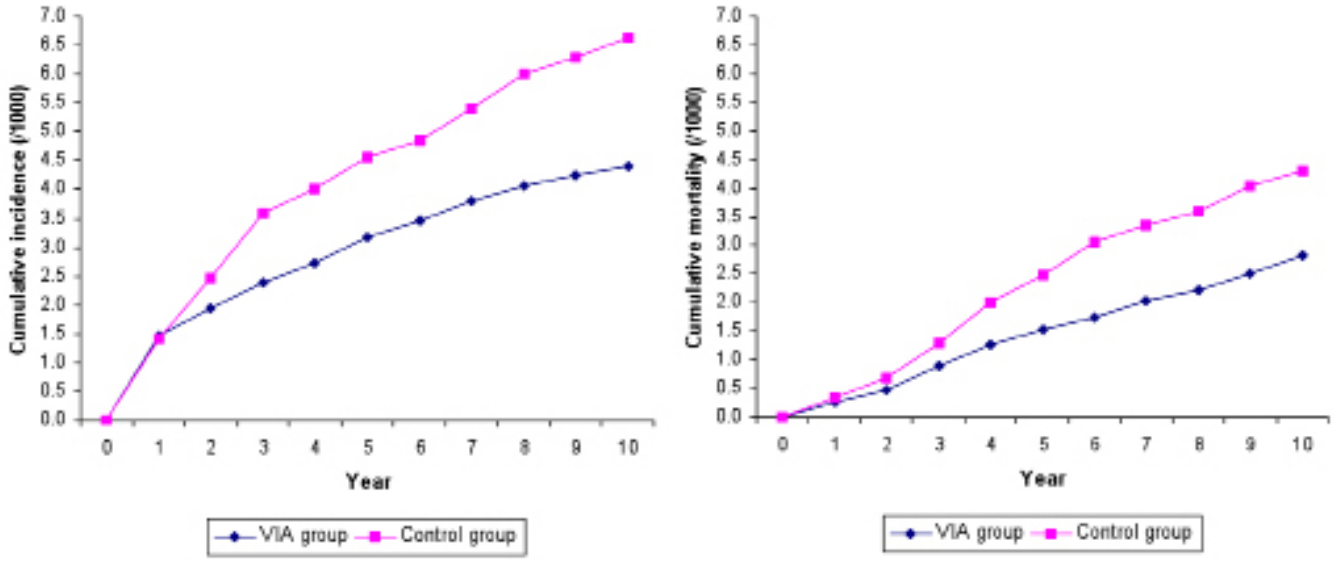

Figure 1. Cumulative cervical cancer incidence and mortality during 2000-2010 in the Dindigul District randomized controlled trial

Figure 1). VIA screening of the control group women has been completed in the Dindigul district study, and HPV testing of the control group women in the Osmanabad study is in progress and will be completed in 2012.

Multicentre randomized HPV vaccination trial

In collaboration with nine national institutions in India, SCR is conducting a randomized clinical trial comparing the efficacy of two versus three doses of HPV vaccination in preventing HPV infection and cervical neoplasia. HPV vaccination was initiated in September 2009. The entire course of vaccination of 20 000 girls would have been completed by the end of August 2010 had the Government of India not temporarily suspended all HPV vaccination trials in India effective April 2010. This followed reports of four deaths in vaccinated cohorts of two programmes of HPV vaccination conducted by another group of investigators in India. As of April 2010, we had vaccinated 17 696 girls partially or fully as per protocol: 8622 had one dose on day 1; 5598 had two doses on days 1 and 60; 1415 had two doses on days 1 and 180 as per protocol in the 2-dose group; 2061 with three doses on days 1, 60 and 180 as per protocol in the 3-dose group. Thus allocated vaccination schedules were interrupted for 14 220 girls while 3476 girls were administered vaccines as per protocol. Blood specimens were collected from 2773 participants at baseline; from 3391 girls at month 7, from 1691 girls at month 12 and from more than 9000 girls in month 18. Preliminary results on the antibody levels at baseline and at 7 months (1 month from the last dose of vaccination as per protocol) indicates that the immunogenicity in the 2-dose group was found to be non-inferior to the 3-dose group with respect to antibodies to HPV 16, 18, 6 and 11. A total of 1799 adverse events, including 68 severe adverse events (none related to HPV vaccination), have been reported. The serology and cervical samples were analysed for antibodies and HPV types at the Rajiv Gandhi Centre for Biotechnology, Trivandrum.

Evaluation of ongoing cervical cancer screening programmes and training initiatives

A descriptive evaluation of ongoing cytology screening programmes in Thailand (Deerasamee *et al.*, 2007; Kuhaprema *et al.*, 2011) and VIA screening initiatives in Bangladesh (Nessa *et al.*, 2010), Mali (Teguete *et al.*, 2011), Angola (Muwonge *et al.*, 2010) and United Republic of Tanzania (Ngoma *et al.* 2010) were carried out. Seven training courses in cervical cancer screening and prevention (four in India, two in China and one in Egypt) were conducted and around 300 doctors and nurses from Asian and African countries were trained. Our collaborative cervical cancer prevention schools in India, Angola, Guinea, United Republic of Tanzania, Brazil and Peru are active in educating human resources in their respective regions.

Breast cancer screening

In January 2006, a cluster randomized controlled trial was initiated in the Trivandrum district, India, to evaluate whether three rounds of triennial clinical breast examination (CBE) can reduce the rate of advanced disease incidence and breast cancer mortality. A total of 115 652 healthy women, aged 30-69 years, were randomly allocated to intervention or control groups. After completion of the first round of screening in May 2009, results were reported in terms of frequency of stage distribution, tumour size, lymph node involvement and breast conservation surgery in the intervention and control groups (Table 4). CBE had 52% sensitivity, 94% specificity, 6% false-positive rate, and 1% positive predictive value in detecting breast cancer. The age-standardized incidence rates for early stage (stage IIA or lower) breast cancer were 18.8 and 8.1 per 100 000 women, and the rates for advanced stage (stage IIB or higher) breast cancer were 19.6 and 21.7 per 100 000 women, in the intervention and control groups, respectively (Sankaranarayanan *et al.*, 2011a). The second round of screening is in progress.

Table 4. Comparison of intermediate outcome measures and treatment modalities in the study groups of Trivandrum breast cancer screening trial

	Intervention group		Control group		P-value
	No.	% (95% CI)	No.	% (95% CI)	
Breast cancers	80		63		
Size of primary tumour, ≤2cm	15	18.8 (10.2 to 27.3)	4	6.3 (0.3 to 12.4)	0.030
Negative pathological node	40	50.0 (39.0 to 61.0)	22	34.9 (23.1 to 46.7)	0.071
Early stage breast cancers (stages I and IIA)	35	43.8 (32.9 to 54.6)	16	25.4 (14.6 to 36.1)	0.023
Advanced stage breast cancers (stages IIB-IV)	36	45.0 (34.1 to 55.9)	43	68.3 (56.8 to 79.7)	0.005
Estrogen receptor-positive breast cancers	28	35.0 (24.5 to 45.5)	23	36.5 (24.6 to 48.4)	0.852
Treatment received					
Surgery	61	76.3 (66.9 to 85.6)	50	79.4 (69.4 to 89.4)	0.657
Radiotherapy	39	48.8 (37.8 to 59.7)	27	42.9 (30.6 to 55.1)	0.483
Chemotherapy	61	76.3 (66.9 to 85.6)	46	73.0 (62.1 to 84.0)	0.658
Hormone therapy	24	30.0 (20.0 to 40.0)	20	31.7 (20.3 to 43.2)	0.822
Received breast conservative surgery	14	17.5 (9.2 to 25.8)	3	4.8 (-0.5 to 10.0)	0.019

Table 5. Oral cancer incidence/mortality rates by number of times screened among individuals with tobacco and alcohol habits in the Trivandrum oral cancer screening trial

Number of times screened	Cases/deaths	Person-yrs of follow-up (PYO)	Incidence/mortality rate per 100 000 PYO	Incidence/mortality hazard ratio (95% CI)
		Oral cancer incidence		
Control	214	252 870	84.6	1.00
Intervention				
0	13	14 250	91.3	1.02 (0.60 - 1.74)
1	68	48 730	139.5	1.61 (1.14 - 2.29)
2	60	71 130	84.3	0.98 (0.73 - 1.32)
3	62	91 030	68.1	0.78 (0.54 - 1.13)
4	37	79 220	46.7	0.53 (0.35 - 0.81)
		Oral cancer mortality		
Control	109	250 700	43.5	1.00
Intervention				
0	9	14 230	63.2	1.73 (0.97 - 3.08)
1	45	48 810	92.2	2.50 (1.81 - 3.46)
2	24	71 250	33.7	0.77 (0.60 - 0.99)
3	15	91 240	16.4	0.35 (0.17 - 0.72)
4	2	79 410	2.5	0.05 (0.01 - 0.28)

Efforts are underway to evaluate the impact of breast cancer awareness in reducing mortality in large population-based studies. The efficacy of transillumination breast screening in detecting breast lumps and breast cancer is being evaluated in India and China.

Oral cancer screening

The cohort (200 000 subjects) of the Trivandrum oral cancer screening study have now been followed-up for 15 years. Results after four rounds of screening indicate a significant (47%) reduction in oral cancer incidence and a 95% reduction in mortality among subjects with tobacco and/or alcohol habits (Table 5). The screening of subjects in the control group has been completed.

Colorectal cancer screening

The goal of the Thailand Colorectal Cancer Screening Pilot Demonstration Project in Lampang Province, Thailand, jointly organized with SCR and the National Cancer Institute, is to evaluate the acceptability, feasibility, organization, implementation, monitoring and effectiveness of colorectal cancer (CRC) screening using a faecal occult blood test (FOBT) followed by a colonoscopy in those with a positive FOBT. By integrating this screening effort into the existing public health services, we intend to inform and guide the eventual large-scale CRC screening programme covering the entire country. This study aims to recruit around 150 000 subjects aged 50-65 years.

Cancer survival in Africa, Asia, the Caribbean and Central America

Population-based cancer survival data, a key indicator for monitoring progress against cancer, are not widely available in low- and middle-income countries. Survival of cancer-specific patients diagnosed in 1990–2001, and followed-up to 2003, in 25 population-based cancer registries from 12 countries in sub-Saharan Africa, Central America and Asia, were analysed by actuarial method. The five-year age-standardized relative survival (ASRS) and observed survival by clinical extent of disease varied drastically between countries. Five-year survival ranged from 76–82% for breast, 63–79% for cervix, 71–78% for bladder and 44–60% for large bowel cancers in China, Singapore, Republic of Korea and Turkey. Survival rates were the lowest, not exceeding 22% for any cancer site, in The Gambia in West Africa. Locally advanced disease ranged from 22–66% for different cancers and survival decreased with advanced stages. Survival variations correlate well with the early detection initiatives and development of health services. The wide disparity in cancer survival between countries and regions observed emphasizes the need for planned, urgent investments in improving awareness, population-based cancer registration, early detection programmes, health services infrastructure and human resources. (Sankaranarayanan *et al.*, 2010; Sankaranarayanan *et al.*, 2011b; Sankaranarayanan & Swaninathan, 2011; Sankaranarayanan *et al.*, 2011c).

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Quality Assurance Group

The Quality Assurance Group (QAS) aims to expand and disseminate information essential to maximizing the benefit and minimizing the harm of population-based cancer prevention programmes. Previous projects have dealt with secondary prevention through cancer screening. In recent years, complementary primary prevention, such as vaccination against human papillomavirus infection and promotion of healthy lifestyle, have also been addressed. The focus of population-based programmes is to give each eligible individual an equal chance of benefiting from an intervention. This makes the benefits of cancer prevention accessible to the widest number of people and thereby maximizes the positive impact on overall control of cancer and other chronic diseases.

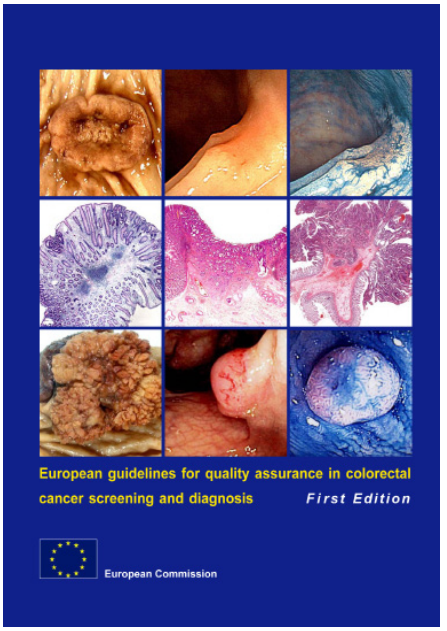


Figure 1. European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis

The population-based approach to programme implementation is also recommended because it provides an organizational framework conducive to effective management and continuous improvement of health services, such as through linkage with population and cancer registries for optimization of invitation to screening and/or vaccination, and for evaluation of programme performance and impact.

The quality-assured process of population-based cancer screening not only includes identification, information and invitation of the eligible population to attend screening, but it also involves high-quality diagnosis and treatment of individuals with lesions detected through screening. Nationwide implementation of population-based screening programmes, according to evidence-based guidelines, makes high standard diagnostic and therapeutic services accessible to the entire population eligible for screening. Because large numbers of professionals undertake further specialization to meet the screening standards, they also deal with symptomatic patients. Consequently, these nationwide efforts also contribute to widespread improvement in diagnosis and management of cancers which are detected outside of screening programmes.

The activities of the Group are conducted in the framework of international collaborative projects with many experts in a wide range of health care settings, primarily in high, but increasingly also in low- and middle-income settings.

Development and updating of guidelines for quality assurance in cancer screening and diagnosis

Breast, cervical and colorectal cancers account for nearly one fifth of the 7.5 million cancer deaths per year worldwide (Ferlay *et al.*, 2010). Screening people of average risk for these cancers can lower the burden of disease in the population (IARC, 2002; IARC, 2005; Sankaranarayanan *et al.*, 2009; Lansdorp-Vogelaar & von Karsa, 2010). However, screening large segments of the population affects many predominantly healthy individuals and consumes considerable resources. Hence, quality assurance is required to maintain an appropriate balance between benefit and harm (Lansdorp-Vogelaar & von Karsa, 2010; von Karsa *et al.*, 2010).

Colorectal cancer screening

During the biennium, comprehensive evidence-based European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis (Segnan *et al.*, 2010) (Figure 1) have been developed and published in a multi-year project coordinated by the QAS Group. The project involved 49 countries in four continents, primarily in Europe, but also in North and South America, Asia and Australia. Experts from all IARC Participating States contributed.

The 400-page evidence-based Guidelines cover the entire screening process from invitation and organization through diagnosis and management of any abnormalities detected through screening. They provide guiding principles, standards and procedures of quality assurance and best practice, which should be taken into account when establishing and running a colorectal cancer (CRC) screening programme in any resource setting. Although only the non-invasive faecal occult blood test is currently recommended for CRC screening by the EU, the new EU Guidelines also deal with endoscopic screening by colonoscopy or flexible sigmoidoscopy. In total, over 250 recommendations, graded according to the strength of the recommendation and the supporting evidence, are provided.

The new EU Guidelines are the first internationally developed, comprehensive procedures dealing with the entire process of CRC screening. They are also unique in the extensive documentation of the key clinical questions and the respective review that has been conducted to develop the standards and recommendations. Given the broad scope and depth of the Guidelines, only a few important aspects can be mentioned here.

The recommendations dealing with non-polypoid colorectal lesions, particularly in the serrated pathway, some of which are difficult to detect due to their non-polypoid morphology, is a prime example (Chap. 7 in Segnan *et al.* 2010) of the important contribution of the EU Guidelines. Although the existence of these lesions has been previously reported, their high prevalence was only recently recognized in the Western literature (Kudo *et al.*, 2008; Soetikno *et al.*, 2008). The first European protocol for surveillance of people found through screening to be at elevated risk for future development of CRC (Figure 2) is another important example of the innovative character of

the new Guidelines. Surveillance on an inappropriate scale has the potential to expose patients to unnecessary risks and to prohibit implementation of nationwide CRC screening programmes due to unnecessary consumption of limited colonoscopic resources (Chap. 9 in Segnan *et al.*, 2010; Winawer *et al.*, 2006).

The Guidelines also include the first comprehensive classification for histology of lesions detected in screening that is applicable worldwide (Table 1) (Chap. 7 in Segnan *et al.*, 2010; Quirke *et al.*, 2011). The detailed recommendations on communication, particularly on the essential elements to be included in invitation letters and informational brochures for CRC screening, are an additional resource that can help to reduce barriers to participation and therefore help to make high-quality screening available to all who may benefit (Chapters 2 and 10 in Segnan *et al.* 2010).

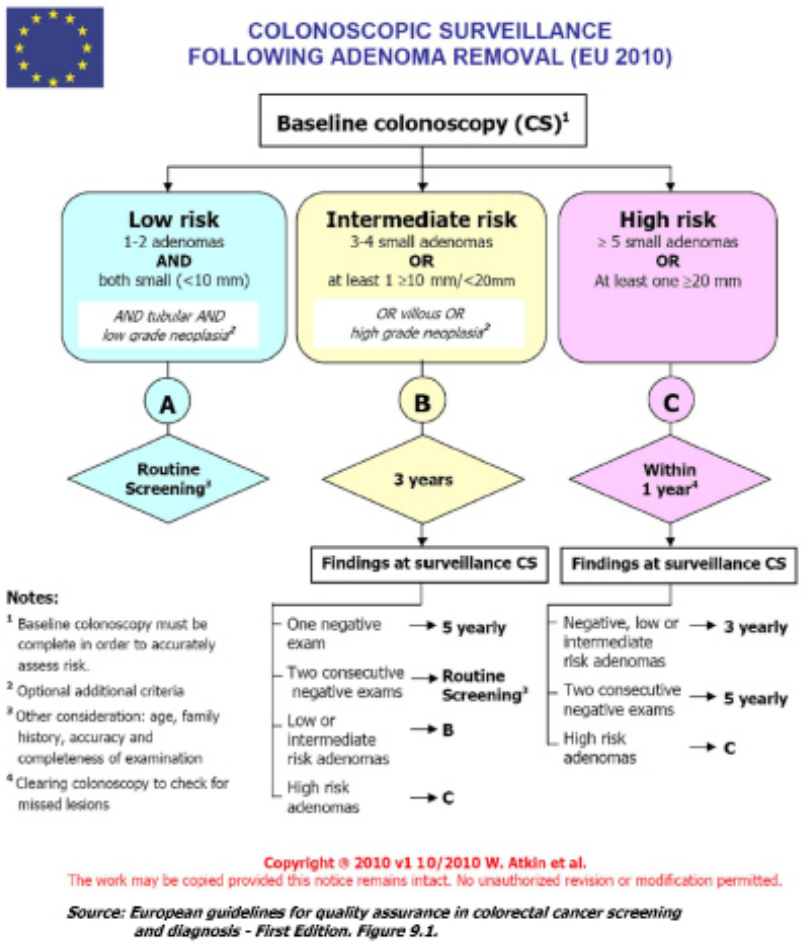
Breast cancer screening

Supplements dealing with histopathology, physico-technical quality control and digital mammography have been developed for the current fourth edition of the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis (Perry *et al.*, 2006). Publication is expected in 2012. These international collaborative efforts have been conducted in the framework of a project coordinated by QAS and co-financed by the EU Health Programme (European Cooperation for development and implementation of Cancer screening and prevention Guidelines (ECCG)).[1]

Cervical cancer screening and vaccination

In the framework of the above-mentioned EU project (ECCG), supplements on HPV testing and vaccination have also been prepared for the current second edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening (Arbyn *et al.*, 2008). This work is currently ongoing with publication expected in 2012.

Figure 2. First protocol for monitoring screened individuals at risk of CRC



Source: European guidelines for quality assurance in colorectal cancer screening and diagnosis - First Edition. Figure 9.1.

Collaboration with WHO in development and implementation of cancer screening guidelines and in promotion of high-quality cancer registration

QAS has also collaborated with WHO headquarters (Departments of Reproductive Health and Research, Chronic Diseases Prevention and Management) and McMasters University in Canada in an ongoing effort to update the current WHO Guide to Essential Practice in Comprehensive Cervical Cancer Control (C4-GEP) (Figure 3) (WHO, 2006). Co-financing has been provided by WHO through a grant from the French National Cancer Institute. Publication of the final revised volume is expected in the next biennium.

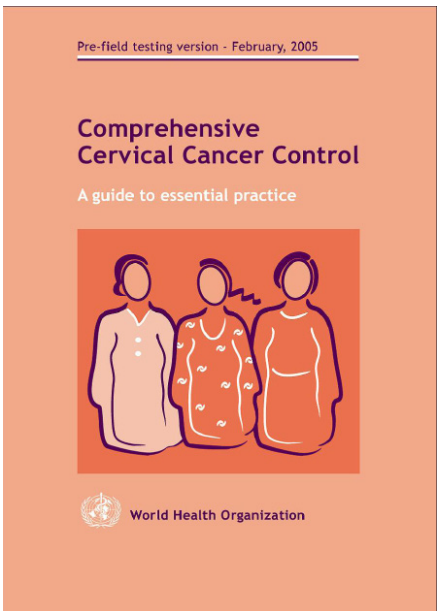


Figure 3. WHO Guide to Essential Practice in Comprehensive Cervical Cancer Control

In collaboration with the same departments at WHO headquarters, the European Regional Office (Director of Programme Management) and the respective WHO country offices, QAS has led joint WHO/IARC missions and workshops in Albania and Belarus. In these workshops, collaborating experts, IARC and WHO staff have assisted researchers and responsible authorities

Table 1. Adaptation of the revised Vienna classification[1] for colorectal cancer screening

1. No neoplasia[2]
Vienna Category 1 (Negative for neoplasia)
2. Mucosal low-grade neoplasia
Vienna Category 3 (Mucosal low-grade neoplasia
Low-grade adenoma
Low-grade dysplasia);
Other common terminology
Mild and moderate dysplasia;
WHO: low-grade intra-epithelial neoplasia
3. Mucosal high-grade neoplasia
Vienna: Category 4.1–4.4 (Mucosal high-grade neoplasia
High-grade adenoma/dysplasia
Non-invasive carcinoma (carcinoma in situ)
Suspicious for invasive carcinoma
Intramucosal carcinoma);
Other common terminology
Severe dysplasia;
High-grade intraepithelial neoplasia;
WHO: high-grade intraepithelial neoplasia
TNM: pTis
4. Carcinoma invading the submucosa or beyond:
4a. Carcinoma confined to submucosa
Vienna: Category 5 (submucosal invasion by carcinoma);
TNM: pT1
4b. Carcinoma beyond submucosa
TNM: pT2-T4

[1] For revised Vienna classification see Dixon (2002), for WHO classification see WHO (2000), for TNM see (TNM Classification of Malignant Tumours, 5th edition 1997; TNM Classification of Malignant Tumours, 6th edition 2002; TNM Classification of Malignant Tumours, 7th edition 2009).
[2] Category 2 of the Vienna Classification (indefinite) is not recommended for screening.
Source: European guidelines for quality assurance in colorectal cancer screening and diagnosis - First Edition. Table 7.1

in the development of plans for integrating population-based programmes for breast and cervical cancer screening into comprehensive efforts to improve cancer control.

Collaboration with cancer registries

A key outcome of the national workshops, conducted in collaboration with WHO, has been unanimous consensus on the need for fully functional cancer registries and effective and reliable linkage between screening data and cancer registry data to assure high-quality cancer screening programmes. The importance of collaboration between cancer screening registries and cancer registries in monitoring and evaluation was also highlighted. Priorities for future efforts were identified at a pan-European network meeting organized by QAS in collaboration with the work package on screening (Figure 4) in the EUROCOURSE[1] project and the Division of Epidemiology & Cancer Prevention in the Cancer Center & Institute of Oncology in Warsaw in May 2010 (Figure 5). The meeting was attended by 120 cancer screening and registration experts from across Europe and from Japan. The meeting was co-financed by the EU through the ECCG and EUROCOURSE projects.

Accreditation

At the request of the European Commission (Directorate Generals for Health and Consumers, and for Enterprise and Industry), the Group has continued an ongoing collaboration with the European cooperation for Accreditation (EA). Activities focused on planning a multi-year project for piloting an EU system for voluntary accreditation of breast cancer screening facilities. Useful experience in this area was also derived from missions of QAS staff and collaborators to Estonia and Malta to assess the progress of and exchange ideas about implementation of national breast cancer screening programmes. A mission to the Kielce region in Poland was also undertaken to prepare a pilot project implementing HPV testing in cervical cancer screening. This investigation was conducted in collaboration with the Division of Epidemiology and Cancer Prevention, Cancer Center and Institute of Oncology in Warsaw, the Holy Cross Cancer Centre and the regional cervical cancer screening programme in Kielce, Poland.

Discussions were also conducted with the Programme for Action in Cancer Therapy (PACT) of the International Atomic Energy Agency, to explore collaboration in the implementation of the accreditation project and to develop a joint proposal. Given the financial scope of the multi-year project, substantial external financing will be required to cover the 40% institutional contribution generally required for Directorate General for Health and Consumer Affairs (DG SANCO) grants.

European Code Against Cancer

The initial phase of a project to update the European Code Against Cancer (Boyle *et al.*, 2003) was completed during the biennium. At the request of DG SANCO, a project proposal to provide co-financing for the next phase of activities has been submitted to the Executive Agency for Health and Consumers.

European partnership for Action Against Cancer

During the biennium, QAS coordinated the development and submission of the application for the work package on cancer screening in the new Action Against Cancer in the framework of the EU Health Programme. Subsequent to approval of the proposal, the Group has provided core scientific and technical support for the work package coordination.

[1] The EUROCOURSE project (EUROpe against Cancer: Optimization of the Use of Registries for Scientific Excellence in research) is funded by the Seventh Framework Programme of the EU. The focus of the activities in work package 5 is developing and improving the interface of cancer registries with cancer screening programmes.

Figure 4.

Global screening report

At the request of DG SANCO, a project proposal has also been developed for updating and expanding the previously published report on implementation of cancer screening in the EU. Similar to the development and updating of the European Guidelines for quality assurance in cancer screening, international experts outside the EU will also be involved in the preparation of the next screening report. Additional funding will be sought during the next biennium to expand these efforts to encompass other regions of the world.

Figure 5.

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Prevention and Implementation Group (PRI)

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Every year more than 7 million people die from cancer, with the majority (75%) of cases occurring in developing countries. This proportion is rapidly increasing with population ageing in those areas. Using what we already know about cancer etiology and effective interventions, it is possible to prevent over 30% of premature deaths from cancer and to cure or prolong survival in another 30% with early detection and proper treatment.

Some examples of preventive interventions include: smoking cessation efforts; promotion of healthy diets, exercise and weight control programmes; and vaccination against hepatitis B to control liver cancer and human papillomavirus to prevent cervical, anal and possibly oropharyngeal cancer. In addition, screening for cervical, colorectal, breast, oral and stomach cancer have been shown to be effective when widely implemented. In the case of cervical cancer, for example, important advances in both primary and secondary prevention have been made in recent years. Several new preventive interventions offer enormous hope for reducing incidence and mortality from this disease, which has been extremely difficult to control in developing countries and remains one of the leading causes of cancer death.

For many cancers, there is still a need to develop safe and affordable preventive interventions. In the case of stomach cancer, another common malignancy, despite ample knowledge about the role of *Helicobacter pylori* in its etiology and the success of expensive endoscopy-based programmes, there is a clear need to investigate the potential of more affordable interventions, like screening with markers of atrophic gastritis or eradication of *Helicobacter pylori,* for example. For most interventions, there is a need to conduct research on how best to implement interventions in different socioeconomic and cultural settings.

It is important to disseminate information on how to apply current knowledge to cancer prevention, to generate new data to improve available interventions, and to investigate new approaches for control of the major cancers.

The objectives of the newly created Prevention and Implementation Group (PRI) are to: evaluate new preventive strategies with particular emphasis on the use of new technologies, including molecular markers; to engage in research on methods to implement existing strategies taking into account social, economic and cultural differences; and to collaborate with decision-makers to implement already available preventive interventions against cancer, particularly in developing countries where the need is highest. An additional objective is to foster technology transfer and generate educational processes for clinicians, public health decision-makers and the public, to make sure the available technology and information is available where it is needed most.

Natural history studies of cervical cancer

The Guanacaste, Costa Rica HPV natural history study (NHS) is a prospective, population-based cohort study with participation of a random sample of more than 10 000 women in a high risk area for cervical cancer, who were recruited, screened and followed for more than seven years beginning in 1993-1994. The study has generated a large series of publications and has clarified multiple aspects of the natural history of the disease, including epidemiologic, virologic, immunologic and genetic variables. In addition, it has provided extensive information on the validity of different screening methods in the region. A series of ancillary studies are being conducted to further investigate the reasons for the high prevalence of HPV infection in older women, to evaluate fluctuations of cervical antibody levels with the menstrual cycle and to define the long-term outcome of treatment of precancerous lesions.

HPV vaccine trial in Guanacaste, Costa Rica

A randomized clinical trial to evaluate the efficacy of the bivalent (HPV 16/18) vaccine was initiated in 2004 as a continuation of the NHS. A total of 7466 women, ages 18–25, were recruited and randomized to receive the HPV vaccine or a hepatitis A vaccine as control. Women were screened at yearly intervals and followed for four years. At the end of follow-up, all women received the vaccines they did not receive at recruitment (crossover) plus a hepatitis B vaccine as an additional benefit. The study confirmed the efficacy of the bivalent vaccine against HPV 16 and 18 and described its cross-protection against HPV 31, 33 and 45 (Herrero *et al.*, 2011). In addition, in stratified analyses, it showed the decline in vaccine efficacy at the population level with increasing age. One of the most interesting findings was the observation that HPV vaccine efficacy against HPV 16 and 18 was equally good among women who received one, two and three doses (Kreimer *et al.*, 2011), while there was no efficacy among women who were positive at the time of vaccination (Hildesheim *et al.*, 2007). Current plans include long-term follow-up of the vaccinated cohort. Given the fact that all women have now received the HPV vaccine, a new unvaccinated control group of about 2500 women was recruited recently to continue the evaluation of efficacy and safety over 10 years. During the Costa Rica HPV vaccine trial, we observed a high prevalence of anal HPV infection among young women. HPV-positive women will be followed with periodic virologic and cytologic examinations to investigate the natural history of anal infections and their relation to anal intraepithelial neoplasia.

Also in the framework of the Costa Rica HPV vaccine trial, we have evaluated and demonstrated high efficacy of the bivalent vaccine against anal infection (Kreimer *et al.*, 2011). These results will be followed over time to ascertain their potential as anal cancer prevention tools. Furthermore, we obtained an oral specimen for HPV testing from all women at their four year visit. Despite the lack of baseline oral HPV results, it will be possible to evaluate vaccine efficacy against prevalent infections in a randomized fashion. Further follow-up of study cohorts will establish efficacy of this intervention to reduce the burden of cervical neoplasia.

ASCUS triage project in Medellín, Colombia

The Atypical Squamous Cells of Unknown Significance (ASCUS) project in Antioquia, Colombia is conducted in collaboration with the Cancer and Infection Group at the University of Antioquia in Colombia. It is a randomized clinical trial of three different approaches to triage women with cytologic diagnosis of ASCUS and is underway in Medellín, Colombia. Approximately 3000 women with an ASCUS are being recruited and randomized to immediate colposcopy, repeat cytology or HPV testing. It is anticipated that the study will provide information on how to manage this frequent diagnosis in the context of the Colombian health system.

Multicentre study of triage methods for HPV-positive women

A screening investigation is being planned to define the best triage strategy for HPV-positive women in screening programmes based on HPV testing as the primary modality. There is now a trend for screening programmes to transition from cytology to HPV testing as the primary screening method, but the positive predictive value of the HPV test remains limited because many women with HPV infection do not develop disease, even when programmes are targeted to women over 30 years of age. It is therefore necessary to investigate the usefulness of a series of triage techniques, including visual inspection and cytology and a series of new biomarkers based on detection of DNA, RNA, proteins or other markers of transformation. The plan is to recruit nearly 100 000 women from several countries initially in Latin America, collect appropriate specimens, and obtain descriptive definitions of their cervical diagnosis in order to evaluate currently available and future triage methods.

Support of screening or vaccination initiatives in Latin America

Argentina is one of the countries that is starting to vaccinate young women with the HPV vaccine and at the same time is implementing HPV testing as the primary screening modality. The initial step in this process is the organization of a large pilot project in the Province of Jujuy, with the collaboration of PRI staff. Similarly, several countries in Latin America are considering or have started implementation of vaccination or HPV testing as their primary strategy (e.g. Mexico, Panama and Chile) with active participation of PRI staff.

Clinical trial of *Helicobacter pylori* eradication

In collaboration with the US Southwest Oncology Group and several centres in Latin America, PRI staff participated in a multicentre trial to evaluate the best option as an eradication treatment against Helicobacter pylori (Greenberg *et al.*, 2011). The eradication rate for the different treatments at six weeks has been published. In the near future the results for one year will be reported, in addition to a series of reports incorporating several biomarkers.

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Office of the Director

Director
Dr Christopher P. Wild

Administrative assistants
Ms Margot Geesink
Ms Susan Haver-Legros

Secretary
Ms Karima Abdedayem

Scientific officer
Dr Eduardo Seleiro

The Director is responsible for providing leadership through the development of a scientific strategy that sets out the overall vision, direction and focus of the Agency's research programme and provides the framework for attaining its mission, in accordance with the Statutes. The IARC Medium-Term Strategy and Implementation Plan for 2010–2014, approved by the Governing Council at its 52nd Session in May 2010, outlines the Agency's directive.

Within the Agency, the Director's Office team assists the Director in the development of specific scientific initiatives and programmes, particularly those involving multiple research Groups. The Director's Office also supports the activities of several advisory groups and committees, most notably the Senior Leadership Team (SLT) (comprising the Director, all Section Heads, the Director of Administration and Finance and the Head of the Communications Group), which advises the Director on scientific strategy.

In addition, the Director's Office assists in the coordination of contacts and relations with IARC's partners, both to expand the Agency's network of scientific collaborations with other groups and institutions, and to develop the relations with governmental and non-governmental organizations and funding agencies with an interest in cancer research, prevention and control. It is also responsible for assisting the Director, Division of Administration and Finance, in relations with the Agency's governance structures and with Participating States.

As well as the team mentioned above, there are four Groups within the Director's Office: the Gambia Hepatitis Intervention Study (GHIS), Communications (COM), Education and Training (ETR), and Laboratory Services and Biobank (LSB). The latter three Groups have a wide range of activities that are relevant across the Agency. Their activities are described elsewhere in this Report.

Communications Group (COM)

Group head
Dr Nicolas Gaudin

Secretary
Ms Bernadette Geoffre

Editor
Mr John Daniel
(until September 2011)

Librarian
Ms Sharon Grant

Institutional webmaster
Ms Maria de la Trinidad Valdivieso Gonzalez

Technical assistants
Mr Antoine Bellon
Ms Latifa Bouanzi
Mr Roland Dray
Ms Sylvia Moutinho

As an integral part of the Director's Office, the Communications (COM) Group is responsible for the uniform presentation of all aspects of IARC's work to the scientific community, the media and the general public, as well as providing a service to the research Groups in all matters related to information.

Publications/editing service

COM assists all scientific Groups in disseminating their research results by providing editorial support and guidance for the publication of articles, papers and op-ed pieces in international scientific journals. They also offer support in the way of graphic services, both for illustrations of publications and posters, and for the layout of the finished print-ready products. The Editor takes an active role in the preparation of manuscripts for submission to scientific journals, as well as for volumes in the book production series. The Editor also forms part of the faculty of the IARC Summer School, and has developed a course 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. This Group reactivated the Advisory Committee on Publications, a consultative committee whose aim is to assess the publication needs and priorities for the Agency.

Dissemination of IARC publications

The recent agreement between IARC and our exclusive dissemination partner, WHO Press, has been instrumental in enabling the publications programme to fund sustained efforts, particularly in the area of the WHO Classification of Tumours ('Blue Books' series), which remains the Agency's bestseller and continues to be among the top selling titles for WHO Press (Figure 1). The Advisory Committee on Publications, whose mission reflects the new strategic vision of the Agency, manages and pilots publication projects in the longer term.

New IARC publications

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

In print:

- Tumours of the Digestive System, WHO Classification of Tumours, 4th edition
- Effectiveness of Tax and Price Policies for Tobacco Control, IARC Handbooks of Cancer Prevention Volume 14
- Cancer Survival in Africa, Asia, the Caribbean and Central America, IARC Scientific Publications Volume 162
- Molecular Epidemiology and Biomarkers, IARC Scientific Publications Volume 163
- Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures: IARC Monographs Volume 92
- Carbon Black, Titanium Dioxide, and Talc: IARC Monographs Volume 93
- Ingested Nitrate and Nitrite and Cyanobacterial Peptide Toxins: IARC Monographs Volume 94
- Household Use of Solid Fuels and High-temperature Frying: IARC Monographs Volume 95
- Alcohol Consumption and Ethyl Carbamate: IARC Monographs Volume 96
- Painting, Firefighting, and Shiftwork: IARC Monographs Volume 98
- Some Aromatic Amines, Organic Dyes, and Related Exposures: IARC Monographs Volume 99

In electronic format:

- IARC Biennial Report 2008–2009
- Rapport Biennial 2008–2009 (French version of above title)
- Methods for Evaluating Tobacco Control Policies: IARC Handbooks of Cancer Prevention Volume 12
- Evaluating the Effectiveness of Smoke-free Policies: IARC Handbooks of Cancer Prevention Volume 13
- Cancer Survival in Africa, Asia, the Caribbean and Central America, IARC Scientific Publications Volume 162
- World Cancer Report 2008, Non-Serial IARC publication
- Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures: IARC Monographs Volume 92
- Carbon Black, Titanium Dioxide, and Talc: IARC Monographs Volume 93
- Ingested Nitrate and Nitrite and Cyanobacterial Peptide Toxins: IARC Monographs Volume 94
- Household Use of Solid Fuels and High-temperature Frying: IARC Monographs Volume 95
- Alcohol Consumption and Ethyl Carbamate: IARC Monographs Volume 96
- Painting, Firefighting, and Shiftwork: IARC Monographs Volume 98
- Some Aromatic Amines, Organic Dyes, and Related Exposures: IARC Monographs Volume 99
- Identification of Research Needs to Resolve the Carcinogenicity of High-priority IARC Carcinogens: IARC Technical Publication No. 42.
- Pharmaceuticals: IARC Monographs Volume 100A
- Biological Agents: IARC Monographs Volume 100B

In addition, the preparation of an IARC Technical Publication on Management of Mycotoxins in Food and Feeds for

Figure 1. COM maintains IARC's presence at international meetings, e.g. the World Health Assembly

Improving Public Health is now close to publication and production in print. Further, several online electronic resources were made available from the centralized online publications databank, including access to GLOBOCAN 2008, launched in June 2010, as well as digital atlases for training, prepared by the Screening Group, and tools for cancer registries.

For ease of reference, the relevant web page for IARC publications in PDF format (freely accessible) is: http://www.iarc.fr/en/publications/pdfs-online/. The full list of IARC publications and direct link to the IARC online book order platform and/or to the free PDF document is: http://www.iarc.fr/en/publications/list/.

To make online ordering of publications simple, a computer with direct access to IARC's publications catalogue and to the WHO Press online ordering facility has been installed in the IARC entrance hall for use by visitors.

Web services

The Agency's bilingual internet site is maintained by COM. As a primary means of dissemination of research results, the IARC website ensures greater visibility of investigative outcomes from various internal cancer databases and research programmes' websites. As a result of the analysis of human resource needs in this area conducted in 2010, the Web team has gained one post and is now composed of one Professional Institutional Webmaster, assisted by one General Service Webmaster Assistant.

The Web team also makes certain that the presentation of all IARC research material available through the web and IARC subsites is standardized to promote an effective corporate image. To this end, special effort has been made to bring into line various IARC subsites with IARC's corporate image: http://www-p53.iarc.fr/, http://monographs.iarc.fr/, http://epic.iarc.fr/, http://ilcco.iarc.fr/, http://ilcs.iarc.fr/, http://inhance.iarc.fr/, http://welas.iarc.fr, http://ethics.iarc.fr/ and http://governance.iarc.fr/, and to coordinate action with web focal points regarding the harmonization of websites: http://www-dep.iarc.fr/ and http://screening.iarc.fr/.

The team also helps to analyse the web needs of the IARC Groups and to conceptualize and guide the process of development, and the updating and upgrading of various Groups' websites. During this biennium, the Web service launched a number of new websites:

Public websites:
http://synergy.iarc.fr,
http://agricoh.iarc.fr,
http://iicc.iarc.fr and
http://accis.iarc.fr/

Meetings' websites:
http://www.iarc.fr/p53isoforms/,
http://www.iarc.fr/oncogenicviruses2010/ and
http://www.iarc.fr/oncogenicviruses2012/

Internal websites
http://library.iarc.fr/,
http://igo.iarc.fr/ (Grants Office),
http://intranet.iarc.fr/SAC/index.php (Staff Association) and
http://ohsc.iarc.fr/ (Occupational Health and Safety Committee).

The Web service ensures greater visibility of the key IARC activities through the IARC home page (http://www.iarc.fr/).

The COM group collects results from the various research Groups and disseminates them through the 'IARC News' facility. It also provides visibility and functionality for GLOBOCAN 2008 from the IARC home page.

As part of the continuous process of improving the IARC website, new features have been developed like Google Custom Search and RSS feeds. In addition, new sections have been added to the website: Office of the Director, IARC Publications–Cancer Screening Manuals and Guidelines, and IARC Publications–IARC CancerBases and Related Electronic Resources.

In 2011, the Web services team carried out the evaluation of several web analytical tool options to monitor and evaluate the traffic and usage of IARC websites. URCHIN 7 was selected and is now being customized across all IARC websites.

COM also maintains the IARC intranet, which provides staff with many administrative resources and information for internal use (e.g. library, occupational health and safety committee, etc.).

Public and media relations

The Public Relations Service acts as liaison between the Agency and the media by writing and distributing press releases and organizing press conferences (Figure 2). By means of a database of media contacts around the world, the Service dispatches press releases to and maintains regular contact with over 4000 press agencies, individual journalists and decision-makers. The impact of this effort is

Figure 2. Global Press conference at IARC's Headquarters: the evaluation of radiofrequency electromagnetic fields, including mobile phones, drew intense media attention.

Figure 3. COM organizes the training of IARC staff for media interaction with the support of the WHO Headquarters' media team.

evident from the global news coverage surrounding several press releases over the biennium (Figure 2). The profile of the media impact is being observed by news monitoring services led by COM and correlates closely to media launches.

This Service also coordinates press releases on new investigations within the Monographs programme (Figure 3) by way of publication of a summary in the Lancet Oncology Policy Watch section, which offers the Agency a regular tribune for independent and transparent results (Figure 3).

Library

The mission of the IARC Library is to support the Agency's information and research needs by providing a wide range of electronic resources, a traditional print collection and responsive, user-centred services.

The Library is committed to providing access to information through acquisition, organization and management of collections. The cost of online information is high and demand for it is rapidly expanding. The Library works closely with local libraries in Lyon and with WHO Libraries & Information Networks for Knowledge to provide additional options for information access for IARC users. In addition, the Library's highly efficient Document Delivery Service ensures a rapid turnaround time between requests and delivery of documents. The IARC Library is pleased to provide access to its collections and services to institutions or individuals.

The Library also offers orientation and training to staff, fellows, students and visiting scientists, either individually or in groups. These sessions focus on the effective use of information resources, information management and copyright education. Information consultations, literature searches and participation in the IARC Summer School are additional core activities.

The Library's intranet website reflects our focus on providing access to accurate and reliable information for our primary audience: IARC staff, fellows, students and visiting scientists.

The Library monitors the peer-reviewed publications of the Agency that result from our research. This activity contributes to the visibility of IARC through the dissemination of the information relating to these publications via the institutional website. Through its technical expertise, the Library actively participates in the publications programme of the Agency.

Translation

The Translation Service provides translations from English to French of all official documents of the Governing Council of IARC, as well as articles, technical documents, correspondence, memoranda and other texts for the scientific and administrative Groups. It also organizes successful language courses in both working languages for the Agency's staff, as well as administering the United Nations language proficiency examinations.

Education and Training Group (ETR)

Group head
Miss M. Heanue (until April 2011)

Acting head
Dr E. Seleiro (from 15 July 2010)

Responsible officer, fellowship programme
Dr Z. Herceg

Senior visiting scientist
Dr R. Saracci

Assistant, fellowship programme
Mrs E. El Akroud

Assistant, courses programme
Mrs S. Anthony

Education and training in cancer research has been one of the statutory functions of the Agency since its inception in 1966. Through its well-established and highly successful international Fellowship and Courses Programmes, IARC has made a substantial contribution to training generations of cancer researchers worldwide and has been instrumental in the development of cancer research in low- and middle-income countries (LMICs).

The importance of education and training activities within the Agency's mission, was emphasized by the establishment in 2010 of the Education and Training Group (ETR) as a distinct structure within the Office of the Director, with a professional staff to provide leadership and innovation. In addition, an internal Advisory Committee on Education and Training was also established, composed of scientists from across the Agency, which helps to identify, evaluate and coordinate training initiatives.

The educational and training programmes of the Agency are designed to complement and support its research activities. ETR works closely with the scientific Groups to develop and implement training initiatives specifically aimed at countries/regions where lack of resources and expertise prevents the expansion of cancer research. In this context, a new and growing area of activity is to support the development of distance learning resources (see below).

ETR is currently divided into two programmes: training courses and fellowships.

Courses

The activities of the Courses Programme comprise both the IARC Summer School and the organization of specialized courses run by the scientific Groups of the Agency.

Summer school

The IARC Summer School, held in Lyon during June and July each year, provides basic training in cancer epidemiology primarily aimed at scientists from LMICs. The format consists of a one week module on 'Cancer Registration: Principles

Other courses held in Lyon 2010–2011

Course Title	IARC Group	Number of participants	External Collaborators
Course on statistical practice in epidemiology with R	ETR/ICE	28	-

Courses held outside IARC in 2010–2011

Course Title	Location	Number of participants	External Collaborators
MECC cancer registration workshop	Antalya, Turkey	20	MECC
CanReg training course, Casablanca Cancer Registry	Casablanca, Morocco	10	Casablanca Cancer Registry
International course on introduction to cancer registration and its application to cancer epidemiology	Guayaquil, Ecuador	28	PAHO
International course on introduction to cancer registration and its application to cancer epidemiology	Trinidad and Tobago	12	PAHO
Workshop on cancer registration	Stellenbosch, South Africa	54	Stellenbosch University, Cape Town
CanReg 5	Yokohama, Japan	17	IACR
Cervical cancer prevention	Trivandrum, India	200	Regional Cancer Centre, Trivandrum
Cancer registration and descriptive epidemiology: principles and methods course	Mumbai, India	40	UICC/ICRETT
VIA, colposcopy and treatment of cervical neoplasia (visual inspection) course	Barshi, India	18	Tata Memorial Rural Cancer Project, Nargis Dutt Memorial Cancer Hospital, Office of United Nations Population Fund, Ministry of Health and Family Welfare, People's Republic of Bangladesh
Cancer epidemiology courses	EC – Luxembourg and Brussels	16 and 10	European Commission DG SANCO

Course Title	IARC Group	Number of participants
Workshop on effective scientific posters	COM	14
Workshop on publishing in English-language journals	COM	25
Introduction to biostatistics	BST	25
Project management workshop	IGO	14
Workshop on STATA	SCR	24

and Methods,' followed by a two week module on 'Introduction to Cancer Epidemiology.' The programme focuses on epidemiology and biostatistics, with modules on descriptive, analytical and molecular epidemiology, and is designed to provide integrated training to participants who can attend both modules depending on expertise and the availability of funding.

Over the biennium, the IARC Summer School attracted over 414 applications from 64 countries. A total of 60 and 70 participants attended the Summer School in 2010 and 2011, respectively, with approximately 78% originating from LMICs (Algeria, Argentina, Belarus, Bosnia and Herzegovina, Botswana, Bhutan, Brazil, Cameroon, China, Colombia, Congo, Egypt, Ethiopia, Georgia, Ghana, India, Indonesia, Islamic Republic of Iran, Jamaica, Jordan, Kenya, Madagascar, Malawi, Malaysia, Mali, Mexico, Mongolia, Morocco, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Philippines, Rwanda, Sierra Leone, Sri Lanka, South Africa, Sudan, Syrian Arab Republic, Turkey, Uganda, Viet Nam, Yemen and Zambia).

Additional financial support for the Summer School was generously provided by the US National Institutes of Health, National Cancer Institute (NIH/NCI), the Fondation Léa et Napoléon Bullukian and the Nordic Cancer Union.

Other courses

Several additional courses were organized during 2010–2011 in collaboration with Agency Groups (particularly in the areas of cancer registration and screening with CIN and SCR) and in some instances co-organized with external partners and held at diverse locations throughout the world (see Table page 170).

Generic training

With the establishment of ETR came the initiative to run in-house generic training courses and workshops, open to all at IARC and conducted in collaboration with IARC Groups. Several of these courses are now being incorporated into the generic training provided through the IARC Postdoctoral Fellowship Charter (see below).

Other activities

Another noteworthy collaboration in the area of training is the signing of a memorandum of understanding between IARC and the London School of Hygiene and Tropical Medicine to coordinate the timing of their respective flagship courses in Cancer Registration and Cancer Survival. The aim of this collaboration is to facilitate the exchange of course faculty and provide an opportunity for some participants to attend training in these two complementary areas.

Fellowships

The Fellowship Programme coordinates the training of young postdoctoral scientists at the Agency and supports senior scientists to work in cancer research either at the Agency or in an institute in a LMIC.

A major development in this area was the introduction of the 'IARC Postdoctoral Fellowship Charter.' The Charter was developed to reinforce the provision for in-house generic training for all postdoctoral fellows at IARC, as requested by IARC fellows and postdoctoral scientists, and to provide a more structured approach to performance evaluation and career development, by outlining the commitments expected of the postdoctoral fellow, the supervisor and the Agency during the period of training.

As a part of the Charter, a generic training programme has been developed with activities offered in biostatistics, grant writing, scientific publishing, laboratory safety, project management, effective scientific poster preparation, library resources, bibliographic tools, and the IARC Sample Management and Information System, among others.

IARC research training fellowships

The IARC Research Training Fellowships provide an opportunity for postdoctoral scientists who wish to pursue a career in cancer research to train at the Agency. Fellowships are awarded in areas related to the Agency's own programme, with a focus on LMICs and an emphasis on interdisciplinary projects.

Fellows are selected from applicants from any country, with priority given to candidates from, or with a research project relevant to, LMICs. Furthermore, candidates need to provide reasonable assurance that they intend to return to their home country and continue working in cancer research on completion of their Fellowship at IARC. On completion of their training, over 80% of Fellows return to their home country and remain active in cancer research, often supported by a modest research Return Grant.

In 2010–2011, there was a 30% increase in applicants for the IARC Research Training Fellowships compared to recent years. A total of 14 Fellowships were awarded to postdoctoral scientists (from more than 60 applicants) from 12 countries (Australia, People's Republic of China, Colombia, Germany, Indonesia, Republic of Korea, Mexico, the Netherlands, Portugal, Sudan, USA and Zimbabwe).

The IARC Fellowship Programme is partly funded by a generous contribution from the EC-FP7 Marie Curie Actions-People-COFUND programme.

Bilateral fellowships

During 2010–2011, the Agency successfully completed bilateral agreements with the Cancer Council Australia and with the Irish Cancer Society to establish the IARC-Australia and the IARC-Ireland Postdoctoral Fellowships. The first IARC-Australia fellowship was awarded in 2011 to Dr Suzanne Moore from the Queensland Institute of Medical Research in Brisbane, and the first call for applications is being launched for the IARC-Ireland fellowship. The expansion of these bilateral agreements to other organizations in Participating States, as well as institutes offering extra funding, will continue to be actively pursued to expand both the postdoctoral and senior visiting scientist programmes.

Senior visiting scientist awards

The interest in these awards has steadily increased over the past years, reflecting perhaps a growing interest in developing high-level collaborations with Agency scientists. For the Agency, the possibility of hosting eminent researchers, even for relatively short periods, provides a significant boost to its research activities and collaborations and a superb opportunity for the development of its junior scientists.

The Senior Visiting Scientist Award for 2010 was granted to Dr Jia Chen from the Department of Preventive Medicine, Mount Sinai School of Medicine, New York, USA who spent 12 months developing collaborations with the MOC/EGE Groups.

In 2011 the Agency awarded four Senior Visiting Scientist Awards to: Professor Anssi Auvinen from Tampere School of Public Health, Tampere, Finland to spend six months developing collaborations with the ENV Section; to Professor

Joakim Dillner from the Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden to spend 10 months with the ICE Group; to Professor Anna Giuliano from the Department of Cancer Epidemiology, Cancer Epidemiology Program, H. Lee Moffitt Cancer Centre and Research Institute, Tampa, FL, USA to spend six months with the ICE Group; and to Professor Nanny Wermuth from the Department of Mathematics, Division of Mathematical Statistics, Chalmers University of Technology and University of Gothenburg, Gothenburg, Sweden, to spend 11 months with the BST Group.

Expertise transfer fellowship

These awards aim to promote the training of researchers in LMICs by enabling an established investigator to spend up to 12 months in a host institute in an LMIC to train and develop collaborations in an area related to the Agency's research programme.

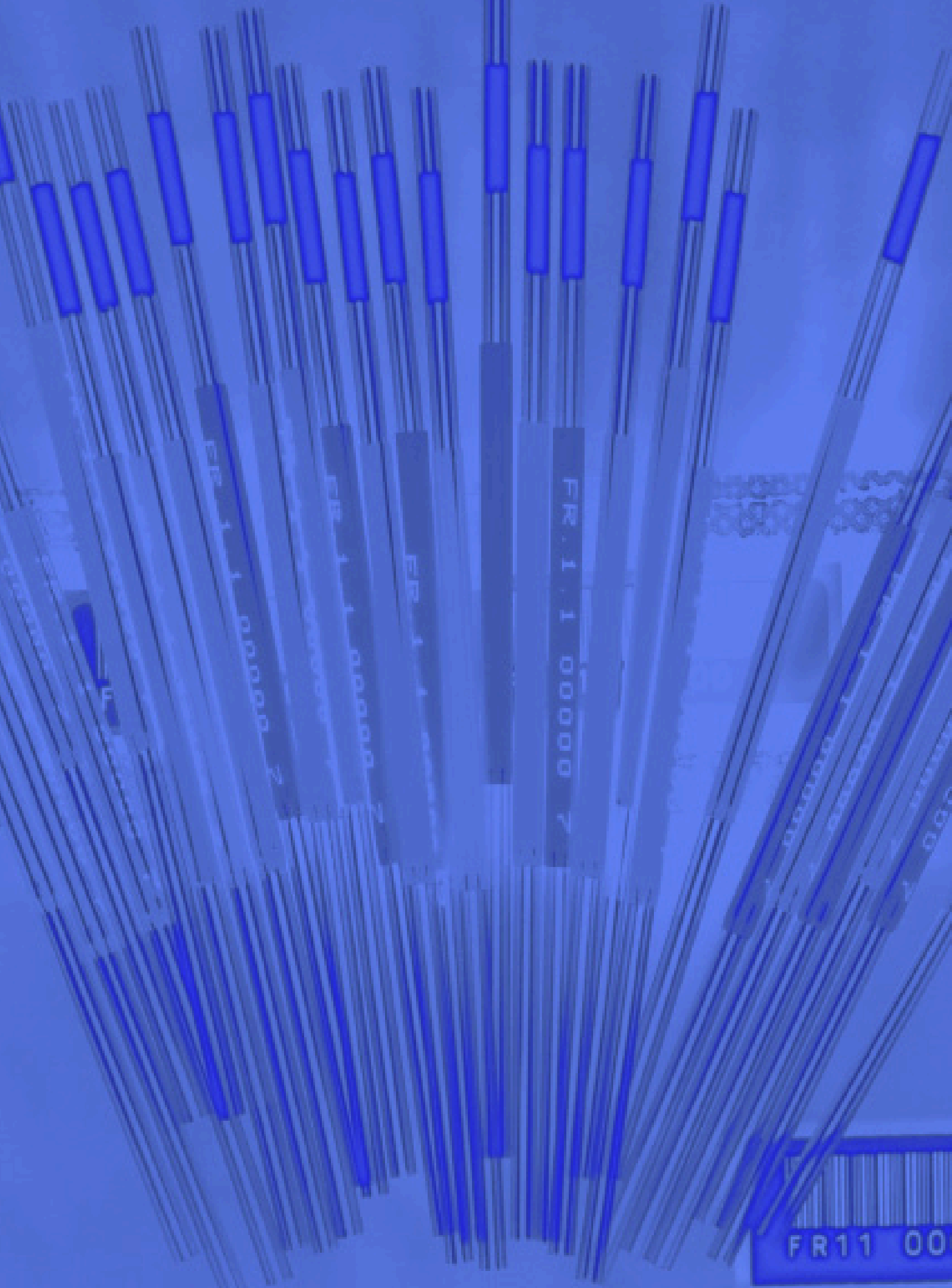
No award was made in 2010. In 2011 the Expertise Transfer Fellowship was awarded to Dr Jean-Michel Lutz from the National Institute for Cancer Epidemiology and Registration (NICER), Zurich, Switzerland to spend 12 months at the National Cancer Registry in Montevideo, Uruguay.

Other postdoctoral scientists at IARC

In addition to the IARC postdoctoral fellows, the Agency hosts a much greater number of postdoctoral scientists supported by project funds from the Groups. In the biennium 2010–2011, IARC welcomed approximately 47 postdocs from 23 countries. The introduction of the Charter, mentioned above, provides a more structured training for young scientists coming to the Agency irrespective of their funding source.

Future directions

In addition to these initiatives, ETR is actively seeking to develop a distance learning programme by initiating partnerships with IAEA-PACT, the Institut Catalan d'Oncologia in Spain, WHO and UICC on the Virtual University for Cancer Control network (VUCCnet). In particular, IARC has been invited to contribute academically to the development and review of e-learning modules for the VUCCnet. As a first step, the focus will be on developing a cervical cancer prevention training module.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Laboratory Services and Biobank Group (LSB)

Group head
Dr Maimuna Mendy

Secretary
Dominique Bouchard

Laboratory services
Brigitte Chapot
Nicole Farina
Maria Maranhao
Marcelle Essertel

Biobank
Elodie Caboux
Elodie Colney
Thomas Cler
Gertrude Tchoua
Jose Garcia
Sophie Guillot
Christophe Lallemand

The Laboratory Services and Biobank Group (LSB) was established in 2010 to address the growing complexity of and rapidly increasing demand for laboratory services and the biobank at IARC. The Group, which is under the Office of the Director, became fully functional when the Head took up the position in October 2010. The creation of LSB provides an opportunity for all laboratory Groups to shape the future of the Agency's laboratories, by strengthening shared facilities and identifying priorities for acquisition of state-of-the-art technology. The Group's formation also ensures the smooth running of a centralized biobank to facilitate the sharing of biological resources and to create new opportunities for research collaboration. LSB is supported by the Laboratory Steering Committee (LSC) and the Biobank Steering Committee (BSC).

Biobank

The IARC Biobank, which is mainly population-based, holds large sample collections from prevalence and risk factor studies and from multiple smaller collections. In total, the Biobank comprises over four million biological specimens. The smaller collections often correspond to pilot studies conducted in low-income countries. Although the majority of the studies are active, some of the collections are archives of important past studies and are not the subject of current research. Samples are stored in liquid nitrogen, in freezers or at ambient temperature (in the case of paraffin blocks and blood filter paper). The Biobank also maintains a sample collection from the European Prospective Investigation into Nutrition and Cancer (EPIC) study, which forms the largest collection in the Biobank. Although EPIC has its own governance under the general guidance of its Steering Committee, the size and level of activity of the EPIC study has a strong impact on the Biobank's services.

Centralized biorepository

An important objective of LSB is to create and maintain a centralized structure by employing a standardized sample management tool. In 2008–2009, following the acquisition of a Laboratory Information Management System supported by an Oracle database, IARC developed its own electronic system for biospecimen/biobank management (SAMI). SAMI, a joint initiative between the Biobank group, GCS and ITS, has undergone improvements and upgrading in the past year. Following its validation under the implementation program, specific data fields for additional epidemiology and sample data have been included along with improved facilities for monitoring sample movement. Similarly, standard operating procedures for sample deposition, data collection and data importation have been developed for users.

The Biobank's resources offer opportunities for collaboration with the international research community. The availability of biological material of diverse geographical origin from different cancer sites from studies conducted through varying epidemiology study designs, provides a valuable resource for biomarker and genetic studies, cancer etiology and risk factor studies.

Biobank services

The aim of the Group is to provide a reliable pre-analytical sample processing service for research projects at IARC and outside the Agency. Over the past 10 years, the emergence of 'omics' technologies has made it necessary to develop laboratory workflow for pre-analytical processing (extraction of nucleic acid and DNA quantification, aliquoting) and sample distribution of a large series of specimens. In this biennium, the IARC Biobank worked on over 20 projects; the majority (70%) for EPIC-based studies. Among the other projects were studies on breast, prostate, lung, kidney and thyroid cancer and on cardiovascular diseases (EPIC-heart). The Biobank also provides pre-analytical services to IARC-based projects conducted by GCS, GEP, MOC, BMA, NEP, ENV and EGE.

Maintaining a financially sustainable biobank is an important focus of the Group. The IARC Biobank operates on a cost-recovery basis, with a major contribution from the central IARC Regular Budget for infrastructure and staff salaries. Most of the consumables and specific staff costs associated with defined biobanking operations are charged, at least to some extent, to the users through various administrative mechanisms (joint grant applications, collaborative research agreements, invoicing). However, the principles and mechanisms of cost-recovery require constant adaptation to reflect the growing diversity and workload of biobanking activities. The challenge is to make the facilities accessible and affordable to the different categories of users and projects.

International biobanking

Of great importance to IARC is its involvement in developing recommendations, standards and publications aimed at establishing international biobanking practices. The Group continues its participation in and provides leadership for these activities. IARC is a founding member of the Forum of International Biobanking Organization (FIBO) and a participant of Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), the International Society for Biological and Environmental Repositories (ISBER) and the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB). IARC is also involved in the EurocanPlatform, a European Union "7th Framework" project aimed at developing infrastructure for European cancer translational research and promoting collaborative multicentre projects.

Laboratory services

The laboratory services arm of LSB provides generic laboratory support services, including the technical management of health and safety, supervision and coordination of equipment maintenance and purchasing, maintenance of supplies of basic laboratory items, and the provision of glassware services.

Health and safety

In the biennium, training programs for new staff members were conducted on specific laboratory procedures to promote health and safety and good laboratory practices. Courses on working safe in category 2 (L 2) facilities, cell culture techniques, safe handling of liquid nitrogen and pipetting skills were conducted for laboratory staff.

To enhance the safe work environment at IARC, the molecular biology laboratories replaced ethidium bromide with the less

mutagenic Gel Red dye for DNA staining, and nitrile gloves with allergenic latex gloves. In response to the introduction of the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS), laboratory staff were introduced in late 2011 to the new chemical classification. Much of the activities on health and safety issues are conducted in collaboration with the IARC Staff Physician and the Occupational Health and Safety Committee.

Laboratory equipment

LSB is responsible for maintaining current laboratory equipment and procuring new items. To this end, IARC's equipment catalogue was updated and requests for new equipment and maintenance service contracts were reviewed and prioritized. Preventive maintenance contracts were obtained for minor, but critical, equipment items to ensure their continued smooth operation.

In 2011, a next generation sequencing instrument (5500XL ABI) for large-scale targeted sequencing and exome sequencing for genetics and epidemiology studies was purchased. Other major equipment procured in the biennium to support the shared and specialized laboratory research platform, includes a fluorescent microscope, flow cytometer for immunochemistry, and gas chromatograph (see Figures).

LSB has also procured DNA aliquoting robotic apparatus and a multi-well plate reader; a solid phase extraction robot, a real-time PCR detection system and DNA-quantification system; and a high-performance sonicator.

A laboratory store has been opened to provide commonly used items such as disposable plasticware for molecular and cell biology. This service is cost-effective, allows easy access to consumables and provides homogeneity across IARC laboratories.

Financial support

LSB's core activities are funded by IARC. Additional support to maintain the services and facilities provided to collaborators are made available through externally funded projects. Other collaborators include the EPIC steering Commitee and EPIC working group members.

The LSB is grateful to the following for their collaboration:

Benedicte Elena-Herrmann, CRMN, Gilbert Lenoir, LNCC, France; Beate Pesch, BGFA, Federico Canzian, Laure Dossus, Rudolf Kaaks, DKFZ, Heiner Boeing, Tobias Pischon, Potsdam, Germany; Domenico Palli, ISPO, Italy; Marie Braem, Bas Bueno-de-Mesquita, Petra Peeters, UMC, Utrecht, Roel Vermeulen, IRAS, Utrecht, Martine Ros, RIVM, the Netherlands; Xavier Castellsague Pique, Carlos Alberto Gonzalez, Nuria Sala Serra, ICO, Spain; Naomi Allen, Timothy Key, Ruth Travis, Oxford, Adam Butterworth, John Danesh, Nick Wareham, Cambridge, James Flanagan, Elio Riboli, Dora Romaguera-Bosch, Afshan Siddiq, Paolo Vineis, Imperial College, United Kingdom.

The Gambia Hepatitis Intervention Study (GHIS)

Group head
Dr Ramatoulie Njie

National professional officer
Mr Ebrima Bah

The Gambia Hepatitis Intervention Study (GHIS) is a collaborative project undertaken by IARC, the Government of the Republic of the Gambia, and the Medical Research Council, United Kingdom. GHIS was initiated in 1986 to evaluate the effectiveness of hepatitis B virus (HBV) vaccination in childhood for the prevention of infection, chronic liver disease and hepatocellular carcinoma (HCC) in adulthood in a high-risk population. Led by the Director's Office, GHIS is a long-term, high-profile project of the Agency and support in the running of the project is provided by Professor Andrew Hall from the Lonodn School of Hygeine and Tropical Medicine, London, UK.

The project involves three phases. During Phase I (1986–1990), HBV vaccine was phased into the Gambian Expanded Programme on Immunization (EPI) using a 'stepped-wedge' design over a four year period (Gambia Hepatitis Study Group, 1987). The unit of randomization was the EPI team, stratified according to four ecological zones. In total, 124 577 children were recruited, about half received all EPI vaccines and half all vaccines plus HBV. In Phase II (1991–1997), the efficacy of the vaccine against infection and chronic carriage was established. Initiated in 1998, Phase III involves the long-term follow-up of the children in the trial through cancer registration, using HCC as the primary endpoint.

For the purpose of long-term identification of subjects, three methods were established: (1) at recruitment, personal details of children were recorded, such as name, parents' names, birth date, sex, etc.; (2) at the age of four months or older, palm- and footprints of each child were taken; and (3) the usual site of the Bacille Calmette Guérin vaccination and the resulting scar were altered for children in the study.

At the beginning of GHIS, a population-based National Cancer Registry (NCR) was established. Cases are identified through public health facilities and private clinics. Confirmation of clinical diagnosis is supported by the histopathology unit of the National Health Laboratory Services (NHLS). For HCC diagnosis, clinical criteria, ultrasound and α-fetoprotein are used in combination. Both the NCR and the NHLS have received long-term support from IARC, the former representing one of the only population-based cancer registries in sub-Saharan Africa.

Current status

In Phases I & II, vaccine efficacy was shown to be 84% against infection and 94% against chronic carriage at nine years of age (Fortuin *et al.*, 1993; Viviani *et al.*, 1999).

Phase III, which is currently underway, consists of:

(i) Strengthening the detection and ascertainment of cases of primary liver cancer and of chronic liver disease in the population of the Gambia. This has been approached by appointment of a consultant hepatologist (Dr Ramou Njie) to enhance liver cancer diagnosis and management in the public and private health sectors, with allied improvements in imaging (ultrasonography, fibroscan and computed tomography), laboratory and histopathology services. Liver clinics are being set up around the country, with referral centres at the Royal Victoria Hospital in Banjul, MRC unit in Fajara and New Serekunda Hospital in Kanifing. There are plans underway to conduct monthly outreach clinics in other health facilities around the country, using portable equipment and highly sensitive point-of-care tests, with support from the referral centres.

(ii) Continued registration of cancer cases and of cases of chronic liver disease through the population-based NCR.

(iii) Establishing record linkage between HCC cases in the NCR and the GHIS databases of vaccinated and unvaccinated children, so that the net effect of HBV vaccination in preventing liver cancer, the final outcome of the GHIS, can be evaluated. The latest estimates (Viviani *et al.*, 2008) indicate that the number of cases needed to detect a significant difference between vaccinated and unvaccinated groups will be reached when GHIS subjects are around 30 years old. Overall, between 30 and 35 years of total follow-up will be necessary to obtain unequivocal results. Therefore, the final outcome of GHIS is expected between 2017 and 2020. In parallel with the development of the three phases above, the GHIS framework has fostered studies on viral, environmental and genetic risk factors for HCC, biomarkers of HBV Infection, aflatoxin exposure, long-term efficacy of HBV vaccination and monitoring of breakthrough infections. More recently, the Prevention Of Liver Fibrosis and Cancer in Africa (PROLIFICA) programme, a five year European Union-funded multicentre study which includes the Gambia, is expected to generate important information on whether suppression of HBV with an oral nucleotide analogue reduces the risk of liver cancer in West African populations, as well as the feasibility of population screening and treatment of those chronically infected with HBV. Additionally, PROLIFICA will conduct a large HCC case-control study to identify genetic, proteomic and metabonomic biomarkers for liver cancer. The GHIS and PROLIFICA programmes are co-located in the IARC-funded centre at the MRC unit in the Gambia.

Public health value of GHIS

GHIS is the only randomized trial of HBV vaccination in Africa, and one of only two worldwide examining chronic liver disease and HCC as outcomes. The study has demanded a long-term commitment from its partners over a 30–40 year period to achieve these goals.

Through improving the understanding of the risk factors for HCC and the clinical presentation of the disease in West Africa, this study will provide a framework to develop recommendations and guidelines for effective reduction of the burden of liver cancer in high-incidence areas of Africa. These include the development of 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 strategy adopted for GHIS provides a model for the evaluation of the introduction of new vaccines or other

prevention strategies in sub-Saharan African countries and other low-income regions worldwide. The value and feasibility of population-based cancer registration as an integral part of routine medical and hospital practice to assess the long-term effect of interventions, is evident. In addition, the training of staff to implement the intervention, in this case in the Gambian EPI, the NCR and in the NHLS, has added capacity to the delivery of public health services.

Publications

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The Gambia Hepatitis Study Group (1987). The Gambia Hepatitis Intervention Study. *Cancer Res,* 47:5782–5787. PMID:2822233

Viviani S, Carrieri P, Bah E *et al.*; Gambia Hepatitis Intervention Study (2008). 20 years into the Gambia Hepatitis Intervention Study: assessment of initial hypotheses and prospects for evaluation of protective effectiveness against liver cancer. *Cancer Epidemiol Biomarkers Prev,* 17:3216–3223.doi:10.1158/1055-9965.EPI-08-0303 PMID:18990765

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Division of Administration and Finance

Office of Director of Administration and Finance

Director of administration and finance
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Mr David Allen

Administrative officer
Ms Virginie Vocanson

Secretary
Ms Anne-Magali Maillol

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Administrative Services Office

Administrative services officer
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Mr Gérard Guillerminet (until July 2011)

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Assistants (Supplies)
Ms Fabienne Lelong
Ms Sandrine Macé

Assistant (Registry)
Mr François Deloche

Support staff
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Mr Antoine Hernandez (Driver)
Mr Michel Javin (Reproduction equipment operator)
Ms Rita Kibrisliyan (Receptionist)
Mr Ludovic Ripert (Storekeeper)
Ms Valérie Rut (Secretary)
Ms Séverine Sarboni (Clerk, registry)

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Mr Jean-Paul Bonnefond (until May 2010)
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Mr William Goudard
Mr Hafed Lamouchi
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Ms Karine Racinoux

Secretary to IARC Staff Association Committee
Ms Isabelle Poncet (60%)

Social adviser
Ms Christine Astier

Staff physician
Dr Dorothée Cuche

IARC Grants Office

External relations officer
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Secretary
Ms Jessica Fournera (until February 2011)
Ms Nathalie Lamandé

Information Technology Services

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Mr Philippe Damiecki

IT officers
Mr Philippe Boutarin
Mr Christopher Jack

Support staff
Ms Lucile Alteyrac (Assistant, informatics)
Mr Nicolas Hernandez (Temporary assistant, informatics)
Ms Brigitte Kajo (Clerk - 50%) (until September 2011)
Ms Laurence Marnat (Secretary - 50%)

The objective of the Division of Administration and Finance is to manage and develop the administrative policies, resources, and infrastructure of the Agency in order to effectively support the implementation of its scientific programme and enable the accomplishment of the objectives set out in the IARC Statute. The administrative programme, developed in collaboration with the Director and the scientific groups, reflects and responds to their needs and those of the Agency as a whole. This Division coordinates the implementation of the programme through the development of administrative policies and services that promote a favourable working environment and ensure transparency and accountability throughout the Agency. Its main areas of activities were delivered through the Human Resources Services, the Conference, Office and Building Services, and Budget and Finance Services, complemented by the IARC Grants Office. The Administration also supervises the delivery and maintenance of state-of-the-art Information Technology Services.

During the period 2010-2011 the Administration and Finance team made great strides in making sure the Agency functions well and continuously moves towards greater efficiency and accountability standards. These efforts include the adoption of full accrual accounting standard (IPSAS), the continued improved utilization of the new ERP (SAP), an enhanced human resource management capacity, and negotiations with the Ville de Lyon on appropriate working facilities.

Laboratory Steering Committee

The purpose of the Laboratory Steering Committee (LSC) is to oversee the IARC core laboratory facilities and to advise the Director on their most efficient use.

Created in September 2009, the LSC is tasked with the following duties:

I. To oversee the IARC core facilities, i.e. central store, glass washing, shipment of specimens, and laboratory-related safety issues in consultation with the Occupational Health and Safety Committee (OHSC)

II. To advise the Head of LSB with respect to core laboratory services.

III. To work closely with the Head of LSB and IGO to maximize cost recoveries through extra-budgetary means for general core expenditures.

IV. To monitor and propose updates for IARC equipment and central facilities.

V. To identify possible common activities within IARC Groups and facilitate the development of new centralized operations.

VI. To identify possible external collaborative centres with the potential to facilitate IARC activities.

VII. To promote initiatives that could positively influence the workload of IARC staff, safe working conditions and cost efficiencies.

VIII. To advise the Director on opportunities to better match the laboratory organization and function to the IARC Medium-Term Strategy.

The Committee was appointed by the Director for a two year period, with a rotating Chair, and includes the following representatives of IARC scientific Groups:

The LSC significantly contributed to the improvement of IARC laboratory facilities and the purchase of laboratory equipment for the central platform. A noteworthy example is the next generation DNA sequencer purchased in 2011.

Name	Group or function
Dr A. Scalbert	BMA
Ms B. Chapot	LSB
Dr Z. Herceg	EGE
Dr V. Krutovskikh	EGE
Dr F. Le Calvez-Kelm	GCS
Dr J. McKay	GCS
Dr M. Mendy	LSB
Dr H. Ohgaki	MPA
Dr M. Olivier	MOC
Dr S. Rinaldi	BMA
Dr B. Sylla	ICB
Dr M. Tommasino	ICB

Biobank Steering Committee

The number of biological specimens stored at IARC exceeds four million and continues to grow with the ongoing activities of IARC's scientific Groups. The biobanked samples are derived from a conglomerate of studies carried out by IARC over the course of the Agency's history, including the European Prospective Investigation into Cancer and Nutrition (EPIC) study. These investigations, with a variety of scientific goals, have produced a wide range of biological sample types from different countries.

The diversity of scientific activities within the Agency creates some distinctive challenges for biobanking activities. Considerable resources are required for the management of heterogeneous samples and a complex infrastructure is needed to house them for long-term archiving or ongoing use. As the IARC biobank expands and the use of material becomes more varied, additional logistic requirements will be needed in terms of infrastructure, governance and how to best maintain efficient access for the biobank users.

The IARC Biobank Steering Committee (BSC) was created in November 2010. It is tasked with assisting the LSB Head and the Director in the ongoing management of the IARC biobank and ensuring that it meets the needs of its users.

BSC has five key overall duties:

I. To provide advice to the Director regarding the strategic development of current and future IARC biobanking activities and how they fit within the IARC Medium-Term Strategy.

II. To oversee the IARC biobanking activities and provide general guidance to the Head of LSB for the planning of future projects.

III. To provide strategic and technical advice to IARC Groups in their development of new biospecimen collections and biobanking initiatives, and to liaise with the Laboratory Steering Committee regarding immediate and future needs.

IV. To anticipate opportunities and plan for IARC's needs in the broad area of biospecimen collection and use, including identifying requirements for infrastructure and human resources.

V. To ensure that IARC's biobanking practices remain in line with international ethical standards.

The committee is appointed by the Director for a two year period and includes representatives of IARC scientific Groups and administrative staff with an interest in IARC's biobanking activities. Members through 2011 include:

The key discussion points of the Committee through 2011 have included: the role of the sample storage management system (SAMI) and the level of detail included within this database; concerns regarding third party access to IARC biobanks and how this relates to the framework of the individual studies; the governance of the biobank; the cost recovery programs of biobanking activities for internal and external partners; risk/disaster management; and how to develop and ensure that protocols, as well as relevant details regarding the IARC biobank, are shared with the wider scientific community.

Name	Function or Group
Dr J. McKay	GCS, Chair
Dr G. Clifford	ICE
Dr P. Hainaut	MOC
Dr O. Kelm	IGO
Dr F. Le Calvez-Kelm	GCS
Dr H. Ohgaki	MPA
Dr S. Rinaldi	BMA
Dr N. Slimani	DEX
Dr G. Scelo	GEP
Ms E. Caboux	LSB, ex officio
Dr M. Mendy	Head, LSB, ex officio
Dr E. Seleiro	DIR, ex officio
Ms. E. Françon	Head, ASO, ex officio
Dr A. Scalbert	BMA

Ethics Committee

Following changes initiated in 2009 in the ethics process at the Agency, the renewed and enlarged IARC Ethics Committee (IEC) had its first meeting in April 2010.

The IEC is composed of seven external members, one WHO member and four IARC staff members as follows:

- Professor Clement Adebamowo (external member, Surgeon and Bioethicist, University College Hospital, Ibadan, Nigeria)
- Ms Evelyn Bayle (IARC staff member, Programme Assistant, Screening Group)
- Professor Jean-Pierre Boissel (external member, IRB Chair, retired Professor of Clinical Pharmacology, Claude Bernard University, Lyon)
- Dr Béatrice Fervers (external member, Coordinator, Cancer and Environment Unit, Centre Léon Bérard, Lyon)
- Dr Marc Guerrier (external member, Project Leader, Patients and Communications Service, Paris Hospitals)
- Mr Yazid Ikdoumi (external member, Civil Servant working in local government, Lyon)
- Dr Martyn Plummer (IARC staff member, Statistician, Infections and Cancer Epidemiology Group)
- Dr Abha Saxena (WHO staff member, Secretary, WHO Research Ethics Review Committee, Geneva, Switzerland)
- Dr Eduardo Seleiro (IARC staff member, Scientific Officer, Office of the Director)
- Dr Pierre-Jean Souquet (external member, Head, Pneumology and Thoracic Oncology Unit, Lyon-Sud Hospital)
- Dr Bakary Sylla (IARC staff member, Scientist, Infections and Cancer Biology Group)
- Professor Paolo Vineis (external member, IRB Vice-Chair, Chair in Environmental Epidemiology, Imperial College, London, United Kingdom)

In 2010–2011, IEC met seven times (up to June 2011). To optimize participation, videoconferencing facilities are now available for those members who are unable to attend in person.

The first two meetings were dedicated to reviewing and approving the Standard Operating Procedures, Rules and Procedures and the IARC questionnaire which IARC scientists must submit as part of their application. During these seven meetings, 45 applications were evaluated. Thirty-eight were cleared after ethical review, three were requested to be resubmitted or to provide additional information before clearance and four were given conditional clearance pending submission of further information.

During the September 2010 meeting, a decision was made to change the name of the Committee from Institutional Review Board (IRB) to IARC Ethics Committee (IEC) to better reflect the work carried out. Since the beginning of 2011, Dr Eduardo Seleiro, Scientific Officer in the Office of the Director, has become the twelfth member of the IEC to balance internal/external representation.

After revision by Dr Plummer, a more user-friendly version of the IARC questionnaire was made available to IARC staff in June 2011. Furthermore, to facilitate the workings of the IEC, all documents for bi-monthly meetings are now posted on the Ethics Committee website (http://ethics.iarc.fr/) for perusal by members.

The IARC Ethics Advisory Group (EAV) is a small contingent of international experts that has been joined together to provide guidance on issues where the expertise of a specialist might not be available within the IEC. EAV is comprised of three members whose advice will be sought when considered necessary: Professor Sheila McLean, Professor Michael Parker and Dr Rodolfo Saracci have agreed to serve on the EAV.

The Occupational Health and Safety Committee

The members of the IARC Occupational Health and Safety Committee (OHSC) are comprised of representatives of each laboratory floor, the epidemiology groups, the Biological Resources Centre building (BRC), the Latarjet building and the IARC Staff Association. The Administrative Services Officer, the Staff Physician and the Laboratory Safety Officer are ex officio members. The Chair of the OHSC is nominated by the Director.

The Committee met seven times during 2010–2011. The minutes of these meetings are posted on the OHSC website on the intranet.

Among the educational activities related to health and safety at IARC are: a general safety introduction for newcomers, a fire-extinguisher briefing, a course for the emergency first-aid team, training programmes for newcomers in the laboratories and for workers in the Level-2 and Level-3 facilities, and a course on the hazards of handling liquid nitrogen.

The Laboratory Safety Officer, who is a member of the OHSC, is responsible for radioprotection at IARC. The number of people registered to handle radioisotopes remains low (10-15) and experiments involving radioisotopes are becoming less frequent. Following the detection of slightly elevated levels of radiation from the building materials of the inner walls on the 5th and 6th floors of the IARC tower, precautionary measures were taken to protect technical staff involved in working on these walls (drilling, demolition) to avoid exposure to dust. Accreditation was obtained for the use of a radioactive isotope of nickel in a recently acquired gas chromatograph.

General safety measures proposed by OHSC include: the replacement of ethidium bromide – a widely used DNA stain – by a less hazardous dye; the purchase of a transilluminator that uses blue light instead of UV; the transfer of small liquid nitrogen tanks from the tower to the BRC building, where the filling of the tanks is less physically demanding; implementation of procedures to control access to the cryogenic room after regular working hours and during weekends; and introduction of a soft hand soap and replacement of latex gloves to prevent skin irritations.

The questionnaire on the use of dangerous products continues to be administered to all laboratory personnel twice a year. The information is used to monitor the pattern of exposure, identify potential hazards, and aid in the development of specific training programmes to meet health and safety needs of the Agency.

The minor incidents reported during the period 2010–2011 did not cause any serious injury.

IARC Governing and Scientific Councils

The International Agency for Research on Cancer (IARC) is presided over 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 representatives of Participating States and of the Director-General of the World Health Organization. Its research programme is regularly reviewed by a Scientific Council. The Governing Council elects IARC's Director for a five year term. The Council elected Dr Christopher Wild in May 2008 to serve for a five year term; he took office on January 1, 2009.

Scientific Council

The Scientific Council consists of highly qualified scientists selected on the basis of their scientific expertise 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 propose up to two experts to replace that member. Scientific Council members are appointed for four year terms by the Governing Council. The purpose of this Council is, among other things, to advise the Director, to make periodic evaluations of IARC's activities, to make recommendations on the programme of permanent activities and to prepare special projects to be submitted to the Governing Council.

Budget

IARC activities are partially funded by the regular budget contributions paid by its Participating States. In addition, substantial funding comes from extra-budgetary sources, mainly grant awards, from both national and international. The regular budget level for the 2010–2011 biennium was approved in May 2009 at a level of € 37 911 000.

Participating States and Representatives of IARC Governing Councils
Fifty-second Session, 13–14 May 2010

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

Mr Geir Bukholm
Norwegian Knowledge Centre for the Health Services
Oslo

Ms Henrietta Blankson
The Research Council of Norway
Oslo

United Kingdom of Great Britain and Northern Ireland
Dr Mark Palmer, Vice-Chairperson
Medical Research Council
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Australia
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No Representative

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Fifty-third Session, 12–13 May 2011

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IARC Staff Publications 2010–2011

Abedi-Ardekani B, Gouas D, Villar S *et al.* (2011). TP53 Mutations and HBX Status Analysis in Hepatocellular Carcinomas from Iran: Evidence for Lack of Association between HBV Genotype D and TP53 R249S Mutations. *Hepat Res Treat,* 2011:475965. doi:10.1155/2011/475965 PMID:21869931

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