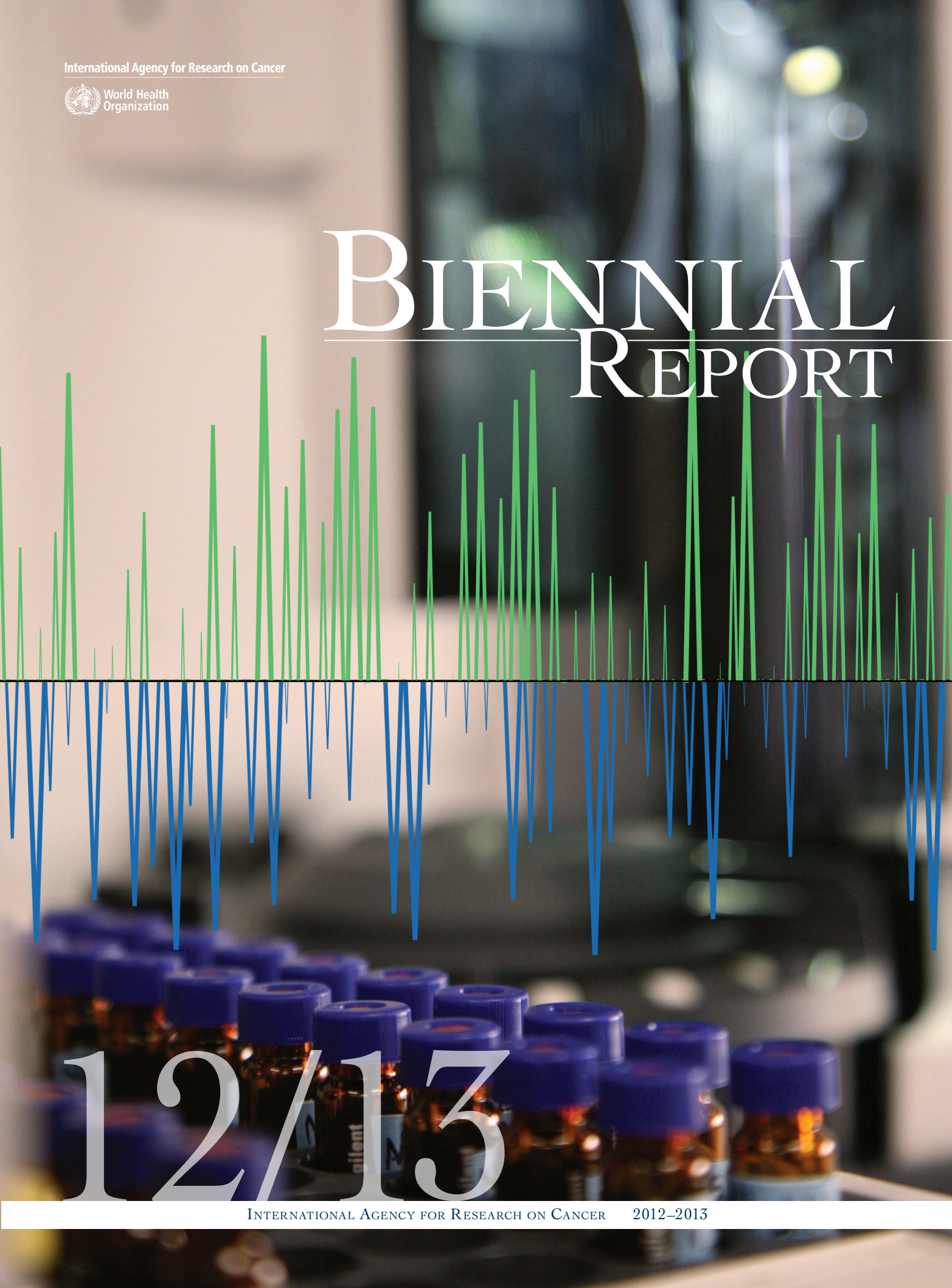
International Agency for Research on Cancer
World Health Organization

# Biennial Report



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International Agency for Research on Cancer 2012–2013

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# Biennial Report

## 2012–2013

International Agency for Research on Cancer

Lyon, France

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# Introduction

**Dr Christopher Wild**

It is an enormous pleasure to introduce this Biennial Report 2012–2013, which provides a summary of the recent achievements of the International Agency for Research on Cancer (IARC). These achievements are a testimony both to the people working at the Agency and to our global network of colleagues and friends who are working with us towards our common goal of reducing the burden of suffering caused by cancer worldwide.

IARC is a research organization that gains new knowledge not only through research projects in epidemiology, biostatistics, and studies of carcinogenic mechanisms but also through the expert assessment of evidence, producing valuable information for the international cancer community and decision-makers in the areas of cancer burden, evaluation of potential carcinogenic agents, prevention strategies, and the classification of tumours. This *research-plus* role is possible only because of the place IARC occupies within the World Health Organization.

The unique nature of IARC is evident through the spectrum of activities covered in the current Report. It demonstrates the high scientific quality of the work emanating from the Agency and the direct relevance of our findings to cancer control and prevention. We are living in exciting times, with cancer research revealing tantalizing links between events at the molecular, population, and clinical levels. Notably, somatic alterations in tumours driven by environmental and lifestyle factors in turn directly affect the prognosis of the patient. The need for an integrated vision, from the molecular level to public health, means that the interdisciplinary approach inherent to IARC has never been more apposite.

The Report also demonstrates that almost 50 years after its creation, the core mission of IARC – to promote international collaboration in cancer research – is more relevant than ever. This Biennial Report also illustrates how the continued response to that core mission has evolved in a marked and dynamic fashion since its inception.

This evolution is nowhere more evident than in the very nature of the partnerships that underpin so much of the Agency's work. It is reflected, for example, in the composition of its Governing Council. In 2013, it was highly significant to see Brazil and Qatar join us as Participating States, bringing fresh representation from two regions, Latin America and the Gulf States. This is a significant trend, reflecting the growing emphasis on cancer as a major public health problem worldwide. It brings with it rich benefits also to those countries who are already long-term supporters of IARC, as new international collaborations and viewpoints shed fresh light on national preoccupations and challenges.

The evolution of IARC is also reflected in the changing nature of many of its scientific collaborations. Growing research capacity in the low- and middle-income countries is providing innovative ideas, regionally-led initiatives, and exchanges of scientists between institutions. Strategic partnerships between IARC and regional cancer networks thus become crucial, as the Agency sets its own priorities in the context of those identified locally. This reflection increasingly highlights, for example, needs in cancer registration, evaluation of interventions, and assessment of how best to implement the successful ones in national health care settings. In turn, this can bring demands for new types of scientific expertise that are needed to enable IARC to continue to respond to the collaborative opportunities of the future.

Finally, in introducing this Biennial Report, I return to the original vision for IARC to promote collaboration – to be a catalyst to promote the *fight for life*. While the 300 people working at IARC provide a dedicated and talented foundation, the Agency is actually a far larger organization comprising a network of many thousands of individuals who come together under the auspices of IARC to achieve its mission. I believe that in this sense of partnership, IARC provides a prime example of what can be achieved through a strong, accountable international organization within the family of the United Nations.

## John Higginson (1922–2013)

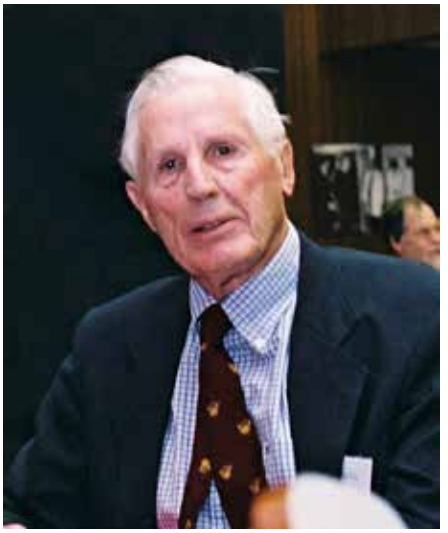
The International Agency for Research on Cancer (IARC) is deeply saddened by the passing away of Dr John Higginson.

An internationally esteemed researcher, Dr Higginson had a special place at IARC and was highly appreciated. In July 1966, Dr Higginson was appointed the first director of IARC and he played a critical role in shaping the then-nascent Agency. He served as director of IARC until 1981.

Born in Belfast, Northern Ireland, on 16 October 1922, Professor Higginson was educated at the Royal Belfast Academical Institution and at Trinity College, Dublin, where he obtained a PhD in biology in 1946 and a doctorate in medicine. From 1947 to 1949, Dr Higginson worked in the Department of Pathology and Bacteriology at the University of Glasgow, and from 1950 to 1958 at the South African Institute for Medical Research, in Johannesburg, where he headed the Geographical Pathology Unit and Cancer Registry.

His studies focused specifically on the role of environmental factors in the development of cancer and cardiovascular disease.

In 1958, Professor Higginson was appointed assistant professor of pathology at the University of Kansas Medical Center, and in 1961 he became a professor of geographical pathology of cancer at the American Cancer Society.



**J. Higginson, 2005**

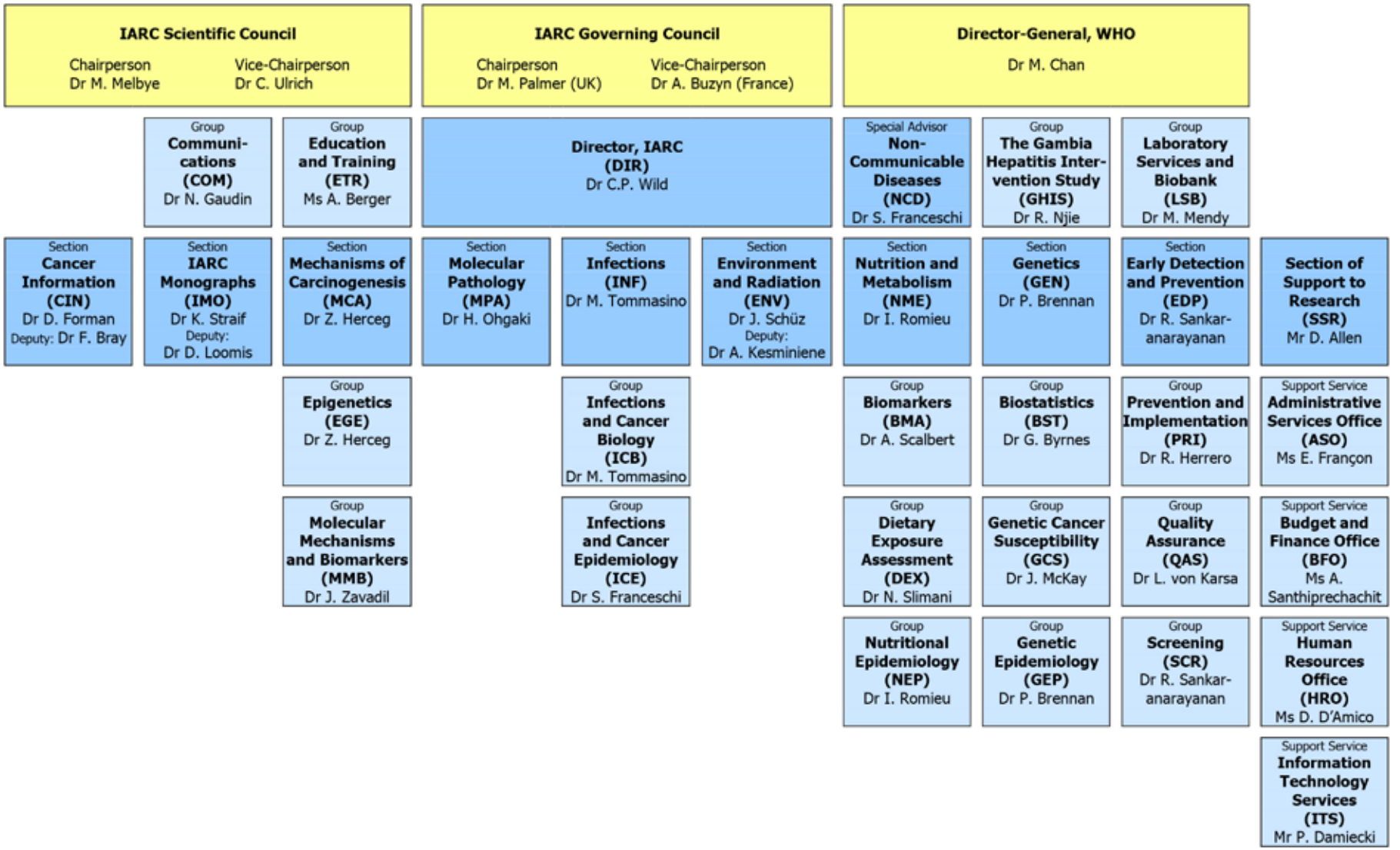
Professor Higginson was a member of the Royal College of Physicians of London, as well as numerous scientific societies, and served on committees of the National Academy of Sciences and the National Institutes of Health in the USA, as well as the International Union against Cancer.

He was the author of numerous scientific papers, mostly on the geographical distribution of cancer, including cancer of the liver and gastrointestinal tract.

*Dr Higginson passed away on 25 September 2013. He will be sadly missed by all who knew him.*

## International Agency for Research on Cancer
## World Health Organization

**21 May 2013**



# IARC Medals of Honour

The IARC Medals of Honour are awarded each year to acknowledge and reward the work of two scientists whose research has made an outstanding contribution to advancing our understanding of the biology or of the epidemiology of cancer. They are usually presented during IARC Day.


Dr Willett


Dr Potter

The theme of IARC Day 2012 (held on 23 October) was Nutrition and Cancer. The IARC Medals of Honour were awarded to Professor John D. Potter (University of Washington, Seattle, USA and Centre for Public Health Research, Massey University, Wellington, New Zealand), who presented the 20th Roger Sohier Lecture – *Nutrition, environment, development, and cancer: casting a wider net* – and to Professor Walter C. Willett (Harvard School of Public Health, Boston, USA) who presented the 9th Sir Richard Doll Lecture – *Diet and cancer: a three-decade follow-up*.

In 2013, the IARC Medals of Honour were awarded to Professor Pelayo Correa (Vanderbilt University Medical Center, Nashville, USA), who presented the 10th Sir Richard Doll Lecture relating to his work on gastric cancer, and to Professor Harold Varmus (Director, National Cancer Institute, Maryland, USA) who presented the 21st Roger Sohier Lecture on his work on the genetics of cancer.

The IARC Cancer and Society lecture series was started during the biennium. The purpose of these lectures is to highlight to all IARC staff the broader social impact of cancer research globally. The inaugural lecture was presented on 28 June 2012 by Dr David Michaels, Assistant Secretary for Occupational Safety and Health, United States Department of Labor and Administrator of the United States Occupational Safety and Health Administration. Dr Michaels' lecture, *Research is necessary but not sufficient: challenges in preventing occupational and environmental cancer*, highlighted the critical role of detailed, authoritative, and independent research evaluations, such as the IARC Monographs, in the development

of policies and regulations to protect workers' safety and the health of the population in general, and the ways in which industry interests can sometimes attempt to interfere with and delay such evaluations.

The second IARC Cancer and Society lecture is planned to coincide with World Cancer Day 2014. It will be presented by Professor Sir Michael Marmot, Director, International Institute for Society and Health, MRC Research Professor of Epidemiology and Public Health, University College London, and will address the topic of social inequalities and cancer.

## 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 retrovirus 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, California, 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
2012 John D. Potter (University of Washington, Seattle, USA and Massey University, Wellington, New Zealand) – Nutrition, environment, development, and cancer: casting a wider net

### Richard Doll Lecture

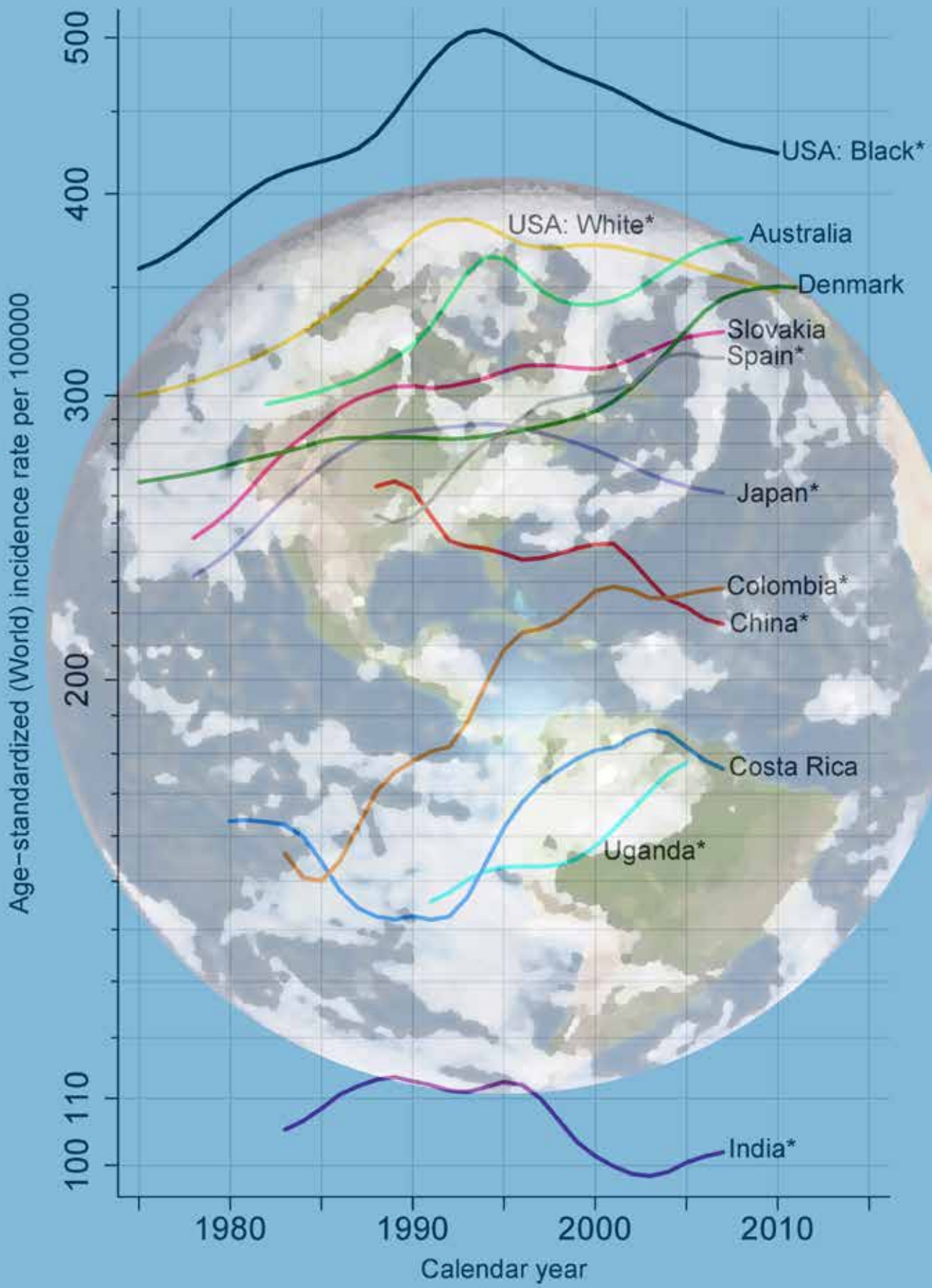
2004 Richard Doll (London, UK) – Fifty years follow-up of British doctors
2005 Brian MacMahon (Needham, Massachusetts, USA) – Epidemiology and the causes of breast cancer
2006 Joseph Fraumeni Jr (National Institutes of Health, USA) – Genes and the Environment in Cancer Causation: An Epidemiologic Perspective
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
2012 Walter C. Willett (Harvard School of Public Health, USA) – Diet and cancer: a three-decade follow-up
2013 Pelayo Correa (Vanderbilt University Medical Center, Nashville, USA)

### 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

### IARC Cancer and Society Lecture

2012 David Michaels (Department of Labor and Occupational Safety and Health Administration, USA) – Research is necessary but not sufficient: challenges in preventing occupational and environmental cancer


Age−standardized (World) incidence rate per 100000
500
400
300
200
100 110
1980
1990
2000
2010
Calendar year
USA: Black*
USA: White*
Australia
Denmark
Slovakia
Spain*
Japan*
Colombia*
China*
Costa Rica
Uganda*
India*

# Section of Cancer Information (CIN)

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**Deputy section head**
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Mr Morten Ervik (until January 2013)
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Dr Nirmala Pandeya
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Mr Mark O'Callaghan (until July 2013)
Dr Brian Rous
Dr Mark Rutherford
(until February 2013)
Mr Jon Shelton (until October 2012)
Dr Patricia Valery (until January 2013)

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Dr Suzanne Moore
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Dr Elisenda Renteria
Dr Monica Sierra

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Ms Karima Chaabna (until July 2013)
Ms Chadia El Khatib (until June 2012)
Ms Jordan Jarvis (until October 2012)
Mr Abdoul Sy (until September 2013)
Ms Yanning Wu (until September 2013)

The goal of the Section of Cancer Information (CIN) is to provide a definitive reference source for information about worldwide cancer statistics. CIN works to fulfil a series of linked objectives to achieve this goal. The primary objective pertains to the collection, analysis, and dissemination of information on the global cancer burden. This is accomplished through collaboration with and provision of support to cancer registries worldwide and through hosting the secretariat of the International Association of Cancer Registries (IACR).

Information obtained from registries is published in the serial reference volumes Cancer Incidence in Five Continents (CI5) and International Incidence of Childhood Cancer (IICC), and in online global cancer statistics tools, including GLOBOCAN, which are available within the CIN web site CancerMondial (http://www-dep.iarc.fr). The 10th volume of CI5 (http://ci5.iarc.fr/) and the 2012 version of GLOBOCAN (http://globocan.iarc.fr) were both published in 2013.

The second objective of CIN is to conduct a research programme in the descriptive epidemiology of cancer, including geographical analyses, time trends, and the estimation of the future burden of the disease for adult and childhood malignancies. These studies are international collaborative efforts aimed at presenting the key indicators

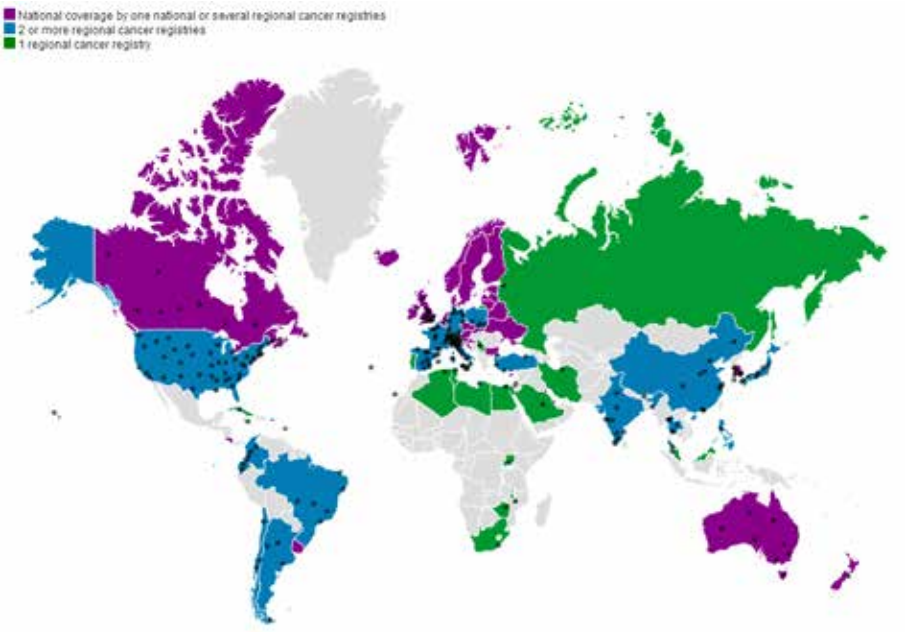
of the cancer burden at global, regional, or national levels. The data are analysed and interpreted so as to enhance our understanding of cancer incidence and mortality and the prospects for cancer prevention and control within the communities under study. New components of the research programme include the development of novel indicators to present the global burden of cancer, such as disability-adjusted life years (DALYs) and analysis of the fraction of cancers worldwide attributable to specific causes of cancer.

To improve the availability of global cancer information, CIN has a third objective: to increase population coverage by high-quality cancer registries, particularly in developing countries. To achieve this, CIN leads the Global Initiative for Cancer Registration (GICR, http://gicr.iarc.fr), which involves collaboration with many international partners. Through GICR, CIN is building a network of regional cancer registry resource centres (Hubs). The Regional Hubs offer a means for providing 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. In 2012, the CIN programme was peer-reviewed and evaluated as of outstanding quality and a perfect fit with the mission of IARC. In the 2012–2013 biennium, CIN has had 58 peer-reviewed papers published.

## New information about the global burden of cancer: 14 million cases worldwide in 2012

CI5 and GLOBOCAN are now established as authoritative sources of information about the global burden and distribution of cancer and are frequently used and cited by cancer researchers and those involved in cancer control planning throughout the world. Work to produce the 10th volume of CI5 (CI5-X), in collaboration with IACR, commenced with the formation in 2011 of an International Editorial Board, which has met frequently by videoconference and has held three face-to-face meetings. After a general invitation to all population-based cancer registries to submit data, responses were received from 372 registries, providing data sets covering 521 populations.

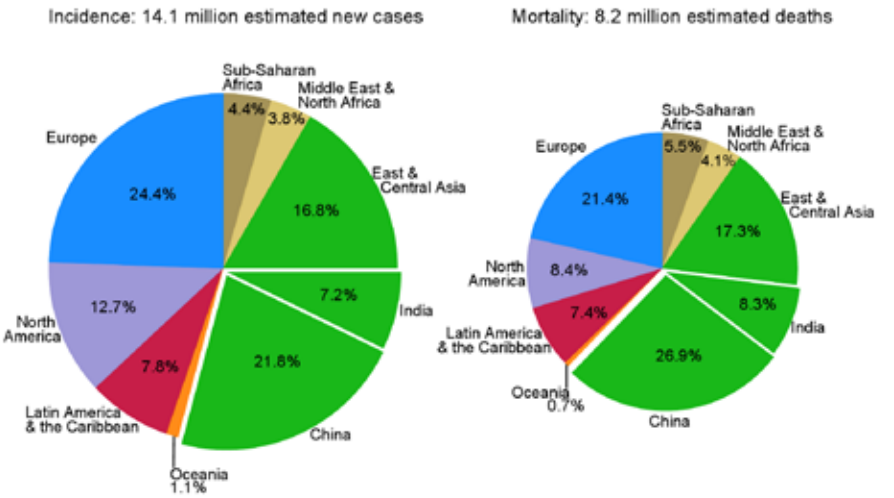
**Figure 1. Map showing locations of the 290 cancer registries (in 68 countries) providing data published in Volume X of *Cancer Incidence in Five Continents.***




After review of all submissions by the Editorial Board, the resulting publication includes data sets from 290 registries that met the Board's quality criteria. These data largely cover incident cancer diagnoses in 2003–2007 and represent 424 populations in 68 countries. The new information contained in CI5-X significantly enhances the temporal and geographical availability of high-quality detailed cancer incidence data. IARC and IACR have also made preparations to publish all the data submitted to CI5-X on a revised IACR web site (http://ci5.iarc.fr/).

Along with the preparation of CI5-X, and making use of data from this and several other resources, including the WHO Mortality Database, CIN has developed an update to GLOBOCAN to provide 2012 estimates of cancer incidence, mortality, and prevalence for 28 major cancer types in 184 countries around

**Figure 2. Estimated global incidence and mortality with proportions by major world regions, for both sexes combined, 2012. (The area of the pie is proportional to the number of new cases or deaths. China and India are shown individually as part of Asia.)**

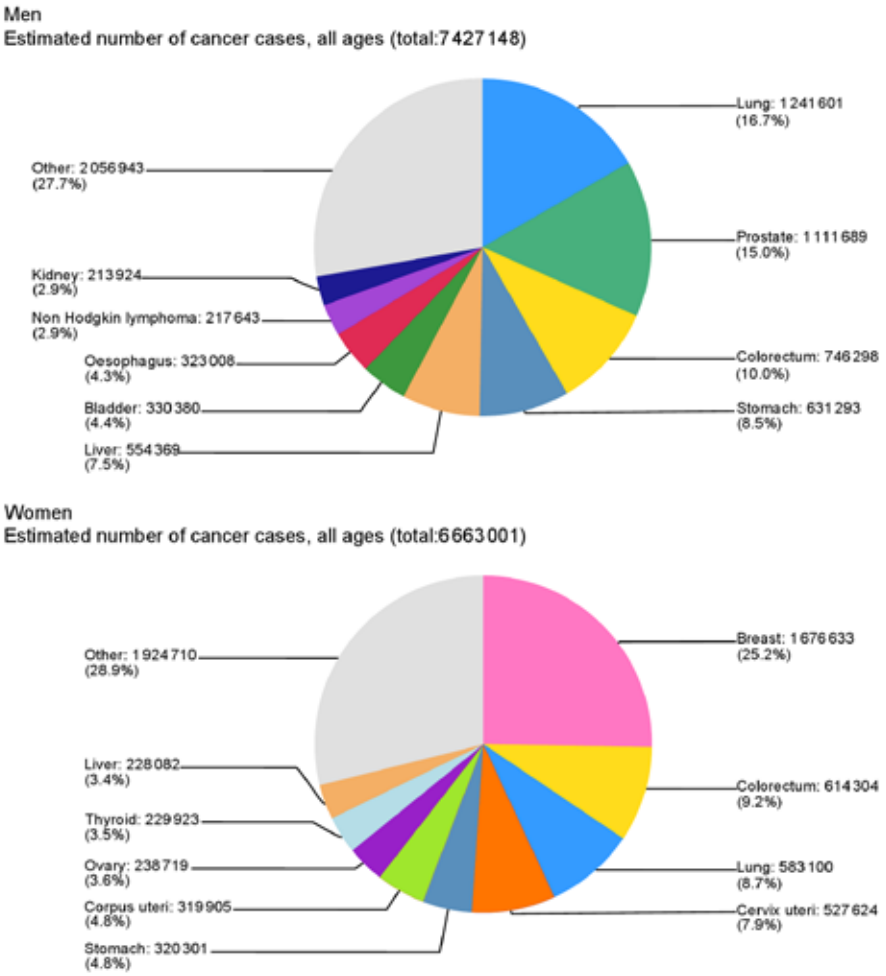


the world. These estimates make use of the best available data for any country. The GLOBOCAN 2012 web site now provides a grading of each country to evaluate the quality of the underlying source incidence and mortality data. An international GLOBOCAN Editorial Advisory Board was appointed to provide input on the selection and interpretation of source data. In 2012, GLOBOCAN estimates that there were 14.1 million new diagnoses of cancer (excluding non-melanoma skin cancer), 8.2 million deaths from cancer, and 32.6 million prevalent cases diagnosed within the previous 5 years. Of the new cancer cases, 8 million (57% of the worldwide total) occurred in developing regions of the world.

CIN ensures that the methodology used in producing the GLOBOCAN estimates is fully described and documented in peer-reviewed papers; for example, the procedures for estimating prevalence were published in Bray *et al.* (2013a). To generate prevalence estimates, these procedures made use of new sources of survival information as a result of more recent and extensive analyses, particularly in developing countries (http://survcan.iarc.fr/). Almost half of the global prevalence of cancer is in areas of very high development, comprising only one sixth of the world's population. Breast cancer is the most prevalent cancer in most countries globally, although cervical cancer is the most prevalent in much of sub-Saharan Africa and South Asia.

To provide more comprehensive insights into the global cancer pattern and its relation to economic development, CIN is using the Human Development Index (HDI) – a composite index based on life expectancy, adult literacy, and per capita gross domestic product – and has been looking at cancer profiles in countries at different HDI levels (Bray *et al.*, 2012). This analysis made extensive use of both CI5 and GLOBOCAN data and showed that cancers of the female breast, lung, colorectum, and prostate accounted for half of the overall cancer burden in the highest HDI regions; in medium HDI regions, cancers of the oesophagus, stomach, and liver were also very common; and in low HDI regions, cervical cancer was more common than

**Figure 3. Estimated world cancer incidence proportions by major sites, for men and women, 2012.**




either breast or liver cancer. In general, the analysis demonstrates that rapid societal and economic transitions in many countries mean that reductions in infection-related cancers are offset by an increasing number of new cases associated with reproductive, dietary, and hormonal risk factors.

A novel measure of the global cancer burden now being estimated within GLOBOCAN is disability-adjusted life years (DALYs) (Soerjomataram *et al.*, 2012a,b). DALYs integrate the commonly used measures of the burden (incidence, mortality, and survival) with measures of disability due to cancer and are calculated by adding the years of life lost (YLL) due to premature mortality and the years lived with a disability (YLD) in survivors. The global DALY is estimated to be more than 169 million years of healthy life, indicating that an individual loses on average about 2 years of healthy life after cancer diagnosis. Irrespective of a country's HDI, the number of years of healthy life lost due to cancer is large, with the highest relative contribution of YLL to the total DALYs estimated in low-resource countries (97%). Colorectal, lung, breast, and prostate cancers were the main contributors to the total DALYs in most world regions, accounting for 18–50% of the total burden of cancer. An additional large burden from infection-related cancers (liver, stomach, and cervix) was estimated at 25% and 27% in sub-Saharan Africa and East Asia, respectively. Results also showed consistently poorer prognosis after cancer diagnosis in low-resource countries, which highlights the need for global public health actions to be increasingly directed towards such settings (Table 1). Currently, plans have been made to extend the project to

study the impact of cancer diagnosis on healthy ageing, to incorporate DALYs in assessment of attributable fraction and effects of intervention, and to use DALYs to estimate the economic burden of cancer.

## Descriptive epidemiology of cancer: monitoring the burden of cancer at the regional and country level and for specific cancers and due to specific causes

### Regional surveillance

Building on CIN's global cancer surveillance activities, two papers have been published exploring in more detail regional patterns in Africa and Europe. The African analysis demonstrates how cancer is an emerging public health problem in the continent, with numbers expected to double in the next 20 years because of rapid population growth and ageing (Jemal *et al.*, 2012). Some specific cancers, notably those of the lung, female breast, and prostate, are being diagnosed with greater frequency due to changes in both lifestyle factors and detection practices associated with urbanization and economic development. The African analysis discusses opportunities for reducing the burden through resource-level-appropriate interventions, including implementation of hepatitis B virus (HBV) and human papillomavirus (HPV) immunization, tobacco control policies, and low-tech early detection for cervical cancer.

The European analysis provides an overview of cancer incidence and mortality in the 40 major countries of Europe and makes use of information from the European Cancer Observatory (ECO, http://eco.iarc.fr) launched in September 2012 (Ferlay *et al.*, 2013). This is a comprehensive web site combining all the information currently available in Europe on cancer incidence, mortality, survival, and prevalence as part of the EUROCOURSE (http://www.eurocourse.org) project (Steliarova-Foucher *et al.*, 2012). The web site provides detailed estimates and country factsheets (EUCAN) for 2012 as well as analytical and presentation tools for cancer registry data (EUREG), and will include a data download mechanism for research use (EUROCIM). All data on the ECO web site are based on data collected by 130 European population-based cancer registries and are added to the web site using a semi-automated system of reception and processing of data through the Registries Portal at https://cinportal.iarc.fr/.

**Table 1. Comparison of rates of DALYs by Human Development Index (compiled from Soerjomataram *et al.* 2012a)**

| HDI | DALYs per 100 000 | YLLs per 100 000 | YLDs per 100 000 | Proportion YLLs/DALYs |
|---|---|---|---|---|
| Very high | 2404 | 2041 | 363 | 84.9 |
| High | 2491 | 2295 | 195 | 92.2 |
| Medium | 2329 | 2207 | 122 | 94.8 |
| Low | 2433 | 2356 | 77 | 96.8 |

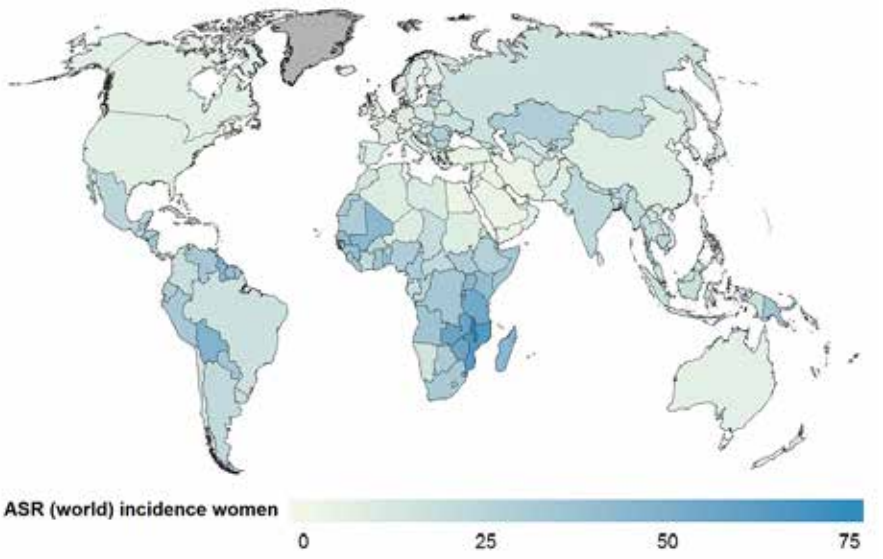
DALYs, disability-adjusted life years; YLDs, years lived with disability; YLLs, years of life lost.

### Country-level surveillance

Several descriptive studies conducted during the biennium have focused on specific countries. They include an updated report on cancer mortality trends in Colombia in 1984–2008. This contrasted trends in the major causes of cancer death with those in other Latin American countries, and assessed the role of national health care reforms (Piñeros *et al.*, 2013). Another study examined the rising trends in breast cancer incidence in Mumbai, India, in 1976–2005, and predicted the cancer burden in 2025 in support of cancer control planning; a near-doubling of incident cases to more than 2500 was estimated for 2025 (Dikshit *et al.*, 2012a).

Given that cancer mortality remains undocumented in various regions and subpopulations of India, IARC collaborated in a nationally representative survey of causes of death in 1.1 million households in 6671 randomly selected small areas (Dikshit *et al.*, 2012b). An estimated 556 400 cancer deaths occurred in India in 2010, 71% of them in persons aged 30–69 years. The high premature mortality burden from tobacco-related, cervical, and other treatable cancers emphasized the role of prevention and earlier detection in reducing cancer deaths, particularly in the rural areas of India presently underserved by cancer services. Other studies have included an analysis of

**Figure 4. Distribution of estimated age-standardized (World) incidence rates (ASR) per 100 000, for cancer of the cervix, 2012.**



testicular cancer incidence in Croatia (Sincic *et al.*, 2012), reporting a 7% per annum increase, one of the largest recorded in Europe and worldwide, and an analysis and elucidation of the reasons for the declining incidence rates of hepatocellular carcinoma in urban Shanghai, China (Gao *et al.*, 2012). Various collaborative studies are in progress, including an analysis of breast and cervical cancer incidence trends in Chennai, India, and cervical cancer mortality trends in Argentina, by region and level of human development.

### Cancer site surveillance

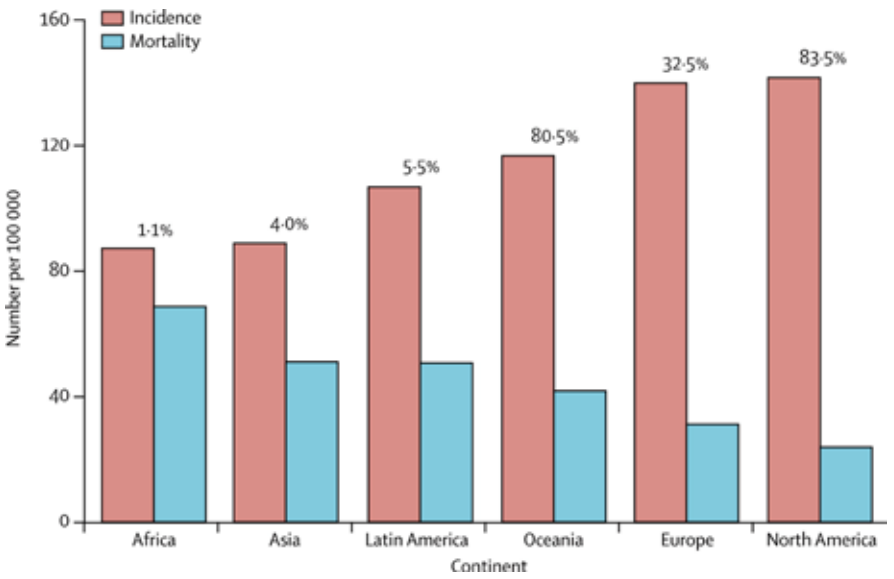
Several descriptive studies have examined specific cancers at the global level. Collaborating with the Section of Environment and Radiation (ENV), we examined melanoma incidence in 39 countries worldwide (Erdmann *et al.*, 2013). While incidence continued to rise in most European countries (at every age), rates were observed to stabilize in Australia/New Zealand, North America, and Norway (at younger ages and among recent cohorts). An age–period–cohort modelling approach to the analysis of cervical cancer trends in 38 countries globally (in collaboration with the Infections and Cancer Epidemiology Group [ICE]) showed that declines in risk over (screening-related) calendar time were observed only in higher-income countries, whereas increasing risk in successive (HPV-related) birth cohorts was seen in most European countries, Japan, and China (Vaccarella *et al.*, 2013). The study underscored the importance of strengthening screening efforts and implementing HPV vaccination programmes, notably in those countries where such cohort effects arise. Another study, part of a continuing series of urological site-specific papers in collaboration with the American Cancer Society, assessed prostate cancer incidence and mortality rates in 40 and 53 countries, respectively (Center *et al.*, 2012). An elevated incidence was seen in more developed countries, while mortality was higher in South America, the Caribbean, and sub-Saharan Africa. In further contrast, incidence increased in most high-income countries, whereas mortality increases were mainly confined to low-resource settings.

Several additional reports have been published on HPV-related cancers. A review estimated that 4.8% of the global burden of cancer could be attributed to HPV infection; this figure varied substantially, from 1.6% in North America to 14.2% in sub-Saharan Africa and 15.5% in India (Forman *et al.*, 2012a). Although cervical cancer accounted for most of this burden (86.9%), the residual burden (13.1%) represents a significant number of cancers of the oropharynx, penis, vulva, vagina, and anus. In collaboration with the United States National Cancer Institute, an international trend analysis in 23 countries revealed increasing oropharyngeal cancer incidence in developed countries, among men, and at younger ages (Chaturvedi *et al.*, 2013). The paper highlighted the importance of HPV infection as an explanatory factor, particularly among men. In a population-based study of incidence and survival trends in Norway in 1987–2007, parallel increases in incidence and survival for oropharyngeal squamous cell cancers were observed; the increased incidence was postulated to be a result of increasing prevalence of HPV-positive tumours (Nygård *et al.*, 2012). An overview of cervical cancer and other HPV-related diseases in central/eastern Europe and central Asia highlighted the elevated cervical cancer rates in certain countries in both regions, and, in the absence of effective screening programmes, an increasing risk of death from cervical cancer among young women (Bray *et al.*, 2013b).

### Childhood cancer surveillance

A recent review article highlighted specific pathological, etiological, and psychosocial issues of cancer in young people (Pritchard-Jones *et al.*, 2013). Age-standardized incidence rates in children (age 0–14 years) vary around the world between 50 and 190 per million and comprise mainly haematological malignancies, central nervous system tumours, embryonal tumours, and sarcomas. In adolescents (age 15–19 years), the haematological neoplasms remain common, and most are lymphomas. Other prominent groups are central nervous system tumours, bone tumours, malignant melanoma, thyroid tumours, and germ cell tumours. Overall incidence rates are 90–300 per million.
Childhood cancer has been a paradigm of therapy success, with survival increasing from 30% in the 1960s to more than 80% today in the populations of high-income countries, even though the recent trends of cancer mortality in childhood populations have reached a plateau. There are very large geographical

**Figure 5. Incidence and mortality rates in children aged 0–14 years according to continent of residence. The percentage of total population covered by cancer registration is also shown. Source: Sullivan *et al.* (2013); reproduced with the permission of the publisher.**



differences in mortality from childhood cancer between developed and developing countries. The percentage of a population covered by cancer registries in each continent is associated concordantly with the incidence rates and inversely with the mortality rates of childhood cancer (Figure 5) (Sullivan *et al.*, 2013). This correlation provides evidence that effective paediatric cancer control programmes that include cancer registration help to improve outcomes (Magrath *et al.*, 2013).

Data on cancer incidence in children and adolescents (age 0–19 years) are being compiled in collaboration with IACR to produce a third volume of *International Incidence of Childhood Cancer* (IICC-3, http://iicc.iarc.fr/), planned to appear in 2014. Approximately 350 cancer registries submitted data, and it is estimated that about 250 peer-approved data sets will be included.

The European Network for Cancer Research in Children and Adolescents (ENCCA, http://www.encca.eu/) aims to improve the management of young people with cancer. CIN is involved in initiating the collection of additional data items with clinical relevance from its network of cancer registries. An extensive questionnaire, asking about current practices and opportunities for registries to expand activities in this direction, was launched in July 2013. The results will inform a standard data set that will be used to launch a call for enhanced data in 2014. Part of the questionnaire also addresses the objectives of another European project, PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup, http://www.pancaresurfup.eu/), aimed at improving the situation of survivors. Data on multiple primaries and late mortality are being collected to produce a baseline status report for Europe. Both projects will contribute to enhanced interpretation of differences in survival.

### Surveillance in indigenous populations

The study of the distribution and determinants of cancer in indigenous populations is an overlooked area of scientific research. From a global perspective, there is a need to identify the similarities and differences between indigenous populations across countries, highlighting disparities and the need for targeted interventions. As part of an IARC-Australia Fellowship, several studies have been completed that combine an extensive review of the literature and an original analysis of available data in different regions or for specific cancer types. This includes an assessment of cancer variations in indigenous populations across the Latin America and Caribbean region (Moore *et al.*, 2013b) and global inequalities in stomach cancer, which noted a rising incidence in certain indigenous groups. Similar exercises exploring childhood cancer profiles among indigenous populations worldwide and a review and analysis of the cancer patterns in the circumpolar region are under way, as is a report aiming to quantify differences in the cancer incidence and mortality rates in indigenous and comparable populations in Australia, New Zealand, Canada, and the USA.

The International Research Network Investigating Cancer among Indigenous Peoples (IRNCIP) has been established to facilitate global research on cancer in indigenous communities. The primary objectives of IRNCIP are to better understand cancer profiles among indigenous people in different countries, interpret results in the context of opportunities for cancer control, and promote awareness among health care providers and policy-makers of relevant cancer issues. This agenda may be further developed in the near future.

### Global attributable risk estimates

Estimates of the number of new cancer cases and deaths attributable to a risk factor are needed for priority setting and for monitoring the disease burden associated with the respective risk factor. In collaboration with ICE, we have estimated the population attributable fraction (PAF) for infectious agents and the corresponding global and regional burdens of cancers associated with such agents (de Martel *et al.*, 2012). In 2008, 2.1 million (16.4%) of the total 12.7 million new cancer cases globally were attributable to infections. This fraction is substantially higher in developing countries (23.4% of the total) than in developed countries (7.5%). The most important infectious agents are *Helicobacter pylori*, hepatitis B and C viruses, and HPV, which together are responsible for 1.9 million cases of gastric, liver, and cervix uteri cancers, respectively. In collaboration with the Section of Nutrition and Metabolism, within a project funded by the World Cancer Research Fund, work has commenced to estimate the PAF for cancer associated with excess body weight. The project requires appropriate data input to derive robust results and also literature reviews to quantify the relative risks of cancers associated with each cancer site. Methodologies are also being reviewed and standardized analytical frameworks are being adopted to estimate both PAF and risk of disease in those exposed. Due to the considerable interest in developing a suite of global and regional PAFs associated with, for example, specific dietary exposures, tobacco smoking, occupational, and, possibly, generic risks or estimating the population impact of interventions (i.e. vaccinations and early detection), we are planning to extend this project to a range of other risk factors established as definite causes of cancer in collaboration with other Sections/Groups within IARC (ENV, Screening Group, Prevention and Implementation Group, Section of Genetics, and Section of IARC Monographs)

### Bringing major improvements to cancer surveillance in developing countries

### The Global Initiative for Cancer Registry Development (GICR)

Subsequent to an IARC Governing Council resolution (May 2009) supporting a special project to improve the coverage and quality of data from cancer registries in developing countries, IARC launched the Global Initiative for Cancer Registry Development (GICR) together with several international partner organizations. GICR was unveiled at the UICC World Cancer Leaders' Summit in November 2011.

The GICR has launched a network of regional registry resource centres (Hubs) as a means to expand the coverage and quality of population-based cancer

registries through increased and tailored support. IARC's role is to coordinate and support the operation of these Regional Hubs, which will become the focal contact points for technical queries from cancer registries, including issues related to the use of the CanReg5 software. Hubs also develop tailored training programmes; conduct advocacy activities in support of cancer registration; and help cancer registries make full use of the data they produce for cancer prevention and control policy and evaluation, and to enhance their output and research capacity. Site visits by IARC and Hub staff are a key component in the evaluation of cancer registry capacity within countries and a way to provide critical recommendations to enhance the operation of cancer registries and bring about improvements in capacity and quality.

Since its launch, GICR has made significant progress with four Regional Hubs established in support of cancer registration in western, central, and south Asia, sub-Saharan Africa (in collaboration with the African Cancer Registry Network), East Asia and North Africa, and Latin America. Discussions are taking place to set up further Regional Hubs for the Caribbean and Pacific Islands. Regional Hubs do not have a uniform structure but adapt to regional circumstances: the two Asian Hubs have physical locations, the sub-Saharan Hub operates as a virtual network, and the Latin American Hub has a physical administrative base and several contributing centres.

During the 2012–2013 biennium, activities by GICR and Regional Hubs included regional training courses (see below); the establishment of collaborative research projects in Africa and in Asia; Collaborative Research Agreements (CRAs) between IARC and cancer registries (e.g. in Sri Lanka, Mongolia, and Indonesia); development and dissemination of advocacy material; presence on the Internet and among the cancer registration community through web sites, newsletters, and networking activities; and extensive interaction with relevant regional stakeholders. CIN staff made site visits to 12 countries in support of population-based cancer registration, providing recommendations to Bangladesh, Bhutan, Cambodia,

**Figure 6. Inauguration of the IARC Regional Hub for Cancer Registration (Tata Memorial Centre, Mumbai, India), October 2012. From left to right: Dr C.P. Wild, IARC Director; Dr R. Badwe, Tata Memorial Centre Director; and Dr R. Dikshit, Regional Hub Principal Investigator.**

Nepal, India, Indonesia, Jamaica, Lao People's Democratic Republic, Puerto Rico, Thailand, Uzbekistan, and Viet Nam.

Financial requirements for GICR increase with the many activities generated by operational Regional Hubs. Fundraising efforts are in progress to ensure adequate support to GICR, with an estimated requirement of US$ 15 million over the next 5 years. The initiative's sustainability strategy focuses on strengthening the capacity of Regional Hubs, increasing regional expertise, and fostering support of cancer registration by national authorities, who should ultimately take responsibility for this fundamental element of cancer control. Progress of the GICR may be followed at http://gicr.iarc.fr.

### CanReg development

CanReg is the cancer registration software package developed by IARC and used in more than 50 countries (mainly developing countries). The CanReg5 software is available for download for free in several languages (presently in English, French, Russian, Portuguese, Spanish, and Chinese) at http://iacr.com.fr. A handbook is also available and is constantly updated. Technical support is available to registries using CanReg on aspects including installation and tailoring, data entry, and analysis.

More than a dozen updates to the software, some major, were released during the biennium. A special focus has been on improving the available analytical capabilities, for example by integrating functionality from R, freely available statistical software, and some powerful libraries. In collaboration with the Northern Ireland Cancer Registry, a tool to facilitate staging of cancer has been developed, which will ultimately be incorporated into CanReg. The first result is a web application available to authorized users via a web browser.

### Training activities

CIN is involved in many varied training activities, ranging from one-to-one mentoring of prospective CanReg5 trainers (eight people trained, from India, Rwanda, Argentina, Nigeria, and Kenya) to organizing major regional courses in cancer registration methods, organized jointly between CIN and the regional Hubs. During the biennium, CIN has hosted such courses in Mumbai, India;

Blantyre, Malawi; Bangkok, Thailand; Jakarta, Indonesia; Cali, Colombia (in Spanish); Buenos Aires, Argentina; and Izmir, Turkey, and has led the cancer registration module for the IARC Summer School. CIN has also provided specific CanReg5 training on courses in The Gambia and has developed a series of webinars on different aspects of CanReg5 management, including installation and customization, data entry, and analysis (all materials are available at http://gicr.iarc.fr/en/resources).

A specialist training course, Paediatric Oncology for Cancer Registries, was held in collaboration with the ENCCA network (http://www.iarc.fr/en/education-training/ENCCAcourse/index.php) in November 2013. The course was designed to help cancer registry personnel understand medical practice, learn about the impact of known prognostic factors on survival and survivorship, and identify the relevant data sources required for collection of enhanced data sets in paediatric oncology.

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Identifying the causes of human cancer is the first step in prevention. The *IARC Monographs Programme* is an international, interdisciplinary approach to carcinogenic hazard identification. Its principal product, the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, is a serial publication that began in 1971 in accordance with one of the fundamental missions of the Agency: to prepare and distribute authoritative information on human cancer and 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, and, since 1987, each Monograph concludes with an evaluation of the overall evidence of carcinogenicity to humans. In general, three volumes of the Monographs are prepared annually. Since 1971, more than 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

has become available in the published scientific literature. More than 100 of these agents have been identified as carcinogenic (Group 1) and more than 300 as *probably carcinogenic or possibly carcinogenic to humans* (Groups 2A and 2B). The Monographs have evolved into the World Health Organization's encyclopaedia on the roles of environmental agents and lifestyle in human cancer causation. National and international health agencies consult 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. Likewise, individuals use the information and conclusions from the Monographs to make better lifestyle decisions 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.

## Overview of activities during the biennium 2012–2013

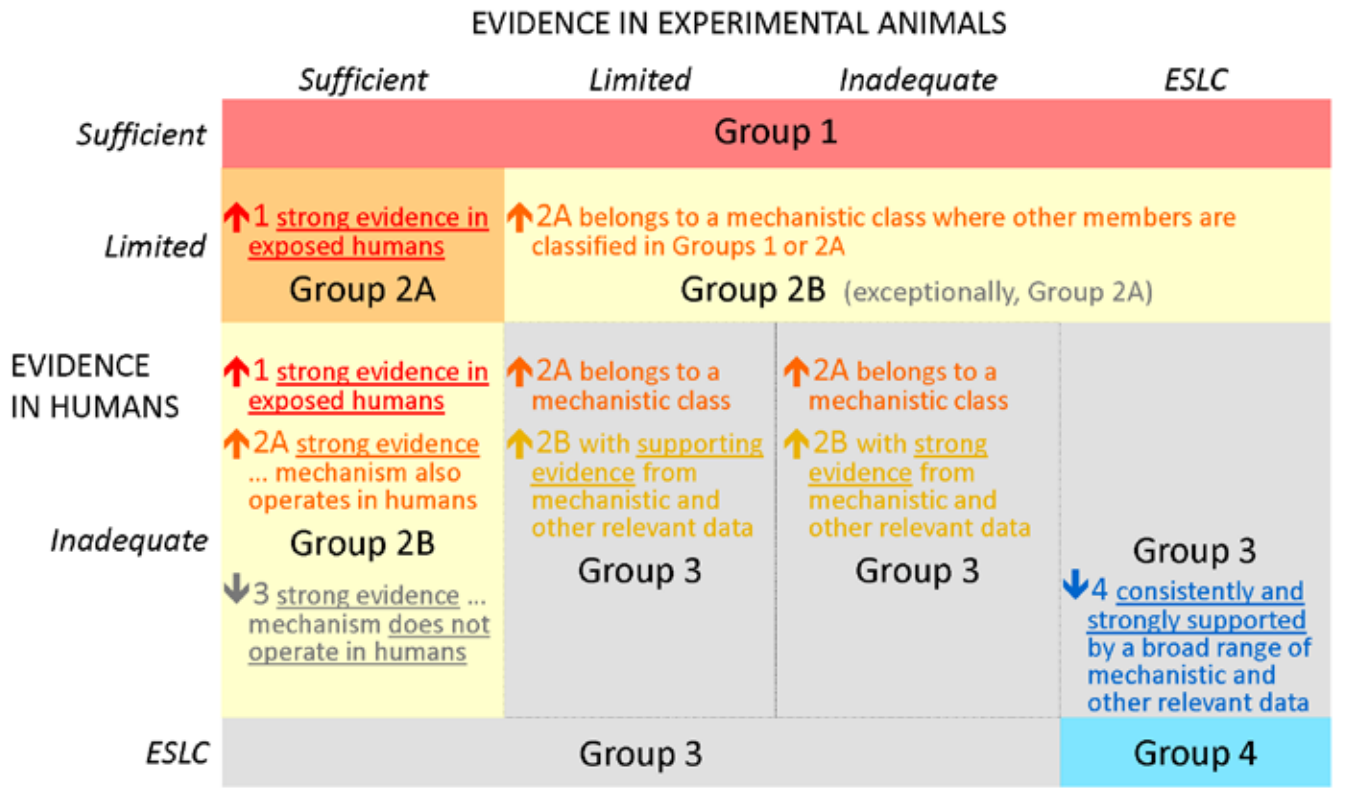
The 2012–2013 biennium saw the publication in print of Volumes 100A–F of *IARC Monographs* updating the more than 100 agents classified by the IARC as Group 1 in Volumes 1–99 (IARC, 2012a–e). Volumes 101–106 (IARC, 2012f; IARC, 2013a–e) were also published online and are freely available on the *IARC Monographs* web site (http://monographs.iarc.fr/). All Volumes since 43 (1989), Supplements 1, 4, and 7, as well as the summary sections of Volumes 1–42 are also available online. Immediately after each meeting, summary reports are published in *The Lancet Oncology*, and these can be freely accessed via the *IARC Monographs* and *The Lancet Oncology* web sites. Six Monographs meetings, two Workshops, and one Advisory Group meeting were held, as listed below.

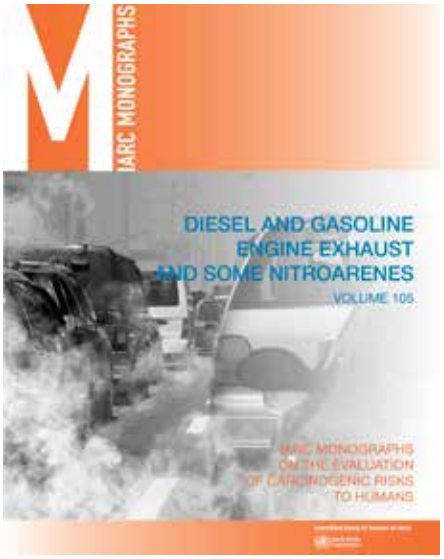
### Volume 104: Polyomaviruses (SV40, BK, JC, and Merkel cell viruses) and malaria (7–14 February 2012)

In February 2012, a Working Group (WG) evaluated several polyomaviruses and malaria. The human polyomaviruses BK virus and JC virus are highly prevalent in humans worldwide and are responsible for lethal non-cancerous diseases in immunosuppressed individuals. Based on *sufficient evidence* of carcinogenicity in experimental animals and *inadequate evidence* in humans, both were classified as Group 2B.

An etiological role of Merkel cell polyomavirus in a rare human skin cancer, Merkel cell carcinoma, is supported by a few case–control studies, several case series, and strong mechanistic data, which led to a Group 2A evaluation. In the 1950s and early 1960s, millions of people received Simian virus 40 (SV40)-contaminated poliovirus vaccines. SV40 is highly tumorigenic in rodents, but the extensive data available did not provide compelling evidence that it infects humans and therefore SV40 was classified as Group 3 (*not classifiable as to its carcinogenicity to humans*). "Malaria caused by infection with *Plasmodium falciparum* in holoendemic areas" was classified as Group 2A based on limited epidemiological evidence that malaria is associated with endemic Burkitt lymphoma (eBL), and strong mechanistic evidence that *P. falciparum* can disturb the immature immune system in young children and reactivate the ubiquitous Epstein–Barr virus, a necessary agent for eBL (Bouvard *et al.*, 2012; IARC, 2013c).

**Figure 1. The *IARC Monographs'* scheme for overall evaluation of carcinogenicity to humans by combining data on cancer in humans, data on cancer in experimental animals, and other relevant data. ESLC, evidence suggests lack of carcinogenicity.**






### Volume 105: Diesel and gasoline engine exhausts and some nitroarenes (5–12 June 2012)

In June 2012, a WG reviewed the carcinogenicity of diesel and gasoline engine exhausts. Diesel engine exhaust was classified as Group 1 based on *sufficient evidence* that exposure is associated with an increased risk of lung cancer. The WG also noted a positive association (*limited evidence*) with an increased risk of bladder cancer. The WG concluded that gasoline engine exhaust was *possibly carcinogenic to humans* (Group 2B). The evaluation of 10 nitroarenes (Table 1) led to mechanistic upgrades of 3-nitrobenzanthrone to Group 2B, and of 1-nitropyrene and 6-nitrochrysene to Group 2A; the Group 2B classification of the other seven nitroarenes was reaffirmed (Benbrahim-Tallaa *et al.*, 2012a; IARC, 2013d).

**Table 1. Evaluations of the nitroarenes**

| Agent | Evidence of carcinogenicity in experimental animals | Mechanistic evidence | Overall evaluation |
|---|---|---|---|
| 3,7-Dinitrofluoranthene | Sufficient | Weak | Group 2B |
| 3,9-Dinitrofluoranthene | Sufficient | Weak | Group 2B |
| 1,3-Dinitropyrene | Sufficient | Weak | Group 2B |
| 1,6-Dinitropyrene | Sufficient | Moderate | Group 2B |
| 1,8-Dinitropyrene | Sufficient | Moderate | Group 2B |
| 3-Nitrobenzanthrone | Limited | Strong | Group 2B[a] |
| 6-Nitrochrysene | Sufficient | Strong | Group 2A[a] |
| 2-Nitrofluorene | Sufficient | Weak | Group 2B |
| 1-Nitropyrene | Sufficient | Strong | Group 2A[a] |
| 4-Nitropyrene | Sufficient | Moderate | Group 2B |

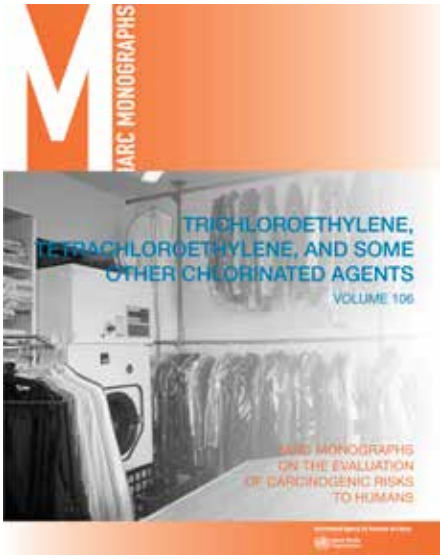
Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans.

[a] Strong mechanistic evidence contributed to the overall evaluation (see text).

Source: Benbrahim-Tallaa *et al.* (2012a); reproduced with permission from Elsevier.

### Volume 106: Trichloroethylene, some other chlorinated solvents, and their metabolites (2–9 October 2012)

In October 2012, a WG reviewed the carcinogenicity of several chlorinated solvents (trichloroethylene, tetrachloroethylene, 1,1,1,2-tetrachloroethane, and 1,1,2,2-tetrachloroethane) and some of their metabolites (dichloroacetic acid, trichloroacetic acid, chloral hydrate). Trichloroethylene was classified as Group 1 based on sufficient evidence for an increased risk of kidney cancer; there was also *limited evidence* for an association with liver cancer and non-Hodgkin lymphoma. Tetrachloroethylene was classified as Group 2A based on limited epidemiological evidence for an increased risk of bladder cancer. Evidence for the carcinogenicity of chloral hydrate was inadequate in epidemiological studies but sufficient in experimental animals. Chloral hydrate was upgraded to Group 2A on the basis of strong evidence of its genotoxicity in most experimental systems and exposed humans. Multiple chronic bioassays in mice demonstrated that dichloroacetic acid, trichloroacetic acid, 1,1,1,2-tetrachloroethane, and 1,1,2,2-tetrachloroethane increased the incidence of hepatocellular tumours as well as tumours in other organs. These agents were classified as Group 2B based on *sufficient evidence* of carcinogenicity in experimental animals (Guha *et al*., 2012).




### Volume 107: Polychlorinated and polybrominated biphenyls (12–19 February 2013)

A total of 209 possible polychlorinated and polybrominated biphenyl (PCB and PBB) congeners have been defined, which differ in the number and position of the chlorines and bromines, respectively. PCBs have been widely used in electrical equipment, while PBBs have been primarily used as flame retardants; numerous studies have reported exposure of workers to these industrial chemical mixtures in many different settings. Due to their widespread use and their chemical stability, PCBs have become ubiquitous as environmental contaminants. On the basis of sufficient evidence in humans that PCBs cause skin cancer and *sufficient evidence* of carcinogenicity in experimental animals, the WG classified PCBs as Group 1. PCBs with a toxic equivalency factor (TEF) as defined by the World Health Organization and commonly referred to as "dioxin-like PCBs," were also classified as Group 1 on the basis of *sufficient evidence* of carcinogenicity in experimental animals and of extensive evidence of an aryl hydrocarbon receptor (AhR)-mediated mechanism of carcinogenesis that is identical to that of

2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD). The carcinogenicity of PCBs overall cannot be solely attributed to the carcinogenicity of the dioxin-like PCBs. On the basis of similarities with PCBs in terms of structure and biological activity, and together with inadequate evidence of carcinogenicity in humans and *sufficient evidence* in experimental animals, PBBs were upgraded to Group 2A (Lauby-Secretan *et al.*, 2013).

### Volume 108: Some drugs and herbal medicines (4–11 June 2013)

In June 2013, a WG reviewed the carcinogenicity of 14 drugs and herbal medicines. The drug pioglitazone was classified as Group 2A based on *limited evidence* in humans that its use is associated with urinary bladder cancer and *sufficient evidence* of carcinogenicity in experimental animals. The drugs digoxin and hydrochlorothiazide were classified as Group 2B based on *limited evidence* in humans that digoxin use is associated with breast cancer and that hydrochlorothiazide use is associated with squamous cell carcinoma of the skin and lip. The drugs primidone, sulfasalazine, pentosan polysulfate sodium, and triamterene, and the herbal medicines (or their components) whole leaf extract of *Aloe vera*, goldenseal root powder, *Ginkgo biloba* leaf extract, kava extract, and pulegone were classified as Group 2B based on sufficient evidence of carcinogenicity in experimental animals. The drugs rosiglitazone and methylene blue were evaluated as Group 3 (Grosse *et al.*, 2013).

### Volume 109: Outdoor air pollution (8–15 October 2013)

In October 2013, a Working Group reviewed the carcinogenicity of outdoor air pollution. A complex mixture of pollutants, outdoor air pollution originates from many natural and anthropogenic sources, including transportation, power generation, industrial activity, biomass burning, and domestic heating and cooking. Air pollution levels also range widely over space and time. The levels of most air pollutants have declined in Europe and North America, while they have risen sharply in some rapidly industrializing countries in Asia and South America. The Working Group unanimously classified outdoor air pollution and particulate matter from outdoor air pollution as Group 1, based on *sufficient evidence* of carcinogenicity in humans and experimental animals and strong mechanistic evidence. Exposure to outdoor air pollution, as measured by several indicators including the concentrations of pollutants in the air and measures of exposure to traffic, is associated with increased risk of lung cancer. There is also limited evidence of an association with bladder cancer. Exposure to particulate matter in outdoor air pollution, as measured by the mass concentration of particles, is also associated with increased risk of lung cancer. In addition, the Working Group concluded that there is strong evidence that exposure to outdoor air pollution is associated, in humans and several other species, with increases in genetic damage, including cytogenetic abnormalities, mutations in both somatic and germ cells, and altered gene expression, which have been linked to increased cancer risk in humans (Loomis *et al.*, 2013).

### Air Pollution and Cancer (IARC Scientific Publication No. 161)

*Air Pollution and Cancer,* published in October 2013 as an e-book, presents the scientific background and rationale for Monograph Volume 109, Outdoor air pollution. The initial drafts of most of the 13 chapters were developed as background documents for the meeting of a Special Advisory Group convened in 2004 to plan a series of Monographs on air pollution, including Volumes 92, 93, 95, 103, and 105, as well as 109. The original chapters were updated and two new chapters and a Working Group report were added to provide a broad overview of the current state of the science related to air pollution and cancer. The topics covered by the report include the characteristics and sources of air pollution, issues in assessing exposure, biomarkers, household sources and exposures, and experimental and mechanistic considerations.


### Workshops on Volume 100: Tumour concordance and mechanisms of carcinogenesis: lessons learned from Volume 100 of the IARC Monographs (16–18 April 2012 & 28–30 November 2012)

As a follow-up to Volume 100, two Workshops were organized on "Tumour concordance between humans and experimental animals" and "Mechanisms involved in human carcinogenesis." The database capturing cancer data in animals and their concordance (or discordance) with human cancers has been finalized and is now subject to biostatistical analysis. The second Workshop redefined and fine-tuned the outline for the database on mechanisms. The proposed content of the forthcoming IARC Scientific Publication, with assigned chapters on concordance and mechanisms, was also discussed. The biostatistical analyses of both databases will be part of this publication.

### Advisory Group meeting on Quantitative Risk Characterization (18–19 November 2013)

This Advisory Group (AG) was requested by IMO and asked *"to provide advice to the Programme on the advisability of adding aspects of quantitative risk evaluations to the more qualitative evaluations currently undertaken".* Through two days of discussions and deliberations, the AG developed a number of recommendations for IMO to consider regarding quantitative risk characterization activities. During these discussions, members of the AG

stressed the importance and public health impact of the qualitative hazard identifications that have been the focus of IMO to date and expressed the opinion that expansion of the *Monographs Programme's* focus into more quantitative evaluations should not be done at the expense of hazard identification. The AG recommended a cautious evolution towards more quantification with a more systematic review of quantitative data, particularly from epidemiological studies on cancer in humans but also on exposure distributions in populations, and description of exposure levels at which cancers in bioassays and other pertinent effects in mechanistic studies were observed. Further, the Monograph Working Groups could review cancer burden and other risk scenarios from the literature. Given limited time and resources, the AG felt that Working Groups should not formally review published risk assessments from other national or international agencies. Outside of the Working Group meetings, the AG identified a need for estimating global cancer burdens and encourages IARC to pursue cancer burden evaluations. The AG also outlined modifications to consider in the Preamble, suggested strengthening the science behind epidemiological exposure–response analyses using workshops and scientific publications, and suggested using databases to capture information from Monograph reviews of the literature. The AG also felt that IARC could play a key role in developing estimates for the global cancer burden from agents reviewed in the Monographs and encouraged IARC to explore ways to implement this. Recommendations from this Advisory Group will be presented at the meeting of the next Advisory Group on Future Priorities for the *IARC Monographs,* which is planned for April 2014.

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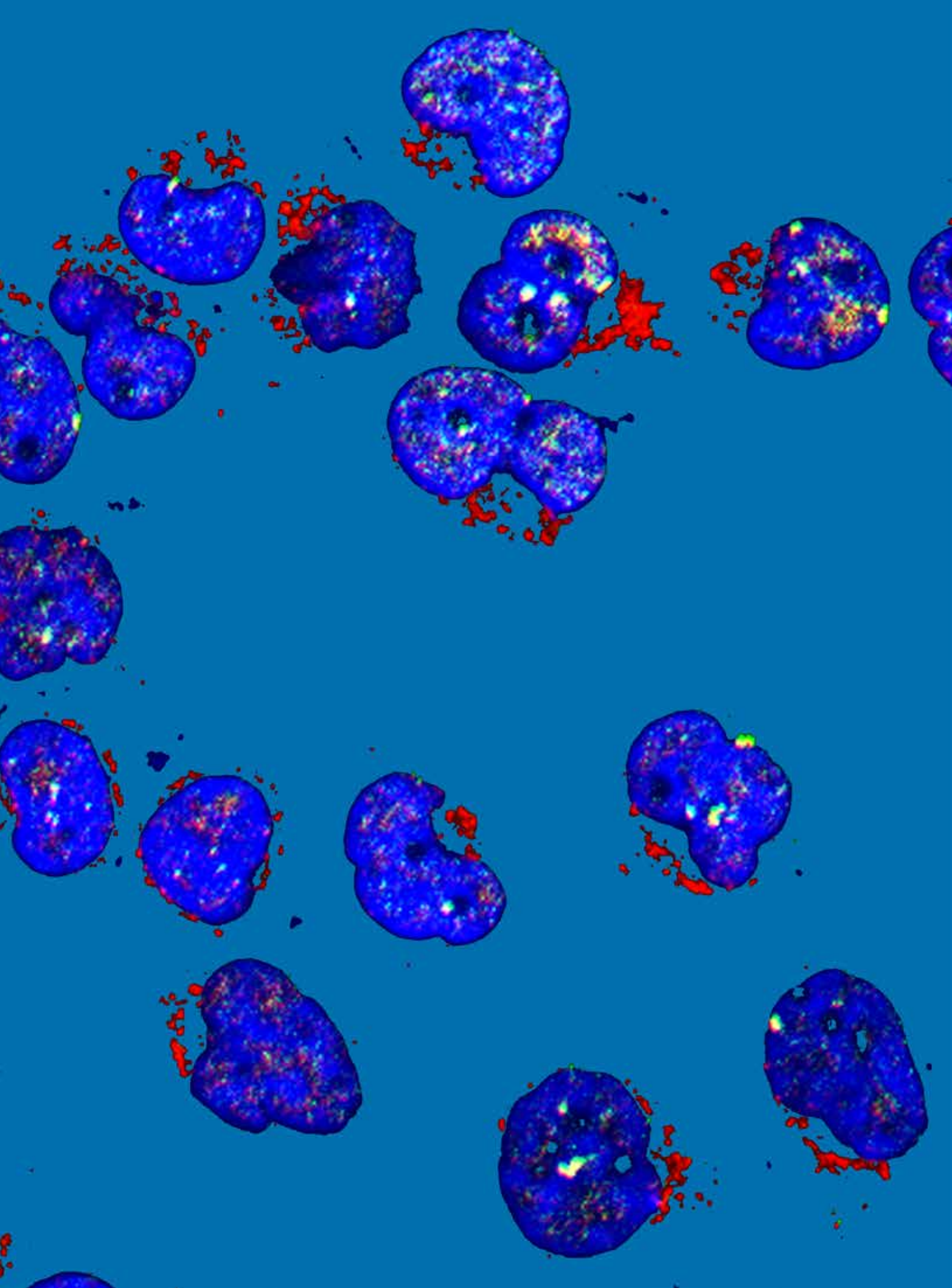

# Section of Mechanisms of Carcinogenesis (MCA)

**Section head**
Dr Zdenko Herceg

Cancers are the consequence of combined genetic and epigenetic changes induced by environmental and lifestyle factors that trigger inappropriate activation or inactivation of specific genes, leading to neoplastic transformation. Although there is consensus that exposures to such factors account for more than two thirds of cancers, meaning that the majority of cancers are potentially avoidable, there is a paucity of evidence about the critical molecular events occurring in the early stages of cancer development or in precursor lesions, as well as the external factors and endogenous cues that trigger these changes. In addition, the challenge posed by cancer genome sequencing efforts is to identify the deregulated genes/pathways and changes in the genome and epigenome that precede and promote tumour development, and to differentiate functionally important drivers from non-functional passenger events. The spectacular advances in genomics and epigenomics have opened up the exciting possibility of simultaneously identifying multiple changes affecting the genome and epigenome of normal, precursor, and cancer cells, as well as their link to the environment. Therefore, it is now possible to improve our understanding of the mechanisms underlying carcinogenesis and define which genetic and epigenetic alterations, or combinations thereof, can be interpreted as reliable biomarkers of exposures.

The broad, long-term goal of the Section of Mechanisms of Carcinogenesis (MCA) is to advance the understanding of mechanisms of carcinogenesis and to contribute to cancer prevention. This is achieved through a multifaceted programme investigating interactions between genes, the epigenome, and the environment. In collaboration with epidemiology groups, MCA contributes to the development of translational studies through the discovery and validation of biomarkers of tumorigenesis and environmental or lifestyle exposures. The Section also aims to promote the development of cancer research relevant to, although not exclusive to, low- and middle-income countries (LMICs) and common cancers related to these regions of the world. Another focus of MCA is the development of genetic/epigenetic methods that are applicable to biobanks associated with case–control and population-based studies. The Section comprises two Groups: the Epigenetics Group (EGE) and the Molecular Mechanisms and Biomarkers Group (MMB), which work in close collaboration with the aim of creating synergies to better exploit and further expand our unique research tools and expertise.

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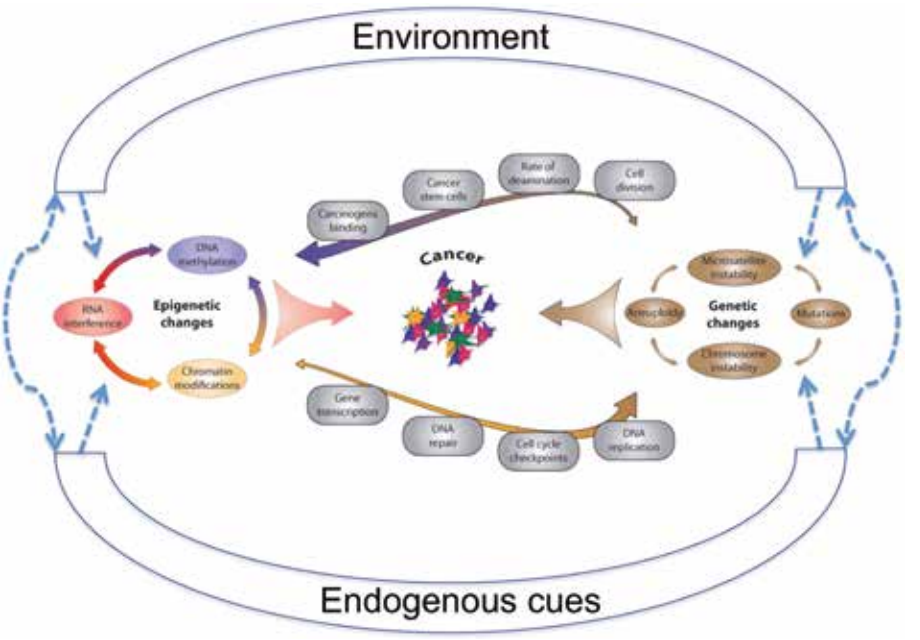
Recent years have witnessed significant advances in our understanding of mechanisms of carcinogenesis. In particular, the importance of epigenetic alterations (methylation, histone modification, small non-coding RNAs) in the development of human cancer opens up new ways in which the environment and lifestyle factors may interact with cells to increase cancer risk (Figure 1) (Herceg *et al.*, 2013). The ubiquity and potential reversibility of epigenetic changes offer interesting opportunities for intervention strategies and biomarker discovery (Herceg *et al.*, 2013; Nogueira da Costa and Herceg, 2012). The Epigenetics Group (EGE) conducts research projects aiming to gain a better mechanistic understanding of tumorigenesis, and discover and validate new epigenetic biomarkers. This programme exploits new concepts in cancer epigenetics and recent technological advances in epigenetics and epigenomics, and is carried out in close collaboration with IARC laboratory scientists and epidemiologists, as well as external groups and consortia.

**Figure 1. Epigenetic mechanisms regulate key cellular processes (such as gene transcription, DNA repair, and differentiation) and play critical roles in cellular responses to environmental exposures and endogenous stimuli. Deregulation of epigenetic mechanisms may promote the development of abnormal phenotypes and cancer. Source: Herceg *et al.* (2013); reproduced with permission from Oxford University Press.**




## Epigenetic changes associated with risk factors for upper aerodigestive tract (UADT) cancers

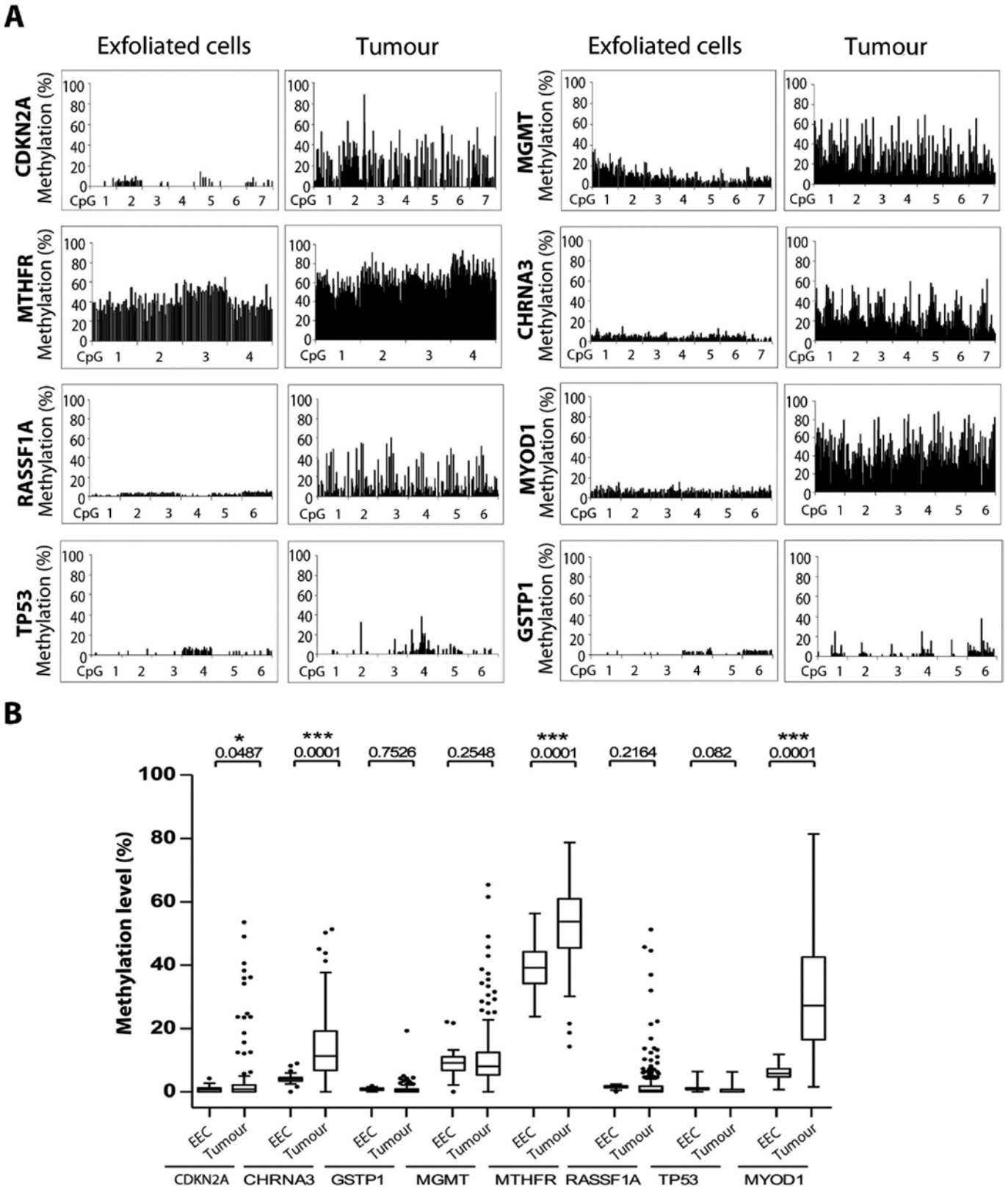
To examine whether the deregulation of the epigenome by environmental, dietary, and lifestyle exposure may disrupt different cellular processes and contribute to cancer risk, we combined quantitative profiling of DNA methylation states in a wide panel of cancer-associated genes using microarray technology and high-throughput pyrosequencing with case–control studies of upper aerodigestive tract (UADT) cancers. Our recent study of promoter methylation in the promoters of more than 800 genes in oesophageal squamous cell carcinoma (ESCC) revealed a panel of differentially methylated genes related to several pathways, including the IL-10 anti-inflammatory signalling pathway and cell communication pathway, indicating that deregulation of these pathways through epigenetic mechanisms may contribute to ESCC.

We further analysed changes in DNA methylation in UADT cancers and their potential association with primary risk factors. To this end, we have taken advantage of a case–control study of UADT cancer involving seven centres in South America, using detailed lifestyle information and quantitative analysis of DNA methylation in a panel of cancer-associated genes. Our analyses revealed a high frequency of aberrant hypermethylation of specific genes, among which we identified new genes (including the nicotinic acetylcholine receptor gene, CHRN3, and the downstream of tyrosine kinase 1, *DOK1*), suggesting that epigenetic deregulation of these genes may promote the development of UADT cancer (Figure 2) (Mani *et al.*, 2012; Siouda *et al.*, 2012). Importantly, we found that sex and age are associated with the methylation states, whereas tobacco smoking and alcohol intake may also influence the methylation levels in specific genes (Mani *et al.*, 2012). Together, these studies identify aberrant DNA methylation patterns in UADT and gastric cancers and suggest a potential mechanism by which environmental factors may deregulate key cellular genes involved in tumour suppression and contribute to these common human cancers.

## Epigenetic changes in surrogate tissue as cancer biomarkers

Because DNA methylation profiles of the human genome are tissue-specific, we tested the possibility that global methylation levels in surrogate tissues, such as blood, may be used in epidemiological studies. We used two independent but complementary methods to assess global methylation levels in peripheral blood DNA from a well-characterized population-based case–control study (the Long Island Breast Cancer Study Project, with more than 2100 peripheral blood samples). Our results, obtained by pyrosequencing-based assay (LUMA) and genome-wide methylation (Illumina Infinium arrays) profiling, revealed greater promoter hypermethylation in breast cancer cases, while methylation levels in repetitive elements (as revealed by LINE-1 methylation assay) were not associated with breast cancer risk (Xu *et al.*, 2012). This study shows that global promoter hypermethylation measured in peripheral blood may be used in breast cancer risk assessment. Further studies on the samples from a prospective cohort, the European Prospective Investigation into

**Figure 2. The DNA methylation levels in upper aerodigestive tract (UADT) tumours and control samples. (A) Summary of the analysis of DNA methylation of individual CpG sites in eight genes in UADT tumours and exfoliated mouth epithelial cells (EEC) (controls). (B) Graphical representation comparing DNA methylation levels in UADT tumours and control (EEC) samples. Box plots of the summary results obtained by the analysis of the mean levels of all CpG sites analysed for a given gene and the statistical significance for differential methylation in tumours compared with EEC samples. Source: Mani *et al.* (2012); reproduced with the permission of the publisher.**

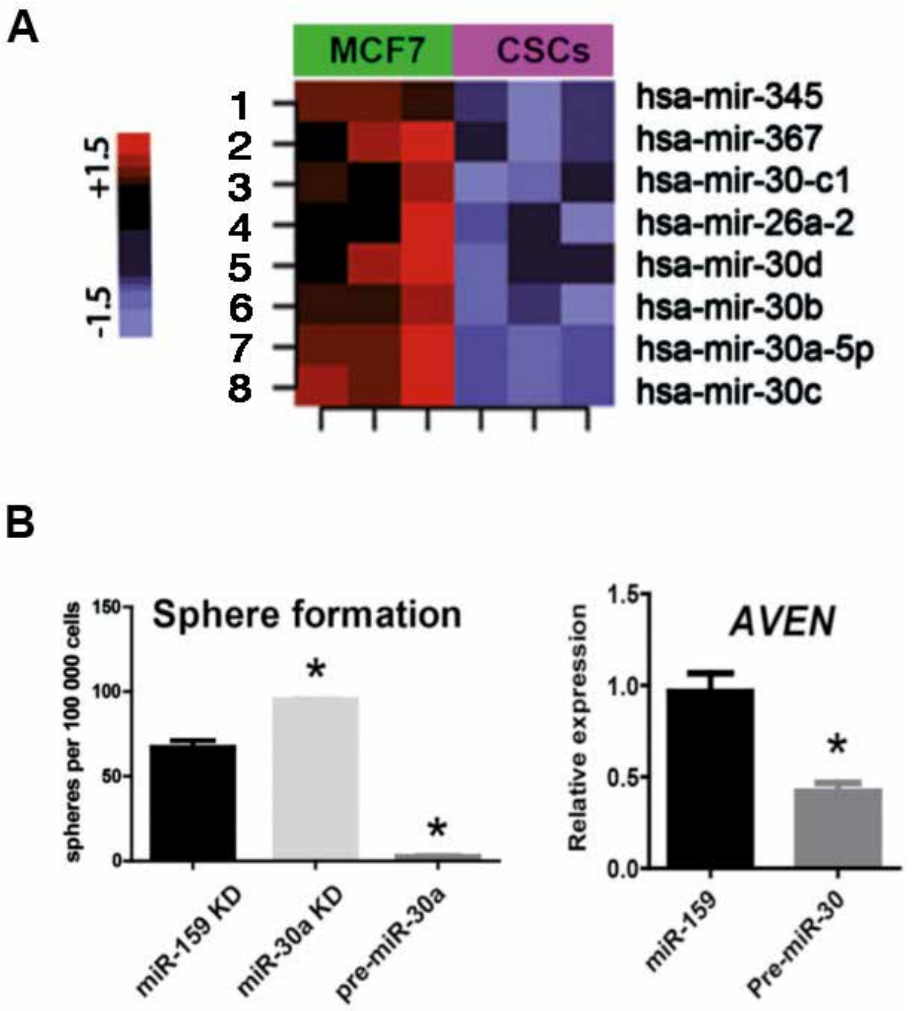


Cancer and Nutrition (EPIC), are under way to assess the value of this marker and address the potential influence of disease onset (reverse causality) and one-carbon metabolism on the methylome of blood DNA.

## Identifying oncogenic microRNAs in cancer development and potential new cancer biomarkers

The recent discovery of a new class of small non-coding RNAs, microRNAs (miRNAs), opened up fresh perspectives in studying mechanisms of carcinogenesis and biomarker research. As miRNAs control developmental programmes in normal stem cells, we explored the hypothesis that miRNAs may have a role in sustaining so-called cancer stem cells (CSCs, also known as breast tumour-initiating cells, BT-ICs). To do this, we performed comprehensive profiling of miRNA expression in a model of putative breast CSCs. We found that CSCs display a unique pattern of miRNA expression, highlighted by a markedly low expression of miR-30 family members (Figure 3). We further showed that the miR-30 family regulates non-attachment growth. A target screening revealed that the miR-30 family modulates the expression of apoptosis- and proliferation-related genes and that some of these targets were able to reverse the effect of miR-30a overexpression (Figure 3). Finally, overexpression of miR-30a in vivo was associated with reduced breast tumour progression (Ouzounova *et al.*, 2013). This is the first analysis of target prediction in a whole family of microRNAs potentially involved in the survival of breast CSCs.

**Figure 3. Identification of microRNAs involved in survival of breast cancer stem cells (CSCs). (A) Comprehensive profiling of microRNA (miRNA) expression in an in vitro model of putative breast CSCs revealed that the miR-30 family is underexpressed in breast CSCs. MCF7 cells were compared with CSCs (selected by their non-attachment growth). (B) miR-30 inhibition (using miR-30a inhibitor oligonucleotides, KD) enhances non-attachment growth, while overexpression (pre-miR-30a) impairs it (left panel). miR-30 targets the anti-apoptotic protein AVEN (right panel). Source: Ouzounova *et al.* (2013); reproduced with the permission of the publisher.**

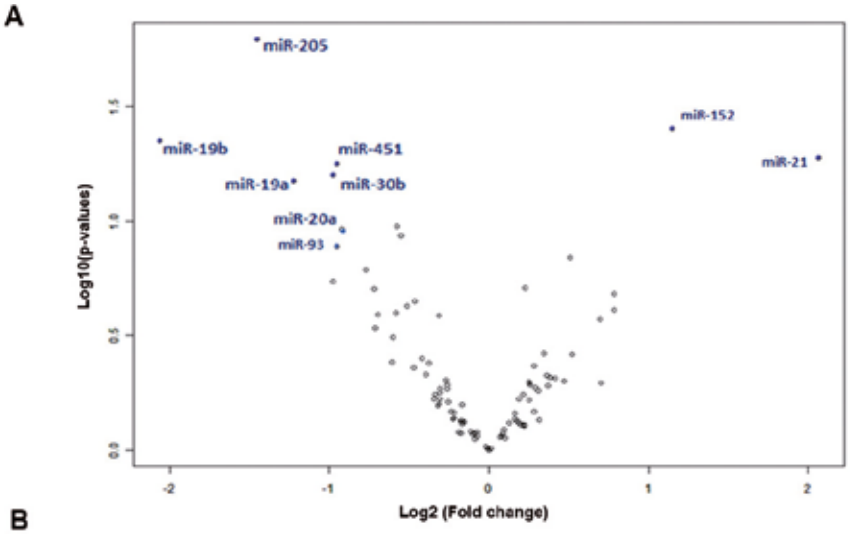



Among different cancer biomarkers, miRNAs are considered the most promising owing to their remarkable stability, their cancer-type specificity, and their presence in body fluids. In a collaborative study between IARC, the N.N. Blokhin Cancer Research Center, Moscow, Russian Federation, and the Hôpital Louis Pradel, Hospices Civils de Lyon, Lyon, France, we compared circulating miRNA profiles in patients with lung squamous cell carcinoma (SCC) before and after tumour removal, assuming that the levels of all tumour-relevant miRNAs would drop after the surgery. Our results revealed a specific panel of the miRNAs (miR-205, -19a, -19b, -30b, and -20a) whose levels decreased strikingly in the blood of patients after lung SCC surgery (Aushev *et al.*, 2013). Interestingly, miRNA profiling of plasma fractions of lung SCC patients revealed high levels of these miRNA species in tumour-specific exosomes; furthermore, several of these miRNAs were also found to be selectively secreted to the medium by cultivated lung cancer cells (Figure 4) (Aushev *et al.*, 2013). These results strengthen the notion that tumour cells secrete miRNA-containing exosomes into circulation, and that miRNA profiling of the exosomal plasma fraction may reveal powerful cancer biomarkers.

## Epigenetic mechanisms in control of cellular processes and cancer

We have previously shown that histone modifications and remodelling are important to provide accessibility to DNA lesions and for efficient DNA repair (Gospodinov and Herceg, 2013a; Sawan *et al.*, 2013). In this study, we identified TRRAP, a critical component of histone acetyltransferase (HAT) complexes, as a novel target of proteolytic degradation in a cell cycle-dependent manner. TRRAP overexpression or mutation-induced stabilization resulted in multiple

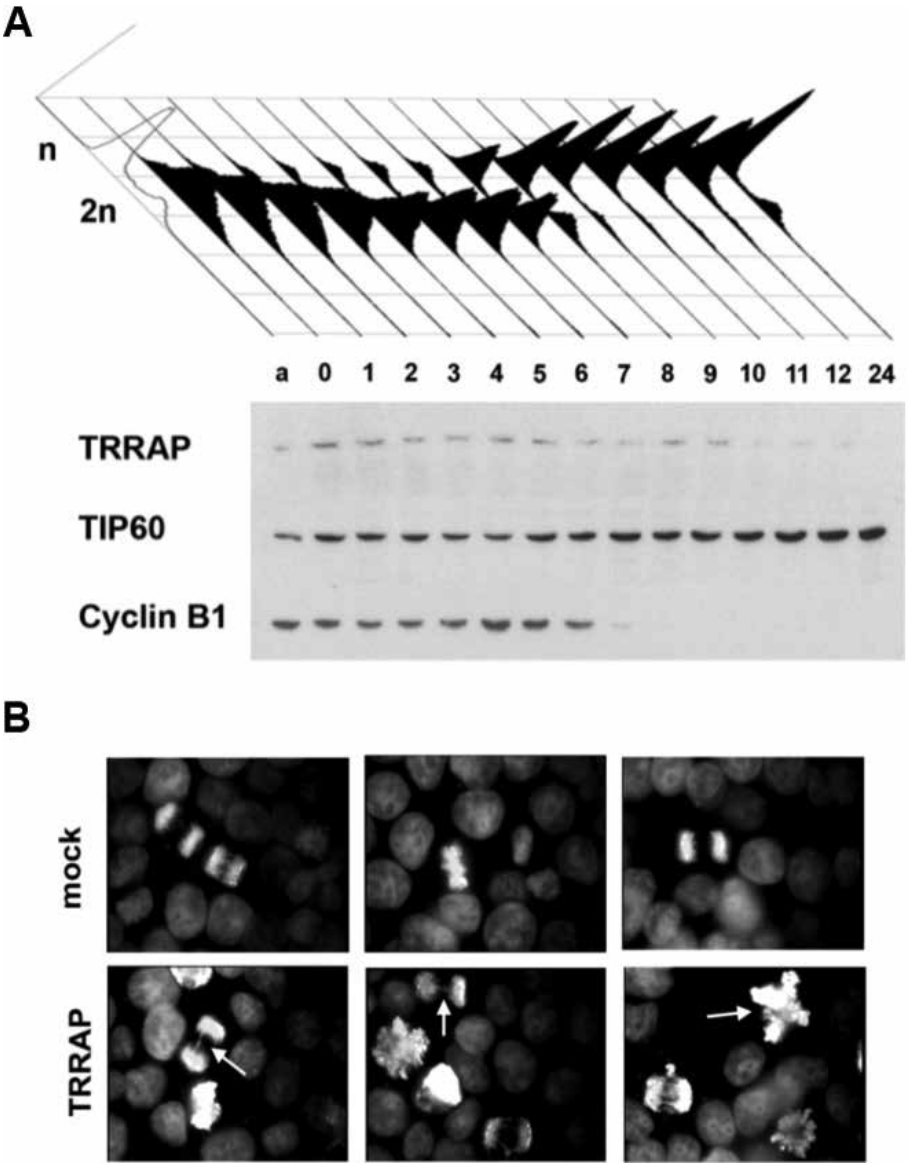
**Figure 4. Comparisons of microRNA (miRNA) patterns in plasma before and after tumour removal reveal new biomarkers of lung cancer. (A) Scatter plot of pre-/post-surgery ratios for expression of the analysed miRNAs in patients with lung cancer. Analysis was performed with BRB-ArrayTools software. The group of miRNAs on the left side of the plot (miR-205, -19a, -19b, -451, -30b, -20a, and -93) are the most abundant in the plasma of lung cancer patients and are reduced in the plasma after tumour removal. (B) Enrichment in expression of various miRNA species in the ExoQuick-precipitated fraction (Exosomal fraction) compared with the ExoQuick-depleted fraction (Exosome-free fraction) of the same pre-operative plasma samples from patients with lung cancer. Source: Aushev *et al.* (2013); reproduced with the permission of the publisher.**




| Rank | Parametric p-value | Fold-change | Unique ID |
|---|---|---|---|
| 1 | < 1e-07 | 0.011 | **let-7a** |
| 2 | < 1e-07 | 0.037 | **let-7c** |
| 3 | 1e-07 | 0.0086 | **let-7f** |
| 4 | 3e-07 | 0.027 | **et-7d** |
| 5 | 6e-07 | 0.0094 | **miR-26a** |
| 6 | 1.8e-06 | 0.033 | **miR-155** |
| 7 | 2.4e-06 | 0.024 | **miR-194** |
| 8 | 2.4e-06 | 0.012 | **miR-30b** |
| 9 | 3.8e-06 | 0.024 | **miR-150** |
| 10 | 3.9e-06 | 0.0034 | **miR-103** |
| 11 | 4.9e-06 | 0.01 | **let-7g** |
| 12 | 8e-06 | 0.013 | **miR-30c** |
| 13 | 1.01e-05 | 0.019 | **miR-191** |
| 14 | 1.43e-05 | 0.026 | **miR-140-5p** |
| 15 | 1.57e-05 | 0.034 | **miR-29a** |
| 16 | 1.66e-05 | 0.033 | **miR-143** |
| 17 | 1.7e-05 | 0.069 | **miR-10b** |
| 18 | 1.72e-05 | 0.076 | **miR-122** |
| 19 | 1.93e-05 | 0.019 | **let-7b** |
| 20 | 2.45e-05 | 0.043 | **miR-21** |

mitotic defects, including lagging chromosomes, chromosome bridges, lack of sister chromatid cohesion, and impaired chromosome condensation (Figure 5). We further found that mitotic defects are associated with a global histone H4 hyperacetylation, indicating that TRRAP and TRRAP-mediated histone acetylation are necessary for proper condensation of chromatin, chromosome segregation, and genomic stability. Together with recent findings of recurrent mutations in the *TRRAP* gene in several cancer types, such as melanoma, pancreatic adenocarcinomas, and hepatocellular carcinoma, our results argue that deregulation of TRRAP/HATs and histone acetylation and the resulting changes in chromatin compaction states may represent an important mechanism of chromosome instability and tumorigenesis.

**Figure 5. Degradation of TRRAP before cell division is critical for proper condensation of chromatin and proper chromosome segregation. (A) Protein levels of the epigenetic regulator TRRAP are cell cycle-dependent. (B) Aberrant TRRAP degradation leads to aberrant mitotic defects and chromosomal aberrations. Source: Ichim *et al.* (2013). *Oncogene*, 41:1187–1203 http://dx.doi.org/10.1038/onc.2012.570 PMID:23318449; reproduced with the permission of the publisher.**




## Development of epigenomic methodologies and profiling strategies applicable to biobanks and population-based cohorts

Remarkable advances in epigenomics have tremendously accelerated research on the mechanisms of carcinogenesis and opened up new perspectives in cancer research (Herceg *et al.*, 2013; Umer and Herceg, 2013; Wild *et al.*, 2013; Nogueira da Costa *et al.*, 2012). EGE has been involved in several long-term projects coordinated by IARC that will continue to make important contributions to cancer research and molecular epidemiology in coming years. These include large prospective cohorts, case–control studies, intervention studies, and consortia (such as the EPIC cohort and the International Childhood Cancer Cohort Consortium [I4C]). Therefore, the development of effective genomic and epigenomic methodologies that are applicable to biobanks associated with population-based studies is among our priorities. For a more comprehensive understanding of the functional elements in the normal human epigenome and cancer epigenome, we have exploited improvements in the throughputs and costs of methylation, histone modifications, and microRNA sequencing brought about by the recent establishment of the pyrosequencing and new-generation array platform (Illumina), as well as the next-generation sequencing (NGS) platform at IARC. EGE has been involved in close collaboration with IARC laboratory scientists and epidemiologists, as well as external groups and consortia, to facilitate the application of these new epigenomics methodologies, allowing cancer epigenomics to move from focused approaches to comprehensive genome-wide approaches. These studies advance our understanding of the epigenetic mechanisms involved in cancer development and may prove to be the reference for future studies aimed at identifying potential biomarkers and molecular targets for prevention (Aury-Landas *et al.*, 2013; Genevois *et al.*, 2013; Kaur *et al.*, 2012; Lee *et al.*, 2013a; Rakosy *et al.*, 2013; Sawan *et al.*, 2013; Siouda *et al.*, 2012; Xu *et al.*, 2012; Zoldoš *et al.*, 2012). They also enhance our collaborations with different groups within and outside IARC, contributing to the overall scientific achievements of the Agency.

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European Commission, Brussels, Belgium
Institut National du Cancer, Paris, France
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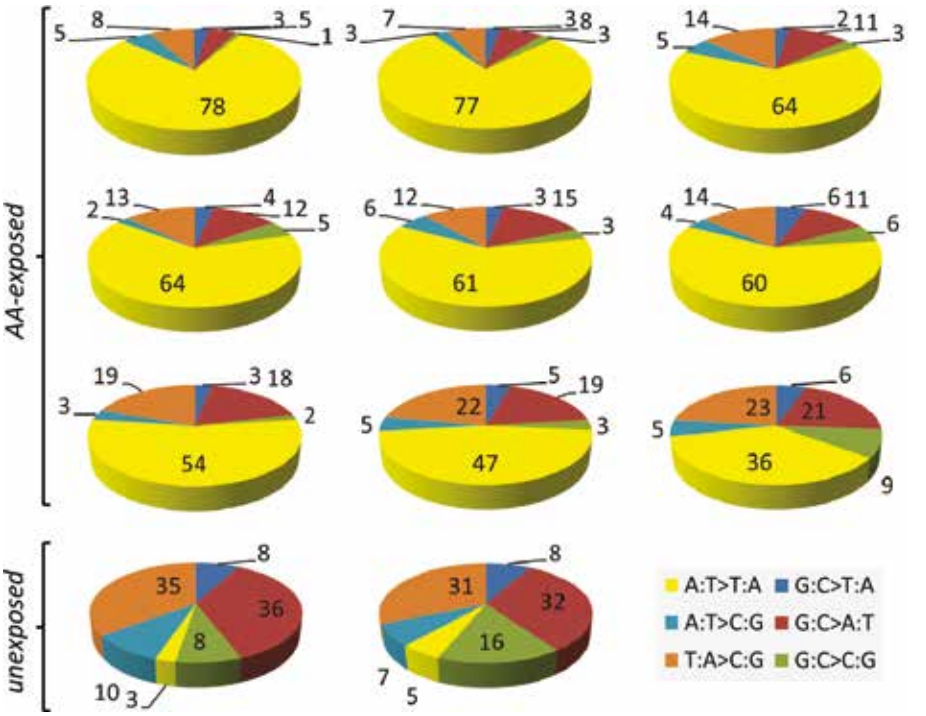
The objective of the Molecular Mechanisms and Biomarkers Group (MMB) is to identify genetic alterations, biomarkers, and molecular mechanisms associated with specific environmental exposures underlying carcinogenesis in humans, and, by using model systems, to distinguish the key *driver* events from non-functional or modifying passenger changes. Using molecular epidemiological and mechanistic approaches, MMB currently investigates urinary tract transitional cell carcinomas linked to dietary exposure to aristolochic acid (AA); triple-negative breast cancer (TNBC), a subtype of breast tumours negative for expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. Next, MMB maintains an online resource (http://www-p53.iarc.fr) on *TP53* mutation patterns and corresponding phenotypes in human cancers. This database compiles comprehensive information on candidate biomarkers of diagnosis, prognosis, and relationships between exposure and cancer etiology. The overall conceptual framework and the results of MMB's work form a basis for future translational cancer prevention programmes on specific human cancers conducted in low- and middle-income countries (LMICs). Here we highlight several of the major findings during the biennium.

## Molecular epidemiology of aristolochic acid-associated urothelial carcinogenesis

MMB participates in an international collaboration to identify genetic alterations and biomarkers associated with urothelial carcinogenesis linked to dietary exposure to AA. AA is a widespread, potent herbal carcinogen (IARC Group 1) and cytotoxin, causing aristolochic acid nephropathy (AAN) and urinary tract urothelial carcinomas (UTUC), with tens to hundreds of millions of individuals estimated to be exposed worldwide. Using high-throughput tumour DNA sequencing, we identified a genome-wide predominance of A:T → T:A transversions, a specific mutation signature of AA exposure (Figure 1). We next determined the UTUC-specific pattern of microRNAs that are currently explored as non-invasive urinary biomarkers of recurrent carcinogenesis

**Figure 1. Identification of the predominant A:T → T:A transversion pattern in aristolochic acid nephropathy (AAN)-associated urinary tract urothelial carcinomas (UTUC) tumour samples. Percentages of individual alterations are shown, as identified by Illumina HiSeq2500 whole-exome sequencing. The average number of mutations per tumour sample was 532 (range, 250–1292).**




in AAN. Collectively, our findings provide an evidence-based rationale for efficient preventive measures and lay the groundwork for cost-effective and high-capacity molecular epidemiological approaches to identify new populations at risk, namely in the LMICs in south and east Asia, and to decrease the AAN-associated cancer burden globally.

## Integrated molecular analysis of triple-negative breast tumours

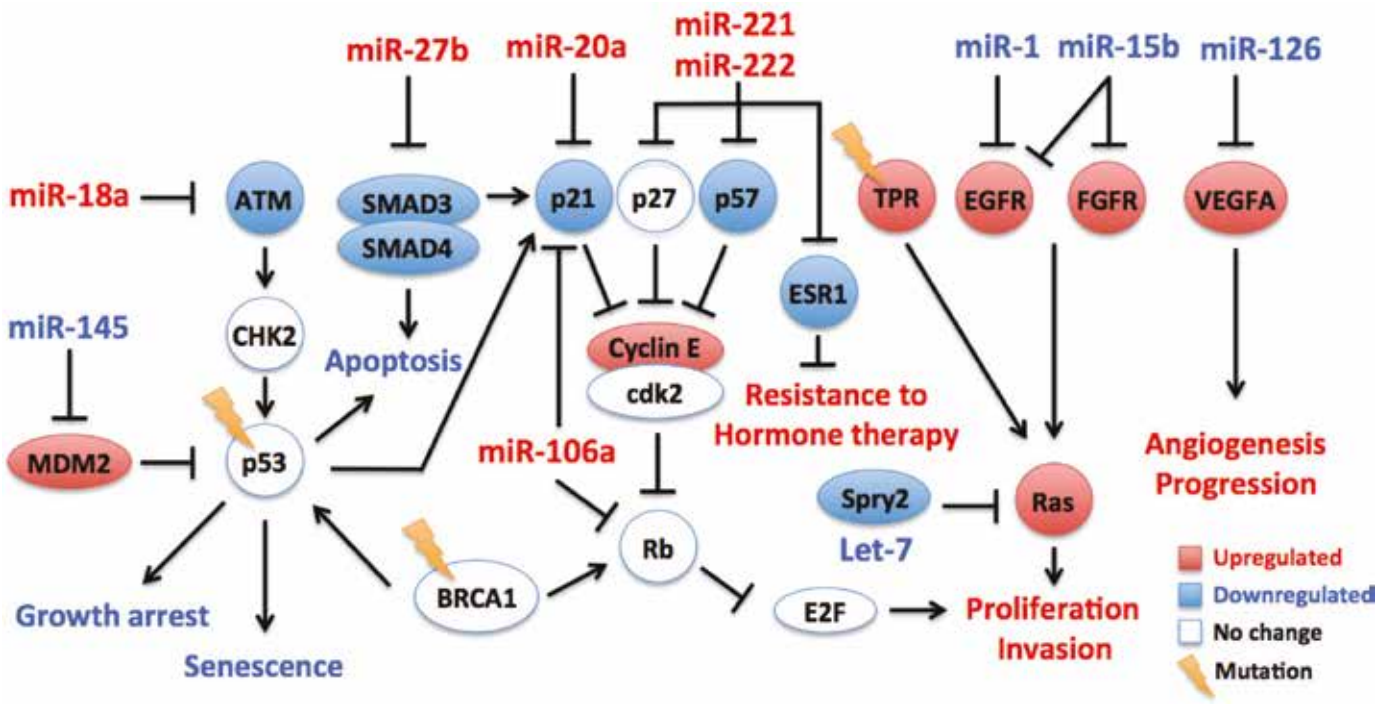
Representing 10–20% of breast cancer subtypes, triple-negative breast tumours (TNBC) is marked by molecular heterogeneity, poor prognosis, and lack of targeted treatment. TNBC is more prevalent in certain populations, such as in Mexicans. We investigated the tumour-specific molecular landscapes of TNBC by integrated high-throughput analyses of archived tumour samples from Mexican patients, combining whole-exome sequencing, transcriptomic (miRNA and mRNA) profiling, and complex bioinformatic analyses. We found deleterious alterations in cancer driver genes such as *TP53* (Table 1), *BRCA1*, *HIF1A*, *RELA*, *PRKG1*, and *KDM6A*, and mutations in DNA-repair genes, consistent with the increased genomic instability observed in TNBC. While the transcriptomic profiling identified signatures of tumour-initiating and -promoting processes, the global aberrant molecular program revealed a degree of ambivalence involving

**Table 1. *TP53* gene mutations in TNBC tumours**

| Mutation type | Alteration | Genomic position (hg19) |
|---|---|---|
| SBS | c.G396C:p.K132N | chr17: 7 578 534 |
| Deletion | c.183_201del:p.61_67del | chr17: 7 578 252–7 578 270 |

SBS, single base substitution; TNBC, triple-negative breast cancer.

**Figure 2. Global gene regulation programs in triple-negative breast cancer (TNBC) tumours in Mexican women, identified by whole-exome sequencing and integrated transcriptomic analysis.**

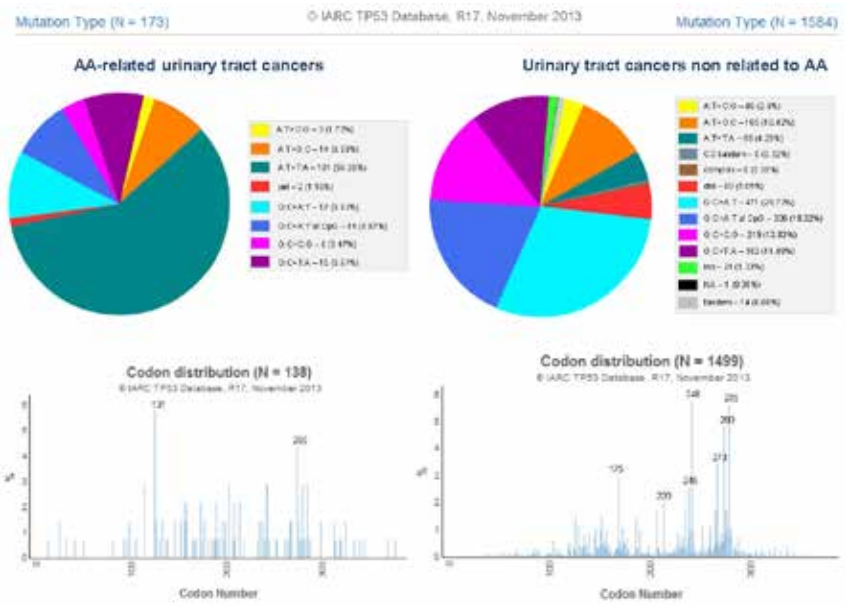



repression of cell cycle control and apoptotic signals and activation of growth- and tumour-promoting cascades (Figure 2).

## The IARC TP53 database of *TP53* gene alterations in human cancers

MMB maintains the IARC *TP53* Database (http://p53.iarc.fr), a public, fully searchable and downloadable online resource with data on gene variations in the most frequently mutated cancer gene. The database allows interpretation of the clinical and biological significance of more than 5000 distinct *TP53* gene variations and provides a wide range of annotations on their structural and functional impacts and on associated tumour pathology, patient demographics, risk factors, and exposures. It compiles data on both germline and somatic variations as well as experimental data on the functional impacts of mutations. The database is a popular resource, which has been cited more than 3700 times in scientific publications and is used worldwide by scientists, clinicians, and trainees. In 2012, the database web site was redesigned to improve its interactivity and allow new data sets to be analysed. MMB also published studies on how research on *TP53* has advanced our understanding of the molecular basis of human cancer, and how this knowledge translates into cancer management, therapy, and epidemiology (Figure 3) (Fernández-Cuesta *et al.*, 2012; Hainaut *et al.*, 2013; Hollstein *et al.*, 2013).

**Figure 3. The IARC TP53 Database web site provides graphical tools for the analysis of mutation patterns in human cancers. It is used as a data mining tool and a reference data set for molecular epidemiology studies. The example graphs show the different mutation patterns observed in urinary tract cancers from acid aristolochic (AA)-exposed patients (left panels showing a predominance of A:T → T:A at specific hotspots) and from patients non-exposed to AA (right panels showing a predominance of G:C → A:T mutations in different hotspots).**



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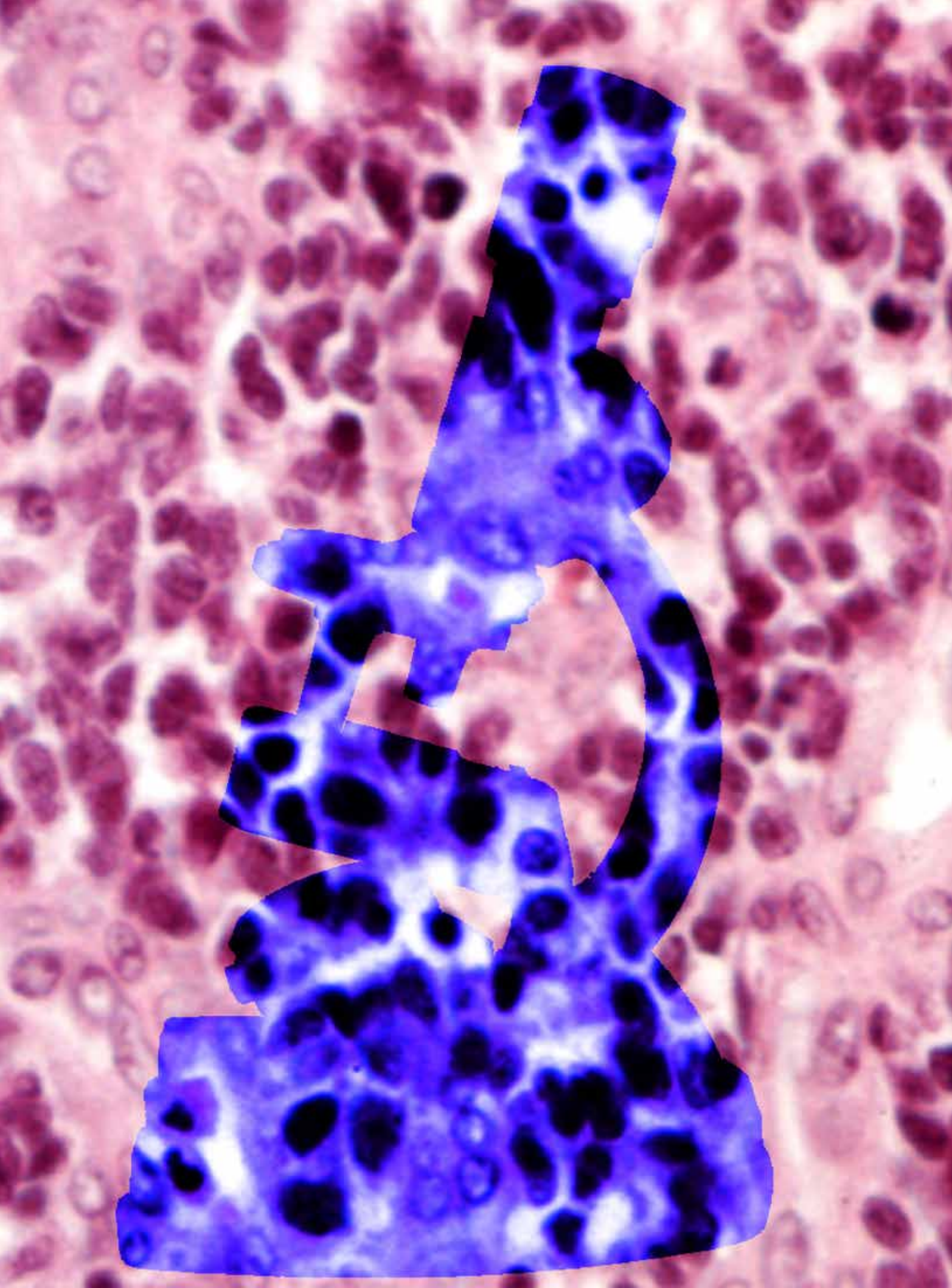

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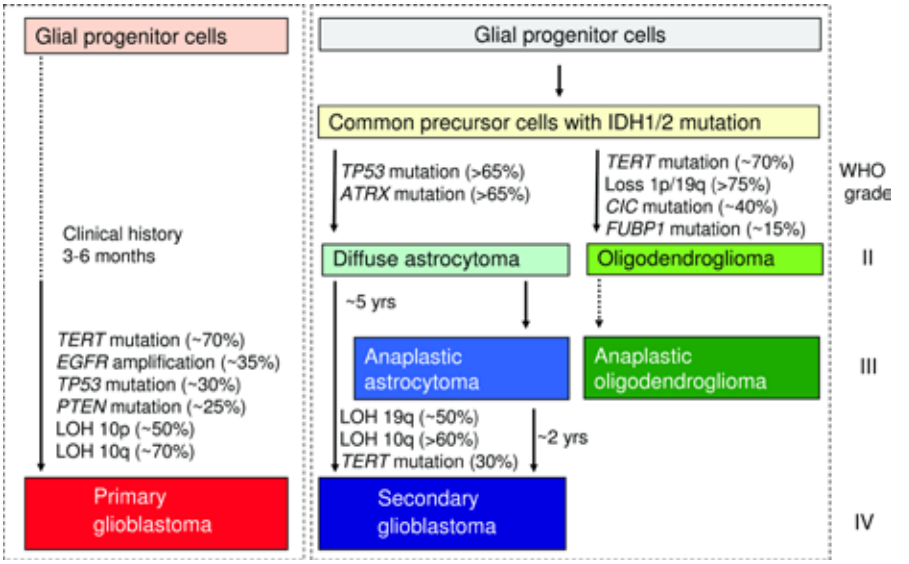
The Section of Molecular Pathology (MPA) studies the molecular basis of human neoplasms, in particular brain tumours, using tumour samples from patients with clinical and follow-up data. Histologically recognized phenotypes are correlated with genotypes and expression profiles in order to elucidate the 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, monitor 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 fourth edition of the World Health Organization (WHO) Classification of Tumours Series (WHO Blue Books). In 2012–2013, the fourth volume (Tumours of the Breast) and fifth volume (Tumours of Soft Tissue and Bone) were published. Currently, work on the sixth volume (Tumours of Female Reproductive Organs) and seventh volume (Tumours of Lung, Pleura, Thymus, and Heart) is in progress. The main projects of MPA during the 2012–2013 biennium are detailed below.

## Genetic pathways to primary and secondary glioblastoma

Glioblastoma is the most common and aggressive malignant brain tumour. Most glioblastomas (~90%) develop rapidly *de novo* in elderly patients without clinical or histological evidence of a less malignant precursor lesion (primary glioblastomas). Secondary glioblastomas progress from low-grade diffuse astrocytoma or anaplastic astrocytoma. They manifest in younger patients, have a lesser degree of necrosis, are preferentially located in the frontal lobe, and carry a significantly better prognosis. Histologically, primary and secondary glioblastomas are largely indistinguishable, but they differ in their genetic and epigenetic profiles. Decisive genetic signposts of secondary glioblastoma are *IDH1* mutations, which are absent in primary glioblastomas and are associated with a hypermethylation phenotype. *IDH1* mutations are the earliest detectable genetic alteration in precursor low-grade diffuse astrocytomas and in oligodendrogliomas, indicating that these tumours are derived from neural precursor cells that differ from those of primary glioblastomas. There is increasing evidence that mutation of *IDH1* is a definitive diagnostic molecular marker of secondary glioblastomas and is more reliable and objective than clinical criteria. Despite a similar histological appearance, primary and secondary glioblastomas are distinct tumour entities that originate from different precursor cells and may require different therapeutic approaches. Genetic pathways to primary and

secondary glioblastoma are outlined in Figure 1.

**Figure 1. Genetic pathways to primary and secondary glioblastoma.**




## Frequent *BRAF* gain in low-grade diffuse gliomas with 1p/19q loss

Chromosomal 7q34 duplication and *BRAF-KIAA1549* fusion are characteristic genetic alterations in pilocytic astrocytomas. Focal gains at chromosome 7q34 appear to be common in diffuse astrocytomas, but their significance is unclear. We assessed *BRAF* gain and *BRAF* mutations in 123 low-grade diffuse gliomas. Quantitative polymerase chain reaction (PCR) revealed *BRAF* gain in 17/50 (34%) oligodendrogliomas, a significantly higher frequency than in diffuse astrocytomas (7/55; 13%; P = 0.011). *BRAF* gain was common in low-grade diffuse gliomas with 1p/19q loss (39%) and those lacking any of the genetic alterations analysed (31%), but was rare in those with *TP53* mutations (2%). Logistic regression analysis showed a significant positive association between 1p/19q loss and *BRAF* gain (P = 0.003) and a significant negative association between *TP53* mutations and *BRAF* gain (P = 0.004). Fluorescence in situ hybridization (FISH) analysis of 26 low-grade diffuse gliomas with *BRAF* gain additionally revealed *BRAF-KIAA1549* fusion in one oligodendroglioma. Sequencing of cDNA in 17 low-grade diffuse gliomas showed *BRAF-KIAA1549* fusion in another oligodendroglioma. These results suggest that low-grade diffuse gliomas with 1p/19q loss have frequent *BRAF* gains, and a small fraction of oligodendrogliomas may show *BRAF-KIAA1549* fusion.

## Molecular mechanisms of mesenchymal differentiation in gliosarcomas

Gliosarcoma is a rare glioblastoma variant characterized by a biphasic tissue pattern with alternating areas that display either glial or mesenchymal differentiation. Previous analyses have shown identical genetic alterations in glial and mesenchymal tumour areas, suggesting that gliosarcomas are genetically monoclonal and that mesenchymal differentiation reflects the elevated genomic instability of glioblastomas. We compared genome-wide chromosomal imbalances using array comparative genomic hybridization in glial and mesenchymal tumour areas of 13 gliosarcomas. The patterns of gain and loss were similar, except for the gain at 13q13.3-q14.1 ($\log_2$ ratio > 3.0), containing the *STOML3*, *FREM2*, and *LHFP* genes, which was restricted to the mesenchymal tumour area of a gliosarcoma. Further analyses of 64 cases of gliosarcoma using quantitative PCR showed amplification of the *STOML3*, *FREM2*, and *LHFP* genes in 14 (22%), 10 (16%), and 7 (11%) mesenchymal tumour areas, respectively, but not in glial tumour areas. These results suggest that the mesenchymal components in a small fraction of gliosarcomas may be derived from glial cells with additional genetic alterations.

We also assessed 40 gliosarcomas for immunoreactivity of Slug, Twist, matrix metalloproteinase-2 (MMP-2), and MMP-9, which are involved in the epithelial–mesenchymal transition (EMT) in epithelial tumours. Nuclear Slug expression was observed in > 50% of neoplastic cells in mesenchymal tumour areas of 33 (83%) gliosarcomas, but not in glial areas ($P < 0.0001$). Nuclear Twist expression was observed in > 50% of neoplastic cells in mesenchymal tumour areas of 35 (88%) gliosarcomas, but glial tumour areas were largely negative except in four cases ($P < 0.0001$). Expression of MMP-2 and MMP-9 was also significantly more extensive in mesenchymal than in glial tumour areas. Of 20 ordinary glioblastomas, none showed Slug or Twist expression in > 10% neoplastic cells. Thus, expression of Slug, Twist, MMP-2, and MMP-9 was characteristic of mesenchymal tumour areas of gliosarcomas, suggesting that mechanisms involved in EMT in epithelial neoplasms may also play a role in mesenchymal differentiation in gliosarcomas.

## Prognostic molecular markers in diffuse astrocytomas

Diffuse astrocytomas (WHO grade II) tend to advance to secondary glioblastomas, but the time until progression and the clinical outcome vary significantly. Despite having distinct genetic profiles, primary and secondary glioblastomas have similar histological features. We hypothesized that the highly malignant phenotype of glioblastoma may be attributable to genetic alterations that are common to both glioblastoma subtypes.

Since loss of heterozygosity (LOH) at 10q has been known to be frequent (> 60%) in both primary and secondary glioblastomas, we first searched for commonly deleted genes at 10q in glioblastomas with *IDH1* mutations (a hallmark of secondary glioblastoma) and those without *IDH1* mutations (typical for primary glioblastoma) in data from The Cancer Genome Atlas (TCGA). With log-ratio thresholds of –1.0, 10 genes were identified; with log-ratio thresholds of –2.0, only the

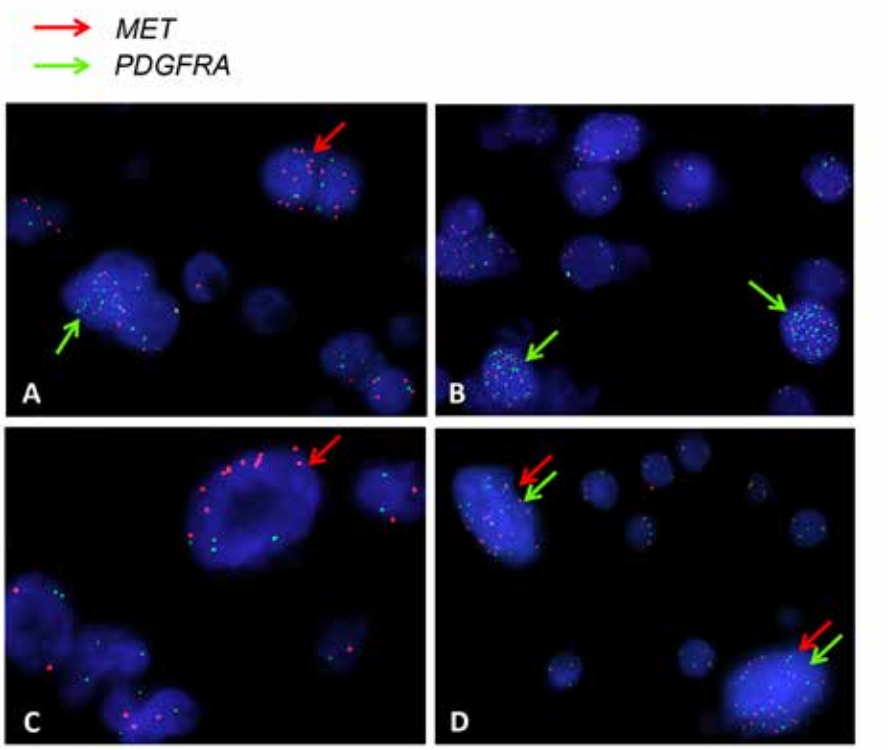
*DMBT1* (deleted in malignant brain tumour 1) gene at 10q26.13 remained as a deleted gene in glioblastomas with or without *IDH1* mutations (12.5% vs 8.0%). We then analysed a total of 404 gliomas by differential PCR and found a *DMBT1* homozygous deletion at a similar frequency in primary and secondary glioblastomas (20% vs 21%). A fraction (11%) of diffuse astrocytomas showed a *DMBT1* homozygous deletion that was significantly associated with shorter overall survival (52.8 vs 84.0 months; $P = 0.003$). These results indicate that a *DMBT1* homozygous deletion is present in a small fraction of diffuse astrocytomas and is associated with an unfavourable clinical outcome.

A similar approach was used to identify commonly (> 35%) amplified genes in glioblastomas with and without *IDH1* mutations in data from TCGA. A total of 25 genes were identified, of which 21 were located at 7q31-34. We then screened 264 gliomas for gain of the *MET* gene at 7q31.2 with quantitative PCR. *MET* gain was detected in primary glioblastomas (47%) and secondary glioblastomas (44%), suggesting that this genetic alteration plays a role in the pathogenesis of both glioblastoma subtypes. It was also common in diffuse astrocytomas (38%), but less frequent in oligodendrogliomas (16%). *MET* gain in diffuse astrocytomas was associated with shorter survival (median, 43.0 vs 70.7 months; $P = 0.004$), suggesting that *MET* gain is a useful prognostic marker for diffuse astrocytomas.

## *PDGFRA* gain in low-grade diffuse gliomas

Glioblastomas with a proneural expression signature are characterized by frequent *IDH1* mutations (i.e. a genetic hallmark of secondary glioblastomas) and *PDGFRA* (platelet-derived growth factor receptor-α) amplification. Mutations in *IDH1/2* are frequent and early genetic events in diffuse astrocytoma, a precursor to secondary glioblastomas, but little is known about the role and timing of *PDGFRA* amplification in these tumours. We assessed *PDGFRA* gain in 342 low-grade diffuse gliomas by quantitative PCR. Gain in *PDGFRA* was detected in 27 (16%) of 166 diffuse astrocytomas, significantly more frequently than in oligodendrogliomas (3%; $P < 0.0001$). Analyses using previously published data from our laboratory showed an inverse correlation between *PDGFRA* gain and *IDH1/2* mutations ($P = 0.018$) or 1p/19q loss ($P < 0.0001$). Most diffuse astrocytomas showed *IDH1/2* mutations and/or *PDGFRA* gain (154 [93%] of 166). Mean survival of diffuse astrocytoma patients with *PDGFRA* gain was 8.8 ± 1.6 years, similar to that of patients with *IDH1/2* mutations (7.8 ± 0.5 years) or *TP53* mutations (7.6 ± 0.6 years), but significantly longer than that of those with *MET* gain (4.4 ± 0.7 years). Dual-colour FISH in 6 diffuse astrocytomas with *PDGFRA*/*MET* co-gain identified by quantitative PCR revealed that *PDGFRA* and *MET* were typically amplified in different tumour cell populations. Tumour cells with co-amplification were also focally observed, suggesting intratumour heterogeneity even in diffuse astrocytomas.

**Figure 2. Dual-colour fluorescence in situ hybridization (FISH) analysis in diffuse astrocytomas shows intratumoral heterogeneity of amplification of *PDGFRA* (green) and *MET* (red). *PDGFRA* amplification and *MET* amplification were observed in separate cells in the same tumour (A). *PDGFRA* amplification (B) or *MET* amplification (C) were seen in individual diffuse astrocytoma cells within the same specimen. Rare tumour cells displayed co-amplification of *PDGFRA* and *MET* (D). Source: Motomura *et al.* (2013); reproduced with the permission of the publisher.**




## Genetic alterations in microRNAs in medulloblastomas

MicroRNAs (miRNAs) regulate a variety of cellular processes via the regulation of multiple target genes. We screened 48 medulloblastomas for mutation, deletion, and amplification of 9 miRNA genes that 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 the *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-135*b (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, 35/48 (73%) medulloblastomas had at least one alteration. Real-time RT-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 the medulloblastoma/primitive neuroectodermal tumour 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.

## 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 is of great importance not only in pathology communities, but also to cancer registration, epidemiology studies, clinical trials, and cancer research in general.

**Figure 3. Cover of *WHO Classification of Tumours of the Breast*, fourth edition.**

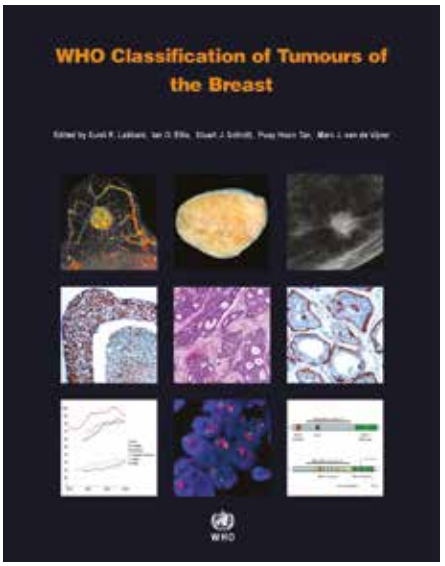



**Figure 4. Working Group members at the consensus and editorial meeting of *WHO Classification of Tumours of Soft Tissue and Bone*. The meeting was held at the University of Zurich, Switzerland, on 18–20 April 2012. Photograph courtesy of Norbert Wey.**

IARC has been responsible for this project since the third 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 latest edition (fourth) of the WHO Classification of Tumours Series 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).

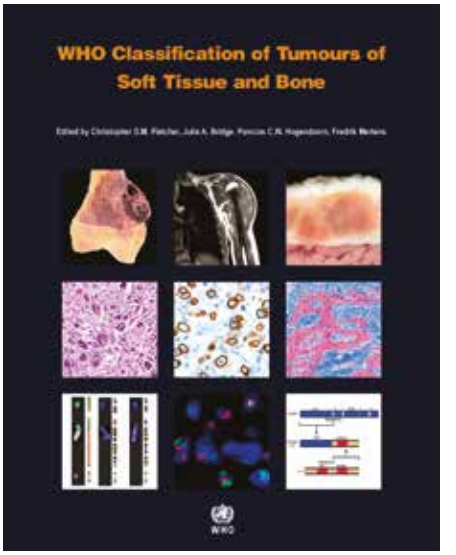
• The first volume of the fourth edition, Tumours of the Central Nervous System, was published in June 2007.

• The second volume, Tumours of Haematopoietic and Lymphoid Tissues, was published in September 2008 and > 35 000 copies have been distributed worldwide.

• The third volume, Tumours of the Digestive System, with four 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.

• The fourth volume, Tumours of the Breast, with five editors (Dr Sunil R. Lakhani, University of Queensland, Brisbane, Australia; Dr Ian Ellis, University of Nottingham, United Kingdom; Dr Stuart Schnitt, Beth Israel

**Figure 5. Cover of *WHO Classification of Tumours of Soft Tissue and Bone*, fourth edition.**



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), was published in July 2012.

• The fifth volume, Tumours of Soft Tissue and Bone, with four 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), was published in January 2013.

• The sixth volume, Tumours of Female Reproductive Organs, with four editors (Dr Robert J. Kurman, Johns Hopkins University, Baltimore, USA; Dr Maria Luisa Carcangiu, Fondazione IRCCS, Institute Nazionale dei Tumori, Milano, Italy; Dr Simon Herrington, Centre for Oncology and Molecular Medicine, Ninewells Hospital and Medical School, Dundee, United Kingdom; and Dr Robert H. Young, Massachusetts General Hospital, Harvard Medical School, Boston, USA), is in preparation. The consensus and editorial meeting was held on 13–15 June 2013, and the book is scheduled to be published in the spring of 2014.

• The seventh volume, Tumours of the Lung, Pleura, Thymus, and Heart, with five editors (Dr William D. Travis, Memorial Sloan Kettering Cancer Center, New York, USA; Dr Alexander Marx, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany; Dr Elisabeth Brambilla, Centre Hospitalier Universitaire de Grenoble, France; Dr Andrew Nicholson, Royal Brompton Hospital, London, United Kingdom; and Dr Allen Burke, University of Maryland, Baltimore, USA), is in preparation and is scheduled to be published in the spring of 2015.

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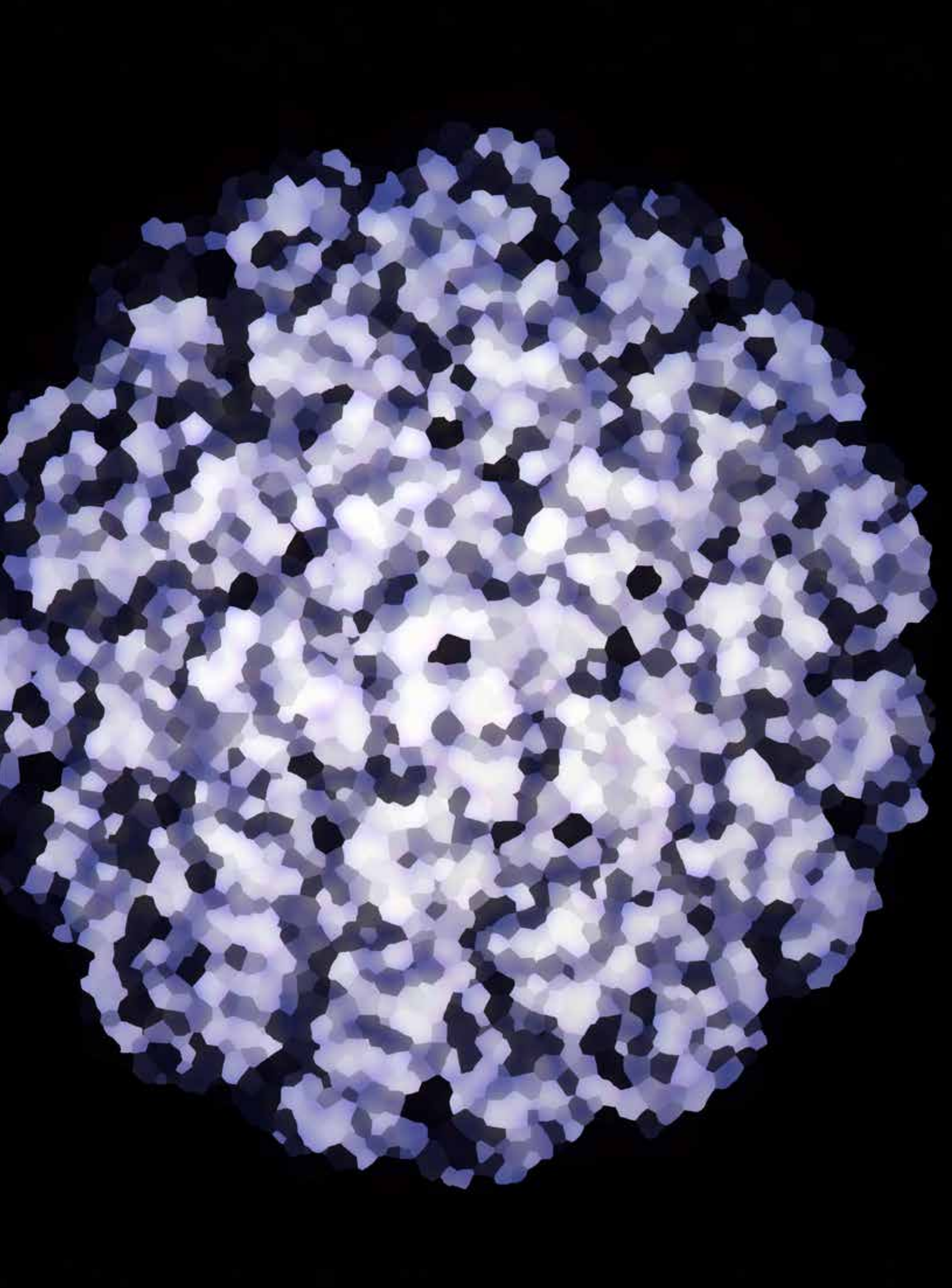

# Section of Infections (INF)

**Section head**
Dr Massimo Tommasino

The Section of Infections (INF) consists of two groups: the Infections and Cancer Biology Group (ICB) and the Infections and Cancer Epidemiology Group (ICE). The groups have similar goals in evaluating the role of infectious agents in human carcinogenesis using complementary strategies. ICB is mainly focused on the characterization of the molecular mechanisms of different infectious agents in altering fundamental cellular events, as well as on the development of laboratory assays that can be used in epidemiological research. The work in ICE centres on performing worldwide epidemiological studies to evaluate the role of infections in human cancers.

In the past two years, ICB has characterized several novel mechanisms of oncogenic viruses, such as human papillomaviruses (HPV), Epstein–Barr virus (EBV), and Merkel cell polyomavirus (MCPyV). ICB has found that different oncogenic viruses have the ability to target the same events in cellular cancer pathways (i.e. evasion of the immune surveillance and induction of cellular transformation). For example, several HPV types, EBV, and MCPyV are able to downregulate the expression of Toll-like receptor 9, which plays a fundamental role in pathogen recognition and activation of innate immunity. In addition, cutaneous HPV type 38 and EBV induce the accumulation of a strong antagonist of the tumour suppressor p53, ΔNp73α.

Recent research efforts in ICE include the estimation of the global burden of cancer attributable to infectious agents and, in particular, the variation in the frequency of HPV infection and HPV-related malignancies. Special efforts have gone into establishing multiyear studies on the effectiveness of HPV vaccination and HPV-based screening in the two low-resource countries, Bhutan and Rwanda, which have been the first to successfully adopt HPV vaccination practices. Finally, ICE has strengthened its efforts to evaluate the determinants of cancer and possible prevention strategies in HIV-positive individuals at a time when their survival is improving even in sub-Saharan Africa.

In addition, ICB and ICE have performed several collaborative studies that led to the characterization of the relationship between mucosal HPV type 16 polymorphisms, geographical distribution, and severity of the cervical disease (Cornet *et al*., 2012a, 2013a, 2013b). The two groups have also joined forces to better define the role of HPV infection in the etiology of cancer of the head and neck in Europe and Asia.

In the 2012–2013 biennium, INF has published articles in high-ranking journals, covering a wide range of topics related to infections and cancer (ICB: 27 publications and 6 articles in press; ICE: 75 publications and 12 articles in press).

# Infections and Cancer Biology Group (ICB)

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Dr Bakary S. Sylla (until August 2012)

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Ms Jennifer Wischhusen
(until July 2013)
Mr Danilo Baldari (until July 2013)
Mr Djamel Saidj (until October 2013)
Ms Maha Siouda
Ms Lisa Kitasato
Ms Laura Pacini

The main goal of the Infections and Cancer Biology Group (ICB) is to elucidate molecular mechanisms of both well-established and potential oncogenic viruses. In the past two years, studies have focused on cutaneous and mucosal HPV types, several members of the polyomavirus family, and EBV. The studies used several in vitro experimental models, including cells that are the natural host of the studied viruses (e.g. primary human keratinocytes for HPVs and primary B-cells for EBV). In particular, functional studies were focused on characterizing the impact of viral proteins on key cellular events in carcinogenesis, such as regulation and inactivation of tumour suppressors and evasion of immune surveillance (Accardi *et al.*, 2013; Chiantore *et al.*, 2012; Cornet *et al.*, 2012a; Hasan *et al.*, 2013; Saidj *et al.*, 2013; Saulnier *et al.*, 2012; Siouda *et al.*, 2012; Thomas *et al.*, 2013; Viarisio *et al.*, 2013). As a complementary strategy to functional studies, laboratory assays have been established for the detection of the DNA or RNA of approximately 120 infectious agents in human specimens. These assays have a high throughput, sensitivity, and specificity, allowing the use of a broad spectrum of human specimens, including skin swabs, saliva, urine, and formalin-fixed, paraffin-embedded tissues. The features of the assays have enabled initiation and completion of several collaborative epidemiological studies that evaluate the role of HPV types and other viruses in different types of cancers; for example, oropharyngeal cancer and non-melanoma skin cancer (NMSC) (Anantharaman *et al.*, 2013; Comar *et al.*, 2012; Halec *et al.*, 2013; Iannacone *et al.*, 2012, 2013a; Polesel *et al.*, 2012a; Rollison *et al.*, 2012). Examples of functional studies completed in the biennium are highlighted in the following paragraphs.

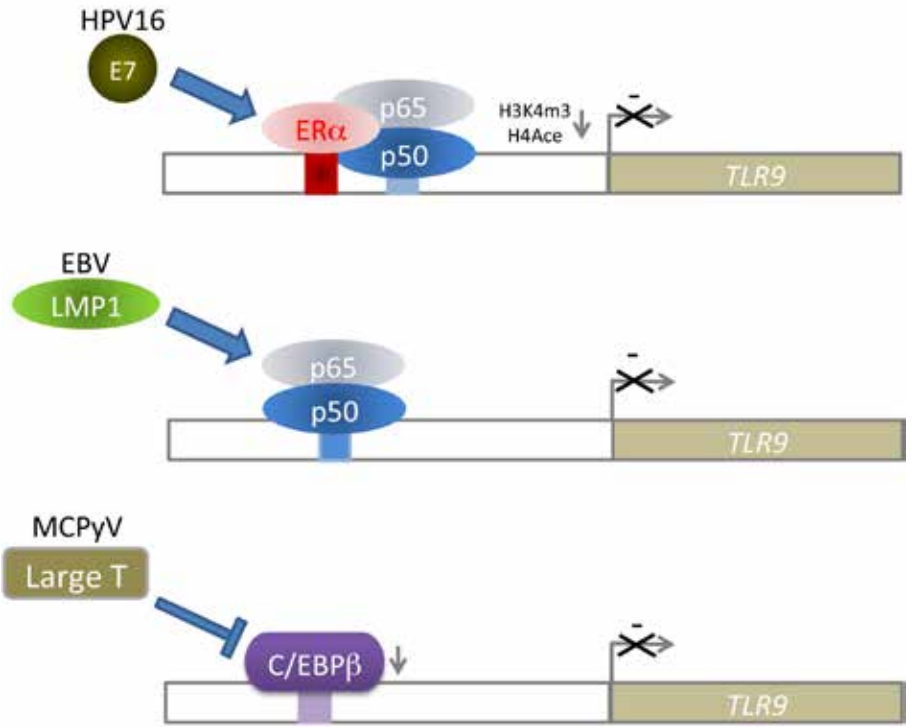
## Several oncogenic viruses target the innate immune response by downregulating TLR9 expression

It has previously been shown that HPV16 and EBV deregulate immunity by suppressing the function of the double-stranded DNA (dsDNA) innate sensor Toll-like receptor 9 (TLR9) (Figure 1). In a recent study, the mechanism of these HPV-induced events was partially dissected. Using in vitro and ex-in vivo models, it was shown that the HPV16 E7 oncoprotein promotes the formation of an inhibitory transcriptional complex containing NF-κB, p50/p65, and ERα (Figure 1). The E7-mediated transcriptional complex also recruited the histone demethylase JARID1B and histone deacetylase HDAC1. The entire complex bound to a specific region on the TLR9 promoter, which resulted in decreased methylation and acetylation of histones upstream of the TLR9 transcription start site. The findings also indicate that the HPV16-induced TLR9 downregulation affects the interferon response, which negatively regulates viral infection (Hasan *et al.*, 2013). The transcription factor ERα is a member of the nuclear receptor family that translocates into the nucleus upon binding to the sex hormone estradiol. Epidemiological studies showed that high levels of circulating estrogens are a risk factor for both breast and HPV-mediated cervical carcinogenesis. Based on data that highlight the inhibitory role of ERα in TLR9 expression, it is hypothesized that ERα signalling favours cervical cancer development in part by promoting an efficient and permanent downregulation of TLR9 messenger RNA (mRNA) levels.

In an independent study, it was demonstrated that the recently isolated oncogenic virus, MCPyV, which is associated with the majority of Merkel cell carcinomas (MCCs), is also able to inhibit the expression of TLR9 by a distinct mechanism (Shahzad *et al.*, 2013). These findings showed that MCPyV large T antigen (LT) expression downregulates TLR9 expression in epithelial and MCC-derived cells. Accordingly, silencing of LT expression results in upregulation of TLR9 mRNA levels. LT inhibits TLR9 expression by decreasing mRNA levels of the C/EBPβ transactivator, a positive regulator of the TLR9 promoter (Figure 1).

In summary, these studies showed that downregulation of TLR9 expression is a

**Figure 1. Oncogenic viruses downregulate TLR9 expression by different mechanisms. HPV16 E7 and EBV LMP1 activate the NF-κB signalling pathway, inducing the translocation of NF-κB complexes (p50/p65), which together with the estrogen receptor alpha (ERα) and epigenetic enzymes are recruited to the TLR9 promoter. The binding of these complexes to TLR9 promoter correlated with a decrease of histone 4 acetylation (H4Ace) and trimethylation of histone H3 at lysine 4 (H3K4m3) and inhibition of TLR9 expression. Large T antigen from MCPyV downregulates the TLR9 mRNA levels by inhibiting the expression of a positive regulator of TLR9 promoter, C/EBPβ. EBV, Epstein–Barr virus; MCPyV, Merkel cell polyomavirus.**



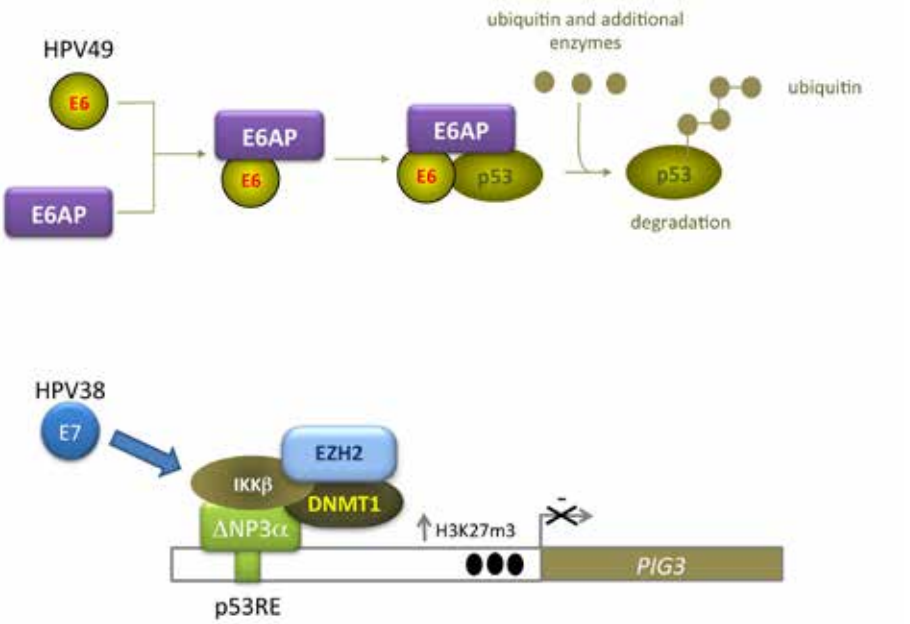
highly conserved phenomenon among the oncogenic viruses, underscoring the importance of this event in virus-mediated carcinogenesis.

### Identification of a novel viral mechanism of inactivation of the p53 tumour suppressor

In the past decade, several epidemiological and biological studies have been performed to evaluate the possible role of cutaneous β HPV types in the development of NMSC. In particular, the biological properties of the oncoproteins E6 and E7 from many β HPV types have been characterized, and it has been observed that certain β HPV types (i.e. HPV38 and 49) display transforming properties (Cornet *et al.*, 2012a). A key event in HPV-mediated cellular transformation is the inactivation of p53 tumour suppressor. The mucosal high-risk HPV types associated with cervical cancer are able to inactivate p53, promoting its degradation via the proteasome pathway, a phenomenon mediated by the viral E6 oncoproteins. It has been observed that β HPV49 E6 is also able to induce p53 degradation, showing for the first time that this property is conserved in E6 from mucosal and cutaneous HPV types (Figure 2). In addition, a novel mechanism of p53 activation of β HPV38 E7 has been characterized. This viral oncoprotein is able to induce accumulation of a strong p53 antagonist, ΔNp73α, that in turn forms a transcriptionally inhibitory complex together with IKKβ and two epigenetic enzymes, namely DNA methyltransferase 1 (DNMT1) and enhancer of zeste homolog 2 (EZH2). HPV38 E7 favours the recruitment of this complex to the p53-regulated promoter, preventing its activation (Saidj *et al.*, 2013) (Figure 2).

Interestingly, it was recently demonstrated that the oncogenic virus EBV is also able to induce accumulation of ΔNp73α via the oncoprotein LMP-1. This phenomenon is mediated by the LMP-1-dependent activation of c-Jun NH2-terminal kinase 1 (JNK-1), which in turn favours the recruitment of p73 to the ΔNp73 promoter. A specific chemical inhibitor of JNK-1 or silencing JNK-1 expression strongly downregulated ΔNp73α mRNA levels in LMP-1-containing cells.

**Figure 2. Beta cutaneous HPV types use different mechanisms to inhibit the transcriptional functions of p53. As high-risk mucosal HPV types, HPV16 E6 targets p53 for degradation via the ubiquitin/proteasome pathway. The E6 oncoprotein from beta cutaneous HPV type 49 associates with the ubiquitin-protein ligase E6AP. The dimeric complex then binds p53 and E6AP catalyses multi-ubiquitination of p53 in the presence of ubiquitin and additional enzymes of the ubiquitin pathway. E6 oncoprotein from beta cutaneous HPV38 induces the accumulation of a p53 antagonist ΔNp73α. The latter binds the p53 responsive elements of p53-regulated promoters and favours the recruitment of additional cellular proteins, i.e. IκBα kinase β (IKKβ), the Polycomb-group 2 member EZH2, and DNA methyltransferase DNMT1. The two epigenetic enzymes, EZH2 and DNMT1, promote the trimethylation of histone H3 at lysine 27 (H3K27me3) and DNA methylation (M), respectively preventing the activation of p53-regulated promoters.**




Accordingly, LMP-1 mutants deficient in activating JNK-1 did not induce ΔNp73α accumulation. Inhibition of ΔNp73α expression in EBV immortalized B cells led to the stimulation of apoptosis and the upregulation of a large number of cellular genes as determined by whole-transcriptome shotgun sequencing (RNA-seq). In particular, the expression of genes encoding products known to have anti-proliferative/pro-apoptotic functions, as well as genes known to be deregulated in different B-cell malignancies, was altered by ΔNp73α downregulation (Accardi *et al.*, 2013).

Together, these findings show that β HPV types share properties with well-established oncogenic viruses. HPV49, similarly to the mucosal high-risk HPV16, promotes p53 degradation via the proteasome pathway. In addition, β HPV38 and EBV are able to antagonize p53 functions, inducing the accumulation of ΔNp73α.

### Role of the DOK1 tumour suppressor in carcinogenesis

Downstream of tyrosine kinase 1 (DOK1) is a newly identified tumour suppressor that downregulates several cellular signalling pathways. DOK1 inhibits cell proliferation and constitutes a negative regulator of the human immune system. These studies have identified a mutated DOK1 in chronic lymphocytic leukaemia exclusively confined in the nucleus, and subsequently shown that the suppressive activity of DOK1 is regulated by its subcellular localization. The role of DOK1 in human neoplasia was further supported by the findings that the expression of the gene was constitutively repressed through promoter hypermethylation in several human cancers, including head and neck, lung, gastric, and liver cancer and Burkitt lymphoma (Saulnier *et al.*, 2012). Additional studies have recently shown that the transcription factor E2F1 regulates the expression of DOK1. DNA

methylation of the DOK1 core promoter region found in head and neck cancer cells hampered the recruitment of E2F1 to the DOK1 promoter and compromised its expression. Interestingly, and similarly to p53 and other established tumour suppressors, E2F1-induced DOK1 transcription occurred in the presence of cellular stresses, such as accumulation of DNA damage induced by etoposide. DOK1 silencing promoted cell proliferation and protected against etoposide-induced apoptosis, indicating that DOK1 acts as a key mediator of cellular stress-induced cell death (Siouda *et al*., 2012).

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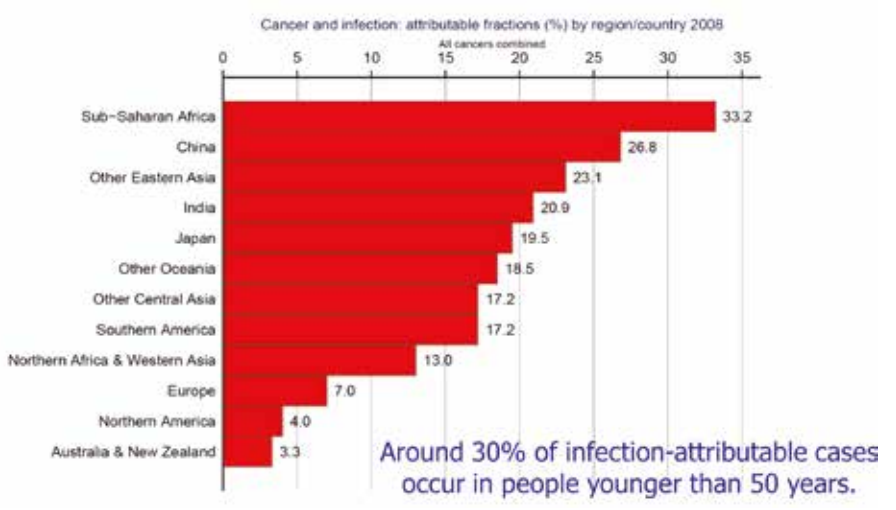
The main goal of the Infections and Cancer Epidemiology Group (ICE) is to elucidate the contribution of infectious agents, such as human papillomavirus (HPV), human immunodeficiency virus (HIV), hepatitis B and C virus (HBV/HCV), and *Helicobacter* species, to the etiology of cancer. For a substantial number of current ICE projects, ICB lends expertise for viral testing or other biological aspects.

In the past two years, exciting new opportunities have emerged to use the knowledge of the infection–cancer link to prevent malignancies associated with HPV and HIV cancer (Chen CJ *et al.*, 2013; Clifford *et al.*, 2013; Crosbie *et al.*, 2013; de Martel *et al.*, 2013; Franceschi and Wild, 2013; Plummer, 2013; Tsu *et al.*, 2012), and these opportunities have allowed ICE to move increasingly into translational research. In addition, ICE is engaged in many inter-Section collaborations, notably with the Section of Cancer Information (CIN) on age-period cohort analyses of selected cancers (Vaccarella *et al.*, 2013a), the Section of Nutrition and Metabolism (NME) on thyroid cancer, the Section of Genetics (GEN) on interaction between HPV and susceptibility genes, and the Section of Early Detection and Prevention (EDP) on the prevention of cancer of the stomach and cervix.

## Global burden of cancer attributable to infections

In collaboration with CIN, ICE used data from Globocan and a variety of literature sources to calculate the fraction of cancer attributable to infection worldwide and in eight geographical regions (de Martel *et al.*, 2012). Overall, 2 million (16.1%) of the total 12.7 million new cancer cases that occurred in 2008 are attributable to infections. This fraction is higher in less developed countries (22.9%) than in more developed countries (7.4%) and varies 10-fold by region, from < 4% in Australia/New Zealand and the USA to 33.2% in sub-Saharan Africa (Figure 1). The most important infectious agents are *Helicobacter pylori*, HBV/HCV, and HPV, which together are responsible for 1.9 million cases of gastric, liver, and cervix uteri cancers, respectively. Application of existing public health methods for infection prevention, such as vaccination, safe injection practices, or antimicrobial treatments, could have a major impact on the future burden of cancer worldwide.

**Figure 1. Variation in infection-attributable cancers (at least 2 million per year, 16% of total cancer cases worldwide). Figure compiled from de Martel *et al.* (2012).**




## HPV and cervical cancer prevention

In the 2012–2013 biennium, ICE's main focus was HPV (Crosbie *et al.*, 2013). For HPV vaccines and HPV-based screening to be successful, accurate knowledge of the infection burden and type-specific distribution of HPV types in different parts of the world is needed. ICE carried out new population-based HPV prevalence surveys on exfoliated cervical cells in Vanuatu (Aruhuri *et al.*, 2012), in the Islamic Republic of Iran (Khodakarami *et al.*, 2012), in China (Zhao *et al.*, 2012), and in Bhutan and Rwanda. Work in Bhutan and Rwanda was the first step of a multiyear project meant to demonstrate the early impact of successful implementation of vaccination against HPV in two low- and middle-income countries (LMICs) (Table 1). Bhutan and Rwanda have achieved the highest HPV vaccine coverage in the developing world (> 90% of adolescent girls in 2010 and 2011), and are also committed to improving their screening programmes through the introduction of HPV test-based screening. The impact of vaccination and screening will therefore be evaluated jointly by ICE. To evaluate the impact of HPV vaccination among adolescent girls in the two countries, a novel type of HPV survey has been conceived based on the collection of urine samples in female

**Table 1. Early impact of the HPV vaccination programme in Rwanda and Bhutan**

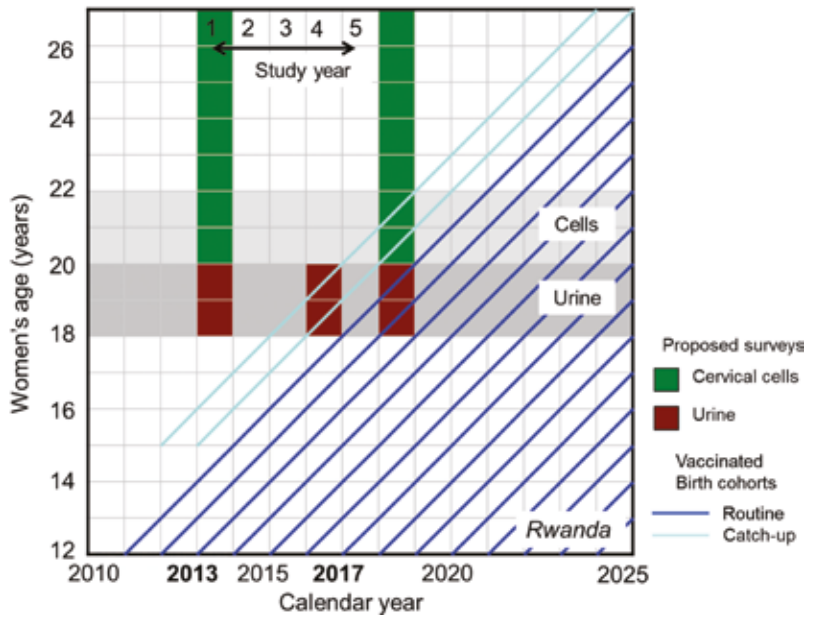
| |
|---|
| **Baseline HPV prevalence survey across a broad age range of unvaccinated women (Year 1)** |
| A cross-sectional survey of ~2500 women, stratified by age, will establish the prevalence of HPV in cervical cytology samples from unvaccinated women in Rwanda. |
| **Invasive cervical cancer (ICC) case series (Year 1)** |
| HPV genotype distribution in tumour biopsies from 100+ ICC cases. |
| **Repeat HPV survey in young, sexually active women (Year 5)** |
| A second cross-sectional survey of 1500 sexually active women aged < 25 years, using the same recruitment and identical HPV testing protocol as the baseline survey. The 5-year impact of the vaccine will be measured by reduction in the prevalence of HPV16/18 DNA infections. |
| **Monitoring type-specific HPV prevalence in urine samples from adolescents (Years 1, 3, and 5)** |
| Avoiding the need for a gynaecological examination has potential to greatly facilitate HPV vaccine impact monitoring. A pilot study of HPV detection in urine from repeat surveys of 1000 18–19-year-olds will be performed. |

students aged 18–19 years. Newly-conceived media and devices for self-collection will avoid DNA degradation in urine samples and allow the shipment to IARC without the need for additional, potentially detrimental, manipulations. The Lexis diagram in Figure 2 shows that in Rwanda, for instance, we will be able to compare the first generation of HPV vaccine recipients with previously unvaccinated women of the same age by 2017 in female students and by 2019 in young women participating in the cervical cell survey. Timely high-quality data on the effectiveness of HPV vaccination and HPV-based screening in the two LMICs that have been the first to successfully adopt HPV vaccination will hopefully encourage and facilitate the introduction of these successful programmes into other LMICs.

In addition, ICE released the first systematic comparison of the distribution of individual HPV types in 115 789 HPV-positive women with and without cervical cancer or pre-neoplastic lesions (Guan *et al.*, 2012, 2013). Figure 3 shows the unique behaviour of HPV16 and 18 among high-risk HPV (hrHPV) types, i.e. their relative rarity in cytologically normal women and a steep increase in their prevalence as cervical lesions become more severe. The global HPV database is kept up-to-date and provides insight into differences in the carcinogenic potential of HPV types in the general female population (Bzhalava *et al.*, 2013; Halec *et al.*, 2013) and in HIV-infected women (De Vuyst *et al.*, 2012b). To further expand the study of factors that influence the geographical variability and different scope for progression into cervical cancer of HPV infections, we also evaluated HPV16 variants in collaboration with ICB (Cornet *et al.*, 2012b, 2013a, 2013b).

Finally, better statistical methods were devised to evaluate and project the benefits of HPV vaccination and screening in HIV-negative and HIV-positive women. HPV vaccination of a single birth cohort of girls aged 9–13 years is recommended as a priority by WHO and supported by the GAVI Alliance. However, ICE showed that according to an ad hoc dynamic model, the addition of a catch-up round of girls aged 12–15 years can bring forward by

**Figure 2. Rwanda: Cervical cell- and urine-based surveys by age, calendar year, cohort, and vaccination status.**




5 years the 50% reduction in HPV16/18 prevalence due to vaccination compared with targeting 11-year-old girls only (Figure 4) (Baussano *et al.*, 2013a). Assuming an affordable vaccine cost, the addition of a catch-up vaccination round is, therefore, worth considering in LMICs to make economies of scale in vaccine delivery and extend vaccine benefits to older adolescents whose future access to cervical screening is uncertain. With respect to screening, concerns were expressed about the lack of specificity of HPV testing in African women, most notably HIV-positive women, due to a very high prevalence of hrHPV types. We showed that the positive predictive value (PPV) for cervical intraepithelial neoplasia (CIN) 2/3 of HPV testing in high-risk populations was very high, particularly in women aged ≥ 45 years because of the accumulation of CIN2/3

**Figure 3. Positivity (± 1.96 SE) for human papillomavirus (HPV) types 16, 18, and 45 as a proportion of HPV-positive samples, by cervical disease grade. ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia grade; ICC, invasive cervical cancer; SE, standard error. Source: Guan *et al.* (2012); reproduced with permission from John Wiley & Sons.**

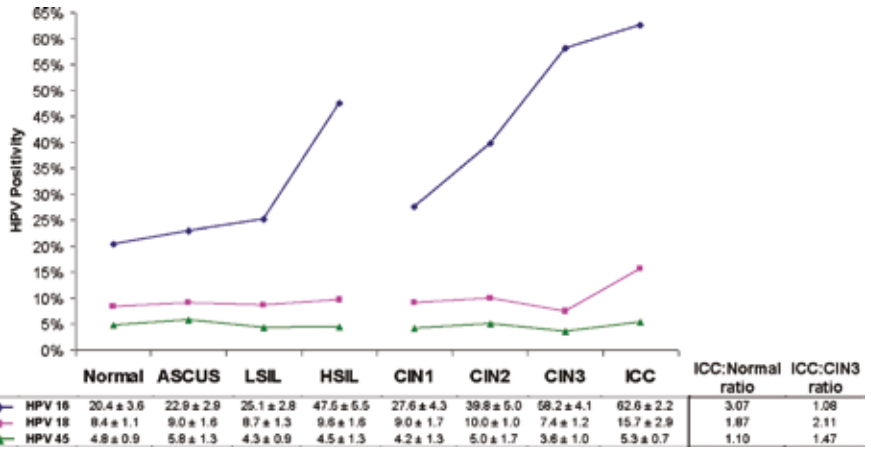
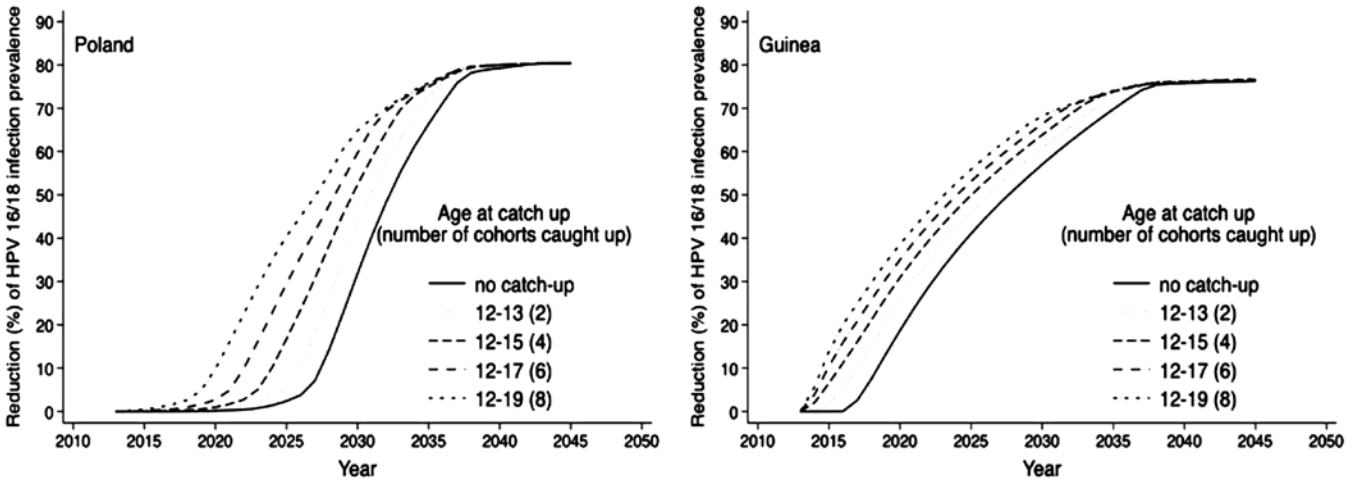


**Figure 4. Reduction (%) of HPV16/18 infection prevalence among women aged ≥35 years by catch-up strategy (best case scenario). Left panel: Poland. Right panel: Guinea. HPV, human papillomavirus. Source: Baussano *et al.* (2013a); reproduced with permission from John Wiley & Sons.**




over time and the lack of adequate cervical screening (Giorgi-Rossi *et al.*, 2012). High PPV demonstrates the efficacy and potential cost-effectiveness of HPV testing in high-risk women despite low test specificity.

### HPV and cancer of the head and neck

The contribution of HPV infection to head and neck cancer (HNC) is still ill-defined, varies greatly by cancer site and world region, and depends on competing causal factors such as tobacco smoking and chewing (Chaturvedi *et al.*, 2013; Gillison *et al.*, 2013). ICE continued evaluating the contribution of lifestyle factors to these malignancies (Chuang *et al.*, 2012a; Garavello *et al.*, 2012; Li *et al.*, 2012; Wyss *et al.*, 2013) and also carried out a meta-analysis of studies in which the prevalence of molecular and serological HPV markers was compared across different HNC cases and cancer-free controls (Combes and Franceschi, 2013). Data on HPV DNA detection by polymerase chain reaction (PCR) and p16 expression in HNC biopsies suggested that the probability of a cancer of the oral cavity or larynx/hypopharynx being attributable to HPV is at least 5-fold lower than that for oropharyngeal cancer. Seropositivity for HPV16 E6 or E7 shows larger differences across sites, but findings vary between studies. Because HPV DNA and p16 detection lack specificity, and E6 and E7 antibody detection lacks sensitivity and reproducibility, these tests are not completely satisfactory. Limited data on markers of HPV-driven carcinogenesis (i.e. in situ hybridization or HPV E6/E7 mRNA), mainly from the USA, suggest that HPV-attributable HNC is rare in the oral cavity (~3%), larynx (~7%), and hypopharynx (~0%). We also showed that HPV positivity was associated with better survival exclusively in oropharyngeal sites and tobacco smoking was a strong prognostic factor (Sethi *et al.*, 2012). Finally, SPLIT (Study on HPV and Precancerous Lesions in the Tonsil), a multicentre study coordinated by ICE, elucidates the prevalence and features of pre-cancerous lesions in cancer-free tonsils according to the presence of HPV markers or tobacco smoking.

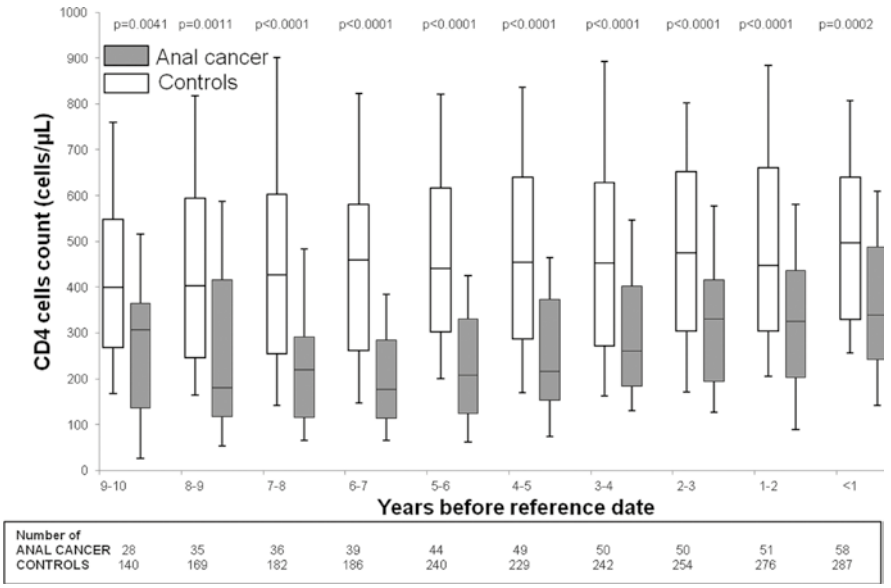
### HIV/AIDS

An issue of current importance to ICE is cancer risk in people with HIV/AIDS (PWHA), now that combined antiretroviral therapy (cART) has improved survival in PWHA and the cancer burden is set to increase as PWHA age. A new record-linkage study from the Swiss HIV Cohort suggested that the approximately 3-fold excess of lung cancer in people with HIV compared with the general population was not clearly associated with the severity of immunosuppression and was mainly attributable to heavy smoking (Clifford *et al.*, 2012). Although HIV-positive people, particularly men who have sex with men, are at excess risk for anal cancer, it has been difficult to disentangle the influences of very high HPV prevalence, immunodeficiency, and cART use. According to a case–control study nested in the Swiss HIV Cohort Study (Bertisch *et al.*, 2013), current smoking was significantly associated with anal cancer (odds ratio [OR], 2.59; 95% confidence interval [CI], 1.25–5.34), as well as low CD4+ cell counts, whether measured at nadir or at cancer diagnosis. ICE's study was the first to show that the influence of CD4+ cell counts appeared to be stronger 6–7 years before (OR for < 200 versus ≥ 500 cells/μL, 14.0; 95% CI, 3.85–50.9) than in proximity to anal cancer diagnosis (Figure 5). Smoking cessation and avoidance of even moderate levels of immunosuppression appear to be important in reducing long-term anal cancer risks.

An ICE study in Kenya suggested that avoidance of even moderate levels of immunosuppression may also be essential to prevent cervical cancer, a disease that was difficult to study in populations in developed countries because of the preventive influence of cervical screening (De Vuyst *et al.*, 2012b). A study of 498 HIV-positive women in Nairobi, Kenya, showed that the burden of hrHPV and CIN2/3 was high and was related to immunosuppression level. However, cART use had a favourable effect on hrHPV prevalence but not on CIN2/3. This may be explained by the fact that cART use in Kenyan women may have been started too late to prevent CIN2/3 (De Vuyst *et al.*, 2012a).

To further explore this issue, ICE is engaged in evaluating the potential impact of cART on cervical cancer prevention (Clifford *et al.*, 2013). Indeed, access to cART is improving in sub-Saharan Africa and other LMICs far more rapidly than is access to high-quality cervical screening. Prolonged survival because of cART use will probably lead to a similar increase in cervical cancer incidence in HIV-infected women as was seen for anal cancer incidence in high-income countries in the first years after cART introduction. If, as for anal cancer, cervical cancer risk is increased at even moderately decreased levels of CD4+ cell counts, then immediate access to and regular use of cART would be key to the prevention of cervical cancer in HIV-positive women in sub-Saharan Africa, in combination with future HPV vaccination and cervical screening (Clifford *et al.*, 2013).

**Figure 5. CD4+ cell counts before reference date among anal cancer cases and controls in Swiss HIV-positive individuals. Source: Bertisch *et al.* (2013); reproduced with permission from Oxford University Press.**




## Innovative statistical methods for epidemiology

Statistical models in cancer research often deal with sources of complexity such as repeated measurements, interval censoring, and hierarchical structure. For example, in the study of multiple HPV infections of the cervix, one needs to separate the sources of variation that make different HPV types cluster together (Carozzi *et al.*, 2012; Vaccarella *et al.*, 2013b). We address the most challenging problems using Bayesian hierarchical models. To support this, ICE has developed the statistical software package JAGS (http://mcmc-jags.sourceforge.net/), which is free and is distributed worldwide. This allows the user to define complex models using the probabilistic programming language BUGS, which are then analysed using Markov chain Monte Carlo simulation. Version 3.3.0 has beAen downloaded > 18 000 times since its release in October 2012.

In collaboration with the Education and Training Group (ETR), ICE offers the course Statistical Practice in Epidemiology with R, an introduction to the R language and environment for statistical analysis and graphics for cancer epidemiologists (http://www.r-project.org) (see also the ETR Report).

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The overall objectives of the Section of Environment and Radiation (ENV) are to investigate environmental, lifestyle, occupational, and radiation-related causes of cancer in human populations. These exogenous factors are explored with the goal of contributing to cancer prevention and increasing our understanding of biological mechanisms of carcinogenesis. ENV achieves these objectives through collaborative international epidemiological studies using a multidisciplinary approach, when possible, or through the initiation of individual analytical epidemiological studies. Another approach used is the coordination of international consortia of epidemiological studies.

Central to ENV is investigation of external environmental exposures, such as pollutants and occupational exposures. One major area of interest is pesticides, with current research on cancer risk in cohorts of agricultural workers and pesticide applicators. Using studies on testicular cancer in France and in the Nordic countries and pooled analyses of studies of childhood leukaemia, ENV is looking at the risk of haematological diseases in these populations and the cancer risk in the offspring of exposed farmers. Other substantial efforts include identifying occupational risk factors for lung cancer, with a focus on the effects of occupational carcinogens, such as asbestos and silica, and of smoking. Lifestyle-related questions are part of

comprehensive studies of cancer when there is potential interaction between environmental and other factors. Such studies, for example those initiated in sub-Saharan African countries, focus on breast, oesophageal, and childhood cancers.

ENV is also involved in many projects related to ionizing radiation, including the effects of protracted low doses of external ionizing radiation from medical diagnostic examinations (e.g. cohort study of children and adolescents exposed to computed tomography) and from occupational activities (e.g. follow-up of workers in the nuclear industry); environmental studies of populations exposed to fallout from the Semipalatinsk nuclear test site or after the Chernobyl nuclear accident; collaboration in studies on in utero exposure to ionizing radiation in the Southern Urals; and studies on the interaction between ionizing radiation and genetic factors, such as thyroid cancer in young people. Collaborations on studying the long-term effects from the Chernobyl nuclear accident are currently under way with colleagues from Fukushima Medical University. With regard to non-ionizing radiation, research activities include investigations of mobile phone use and studies on extremely low-frequency magnetic fields and childhood cancer.

Translating research into prevention policy is particularly important for environmental risk factors, many of which are modifiable. ENV has a large role in IARC's update of the European Code Against Cancer, which makes recommendations of what actions to take to improve general health and reduce the risk of cancer.

### Thyroid cancer after radiation exposure in adulthood

While there is evidence that the risk of thyroid cancer after radiation exposure substantially decreases with increasing age of exposure, lower risk is not equal to no risk. This view was strengthened by a recent IARC study of Chernobyl clean-up workers from Belarus, the Russian Federation, and Baltic countries (Kesminiene *et al.*, 2012), which reported an increase in the risk of thyroid cancer after radiation exposure during the clean-up activities in the Chernobyl area: the excess relative risk (ERR) per 100 mGy was 0.38 (95% confidence interval, 0.10–1.09). The data from the Chernobyl accident provide a valuable opportunity to clarify the risk of thyroid cancer after adult exposure and to plan for responses to nuclear accidents, like the 2011 disaster at the Fukushima Daiichi nuclear power plant, since adults will be responsible for clean-up and remediation activities after any accident.

### Occupational risk factors of lung cancer: the SYNERGY consortium

The SYNERGY project compiles the world's largest database of case–control studies on lung cancer with detailed information on occupation and smoking. The main objectives are to estimate risks at low exposure levels that are relevant for the general population and to estimate joint effects of selected occupational exposures and smoking in the development of lung cancer. The detailed smoking data allow for adjustment by smoking status, and the large data set permits risk estimates in important subpopulations, such as women and never-smokers, as well as by lung cancer cell type. The association between exposures or jobs and lung cancer risk often varies by lung cancer cell type. Although this has rarely been studied before due to small sample sizes, it is important to correctly estimate risks by lung cancer cell type especially when revising threshold levels and establishing compensation schemes for exposed workers and their families.

SYNERGY focuses on exposure to asbestos, silica, chromium, nickel, and polycyclic aromatic hydrocarbons. Collaborators have developed a quantitative job-exposure matrix (SYN-JEM) based on actual exposure measurements (360 000) from multiple countries covering a period of more than 50 years. Different model specifications have been compared to predict historical job-, time, and region-specific exposure levels in the best possible way. Exposure levels have been calculated for each subject by linking the SYN-JEM with the individual occupational histories.

Several other research questions have been addressed in SYNERGY, including whether working in specific jobs – such as hairdresser, welder, baker, bricklayer, or cook – can increase the risk of lung cancer (Table 1). In one study, an increased risk of lung cancer was observed for female

**Table 1. Association between working in certain occupations and the risk of lung cancer from pooled analyses of case-control studies participating in the SYNERGY project**

| Reference | Population | Exposure | Odds ratio 1 (95% confidence interval)[a] | Odds ratio 2 (95% confidence interval)[b] |
|---|---|---|---|---|
| Behrens *et al.*, 2013 | Men | Ever employed as baker | – | 1.08 (0.90–1.31) |
| Behrens *et al.*, 2013 | Women | Ever employed as baker | – | 0.96 (0.47–1.97) |
| Kendzia *et al.*, 2013 | Men | Ever employed as welder | 1.69 | 1.44 (1.25–1.67) |
| Kendzia *et al.*, 2013 | Men | Longest held job including occasional welding | 1.37 | 1.32 (1.17–1.49) |
| Olsson *et al.*, 2013 | Men | Ever employed as men's hairdresser/ barber | 1.17 (0.84–1.61) | 1.09 (0.76–1.59) |
| Olsson *et al.*, 2013 | Women | Ever employed as women's hairdresser | 1.65 (1.16–2.35) | 1.12 (0.75–1.68) |

[a] Odds ratio 1 without adjustment for tobacco smoking habits.
[b] Odds ratio 2 with adjustment for tobacco smoking habits.

hairdressers, which decreased and became non-significant after adjusting for smoking habits; thus, our results suggest that the increased lung cancer risk was due to their smoking behaviours rather than their occupational exposures (Olsson *et al.*, 2013; Figure 1). However, a few female hairdressers employed before 1954 had an increased risk even after adjustment for smoking. Similarly, we observed that, in general, cooks did not experience an increased risk of lung cancer after adjustment for smoking (Behrens *et al.*, 2013). Welding was associated with an elevated lung cancer risk, among both full-time and occasional welders, and the risk increased with duration of employment. In welders, a stronger association was observed with lung cancer in never-smokers and light smokers and with squamous cell lung cancer and small cell lung cancer, but not with adenocarcinoma. Thus, our findings contribute to the increasing evidence that welding is associated with an increased risk of lung cancer (Kendzia *et al.*, 2013). We did not observe an increased lung cancer risk in baking-related professions. Bricklayers experienced an increased lung cancer risk, with a clear increasing trend with length of employment. This is of importance because the association between working as a bricklayer and increased lung cancer risk has not yet been firmly established. In most countries, therefore, lung cancer is not usually recognized as an occupational disease among bricklayers and the affected workers are not compensated. SYNERGY provides additional evidence of increased lung cancer risk among bricklayers, which may contribute to it being considered an occupational disease.

**Figure 1. An increased risk of lung cancer among hairdressers has been reported, but the SYNERGY study proposes that this is due to their smoking behaviour and not to workplace chemicals. © IARC/R. Dray.**

## Cancer in agricultural workers: the AGRICOH consortium

Coordinated by ENV, AGRICOH is a consortium of at present 27 agricultural cohort studies from 11 countries in five continents. Launched in October 2010 in Lyon, AGRICOH promotes pooling of data to study health outcomes associated with agricultural exposures, in particular pesticides, to increase statistical power to study rare diseases (e.g. ovarian, testicular, and thyroid cancers) or uncommon exposures (infrequently applied chemicals), and to replicate findings from individual studies. About half of the cohorts in the consortium collect data on cancer incidence and mortality. The consortium has met in 2011 and 2013 in Barcelona and Utrecht, respectively.

The first pooling project within AGRICOH, led by ENV, is on the risk of lymphomas, leukaemias, and multiple myelomas in association with exposure to pesticides. This 2-year project uses information on crops farmed during different time periods in combination with external data to generate crop-exposure matrices and determine exposure to pesticides when data on chemical exposures were not directly collected. The project is assessing exposure to 17 chemical groups and more than 25 specific active ingredients in approximately 350 000 farmers from France, Norway, and the USA. This study will be completed by November 2014.

ENV and the United States National Cancer Institute are developing a second project to describe cohort-specific cancer burden within the studies included in the consortium. Crude incidence and mortality rates of cancers of all types, as well as age-standardized and gender-specific incidence and mortality rates, will be the main outcomes of this investigation. AGRICOH cohorts joining this project are from Australia ($n$ = 2), France (1), Norway (3), the Republic of Korea (1), and the USA (2). Completion of this study is expected during 2014.

## Breast cancer in sub-Saharan Africa

Breast cancer in sub-Saharan Africa is characterized by disproportionately low survival rates, which, in light of projected increases in the incidence over the coming decades, warrant investigation to determine the relative contributions of biological, health system, and individual-level factors, and for which a strong evidence base in this region is needed. ENV has developed a successful collaboration with the Chris Hani Baragwanath Academic Hospital breast clinic (Soweto, South Africa) based on its unique resource of high-quality clinical information on a large breast cancer case series of more than 1200 patients. To date, the work has revealed findings that are especially relevant to this and similar settings. For example, our research has shown that stage at diagnosis has improved during 2006–2012 within this public sector setting (Figure 2); that residential distance from the hospital is associated with later stage at diagnosis even within a small (20 km) radius; and that the prevalence of receptor-specific subtypes is dominated by disease subtypes with better prognosis, with age-

specific estrogen receptor prevalence similar to that in African women aged 50 years or older (McCormack *et al.*, 2013a). These findings indicate that improvements in survival may be a realistic goal in this region. In addition, we have reported the high proportion (17%) of HIV-positive breast cancer patients at this hospital, which reflects the population-level HIV prevalence and the need to investigate treatment implications (Cubasch *et al.*, 2013).

As an extension of the above-mentioned work, we are partnering with the South African National Cancer Registry and Namibian and Botswanan collaborators to examine the epidemiology of breast cancer subtypes in a wider Southern African effort, the largest of its kind to date. We are also conducting the first general population study of mammographic density, a strong intermediate risk factor for breast cancer, in cooperation with the Pink Drive mobile mammography vans, which provide free mammograms to disadvantaged communities in South Africa (Figure 3).

Recently, ENV initiated the African Breast Cancer – Disparities in Outcomes (ABC-DO) study, funded by the Susan G. Komen foundation and conducted in collaboration with the London School of Hygiene and Tropical Medicine. ABC-DO is a prospective follow-up study of 1800 newly diagnosed breast cancer patients at four public hospitals in South Africa, Namibia, Uganda, and Nigeria. Information will be collected on the entire breast cancer journey leading up to and for up to 3 years after diagnosis. ABC-DO will provide data on the proximal biological factors that are hypothesized to have a direct impact on survival – clinical factors at diagnosis, treatment received, and lifestyle/morbidity factors – as well as distal factors (e.g. health practices, socioeconomic status, cultural beliefs, and education). Given the growing prevalence of mobile phone use in Africa, follow-up methods will be based primarily on telephone interviews to overcome losses to follow-up seen in previous studies. The perspective of ABC-DO is that comparisons of breast cancer survival within Africa (i.e. between settings with similar resources, none of which have general population breast cancer screening) will provide more informative insights than comparisons outside the continent. These comparisons will identify settings with better survival prospects and the reasons for them.

**Figure 2. Relative distribution of stage at breast cancer diagnosis by year of diagnosis at the Chris Hani Baragwanath Breast Cancer Clinic (Soweto, South Africa). Source: McCormack *et al.* (2013a); reproduced with permission from the publisher.**

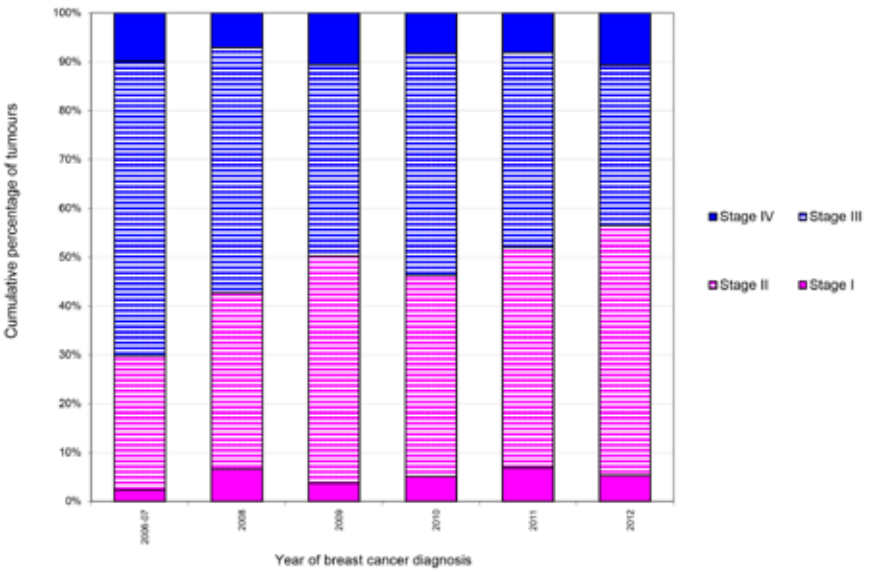



**Figure 3. Pink Drive mobile mammography vans provide free mammograms to disadvantaged communities in South Africa. © IARC/Valerie McCormack.**

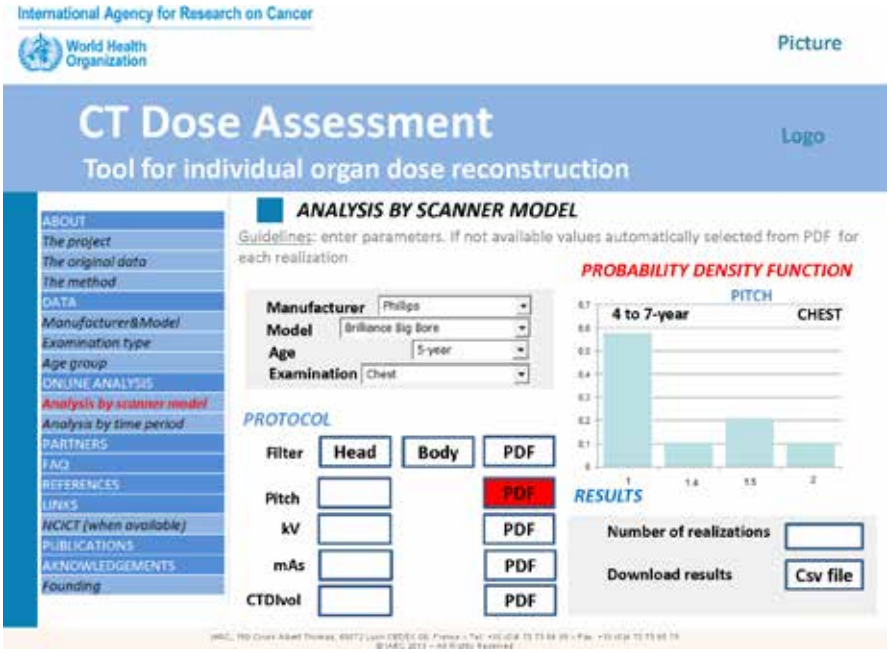

## Diagnostic radiation and risk of childhood cancer: the EPI-CT study

Medical exposure represents the largest man-made source of ionizing radiation exposure and has roughly doubled over the past two decades, mainly due to the growing use of computed tomography (CT) examinations. CT scanning in children and adolescents is of particular concern in radiological protection and public health, as studies of atomic bomb survivors and other populations indicate that children are generally more sensitive to the health effects of radiation than are adults. In addition, recent studies in

the United Kingdom and Australia have reported an increased risk of cancer associated with paediatric CT scans. However, direct estimation of the health impact of radiation from CT scans remains imprecise since, in both studies, ascertainment of radiation doses was performed not at the individual level but by using group-average approaches.

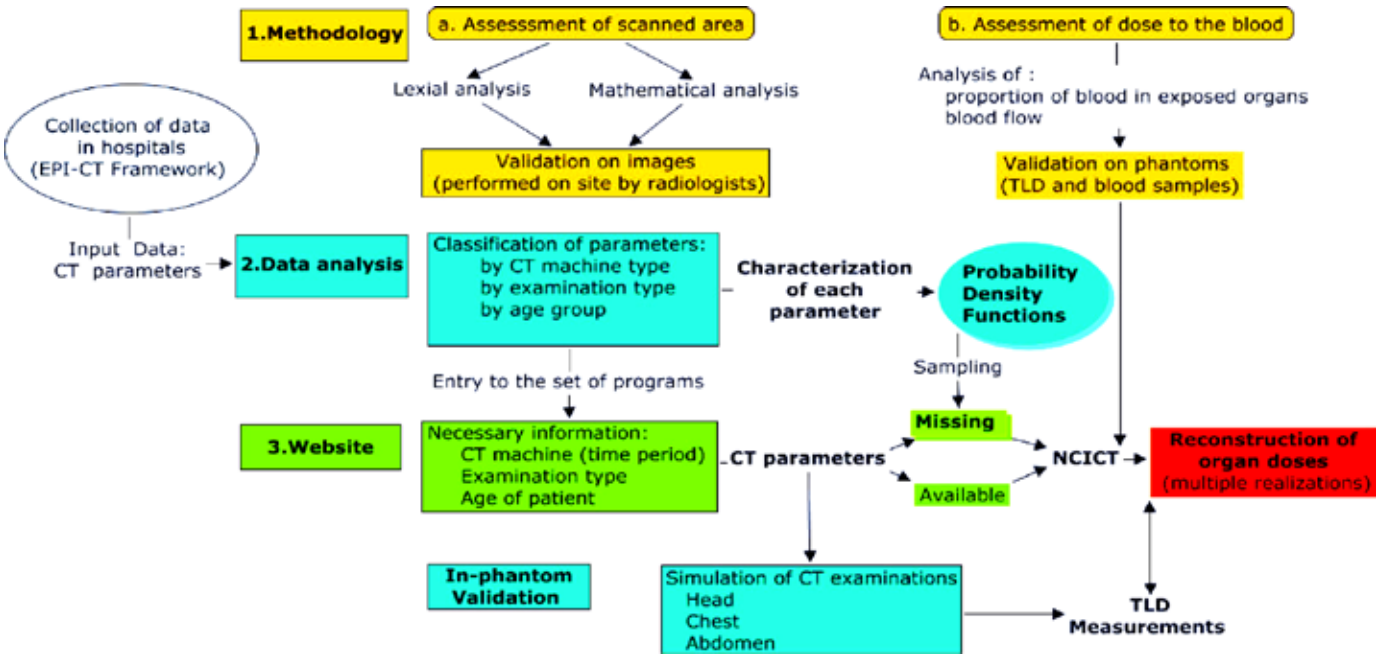
A large European cohort of children who had CT examinations (EPI-CT) is currently being assembled by ENV to enrol more than a million patients from Belgium, Denmark, France, Germany, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Data collection started in October 2011 and will continue through the end of 2013; about 77% of the cohort has already been accrued. Data collection is split into two time periods – before and after introduction of the Picture Archiving Communication System (PACS) (Thierry-Chef *et al.*, 2013). Before PACS, only sparse information about scanner settings, which is essential for reconstructing individual doses, was available from radiology departments. Hence, a multilevel approach was developed to retrieve information from a questionnaire, surveys, scientific publications, and expert interviews. For the years after PACS was introduced, an innovative approach was proposed to automatically extract the information on scanner settings and mathematical descriptions of the contours of exposed organs, allowing mapping to the hybrid computational phantoms and faster automatic reconstruction of individual doses (Figure 4).

**Figure 4. Entry screen of dose assessment for a study on cancer risk in children undergoing computed tomography (CT) examinations.**




EPI-CT also pilot tested a collection of biological samples to assess various biomarkers (microarray gene expression studies, DNA damage by scoring γ-H2AX, and chromosomal aberrations) of exposure related to the biological mechanisms behind the low-dose hypersensitivity observed in paediatric patients exposed to CT (Figure 5). The data collected on the patients is a very important starting point for assessing radiology practices and analysing ways to most effectively administer doses. A separate working group was therefore set up to explore how to optimize the use of paediatric CT procedures and redefine quality criteria for paediatric images.

**Figure 5. Dose reconstruction strategy for the international paediatric computed tomography scan study (EPI-CT).**



The EPI-CT study is unique because of its size, sophisticated dosimetry, and the attention being paid to identify, characterize, and take into account factors that may bias any possible association between the dose from CT scans and cancer risk. This includes, among others, missing CTs and confounding by socioeconomic status and by indication for the CT. It will provide more comprehensive and precise estimates of risk than those available to date, and will strengthen the scientific evidence about the effects of low-dose radiation exposure in young people.

The need for physicians to be cautious when recommending diagnostic procedures involving exposures to ionizing radiation early in life is strengthened by the conclusions of the GENE-RAD-RISK study, which found that ionizing radiation delivered in the course of diagnostic procedures to the chest before the age of 30 years may nearly double breast cancer risk in women who carry a mutation in the *BRCA1* or *BRCA2* gene (Pijpe *et al.*, 2012).

## Electromagnetic fields and risk of cancer

Scientific evaluations classify both extremely low-frequency magnetic fields (ELF-MF) (e.g. resulting from distribution and use of power transmission) and radiofrequency electromagnetic fields (RF-EMF) (e.g. from wireless communication) as *possibly carcinogenic to humans* (IARC Monograph classification Group 2B), indicating a need for further research. In 2001, ELF-MF was classified as Group 2B, and while epidemiological evidence suggests a weak association for childhood leukaemia, experimental studies failed to find a mechanism of action. Under the hypothesis that ELF-MF may promote growth of leukaemia cells, it was proposed that ELF-MF exposure could also be a risk factor for recurrence of disease. A multinational collaboration was initiated to investigate the relationship between ELF-MF and survival and risk of relapse in more than 3000 children with leukaemia from six countries, followed up for 10 years after diagnosis (Schüz *et al.*, 2012). No association was seen, providing no evidence that ELF-MF has a role in predicting the outcome of childhood leukaemia (Figure 6). Due to the widespread use of mobile phones, investigations into brain tumour risk in relation to mobile phone use are more topical. Studies to date are inconsistent; although they do not suggest an overall risk increase, among heavy mobile phone users an increased risk cannot be ruled out. In addition, mobile phones are a recent technology and longer observation periods are needed (Figure 7).

Time trend analyses of glioma, an often malignant type of brain tumour, in the high-quality cancer registries of the Nordic countries did not suggest any incidence increase in mobile phone users (Deltour *et al.*, 2012), confirming the lack of an overall risk increase (Figure 8). An analysis within the prospective United Kingdom Million Women study, including 800 000 middle-aged women, did not

**Figure 6. In an international pooled analysis, no increase in mortality was reported with increasing exposure to residential extremely low-frequency magnetic fields (ELF-MF) in children with acute lymphoblastic leukaemia. Pooled odds ratios and their 95% confidence intervals (vertical axis) are shown by increasing levels of exposure to ELF-MF (reference category, < 0.1 µT). Figure compiled from Schüz *et al.* (2012).**

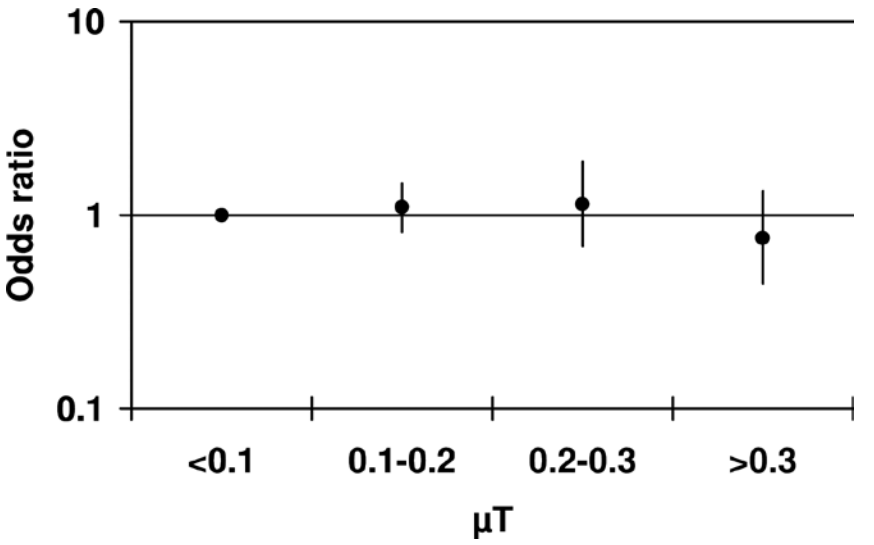
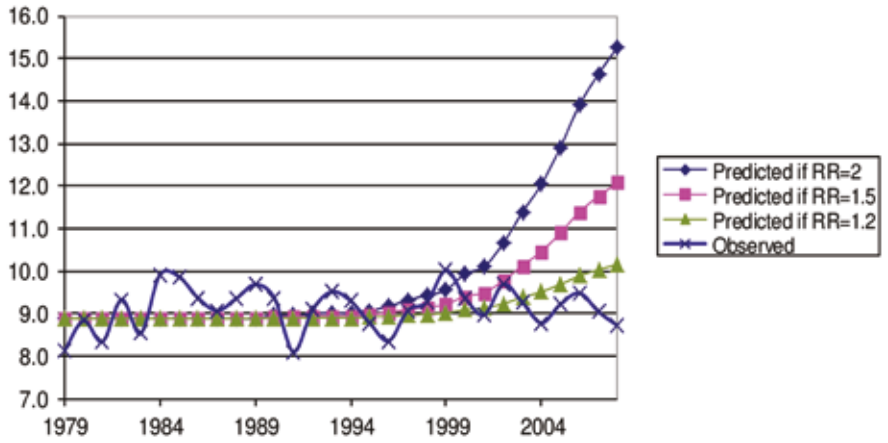



**Figure 7. Although there is little evidence that mobile phone use increases the risk of cancer, more research is needed in very heavy users, for exposure durations longer than 20 years, and in users who start at a young age. Photograph courtesy of Florentina Kindler.**

show any association of mobile phone use with glioma or meningioma, but an association with acoustic neuroma remained a possibility (Benson *et al.*, 2013). Most of the energy from a mobile phone is absorbed by the skin; therefore, the risk of skin cancer of the head was also investigated. No evidence of an increased risk was reported from a cohort subdividing the entire Danish population into subscribers of mobile phones between 1982 and 1995 and non-subscribers or later subscribers (Poulsen *et al.*, 2013). In general, it appears that the more recent studies attenuate the findings of previous mainly case–control studies, but prospective studies enrolling specifically the heaviest users of mobile phones are merited.

**Figure 8. Observed time trends in the incidence rate of glioma among men aged 40–59 years in the Nordic countries (Denmark, Finland, Norway, and Sweden) compared with predicted changes in the incidence rates if 10 years or more of regular mobile phone use were to be associated with an increase in glioma risk of 100%, 50%, or 20%, respectively. Figure compiled from data in Deltour *et al.* (2012). RR, relative risk.**




## Other major activities on environmental and radiation-related risk factors

To address the disproportionately high incidence rates of oesophageal squamous cell carcinoma in East Africa and Southern Africa, ENV established a research network from six countries across the region. Its kick-off meeting was held in September 2013 to decide on research priorities primarily focused on the evaluation and identification of setting-relevant modifiable environmental and lifestyle risk factors for this disease.

A pilot case–control study was conducted on lifestyle factors and upper digestive tract cancers in Addis Ababa, Ethiopia, in collaboration with national and United States partners. This first feasibility study completed in Africa is identifying requirements of a full-scale case–control study to investigate the role of suspected risk factors (e.g. khat chewing; Figure 9) and established risk factors (e.g. tobacco, alcohol) for cancers of the oral cavity, pharynx, and oesophagus. The study enrolled 410 cases and controls between May 2012 and April 2013, and data analyses are under way.

**Figure 9. Khat, a plant chewed in Yemen and East Africa, contains amphetamine-like stimulants and is classified as a drug of abuse by WHO. However, its production and consumption is legal in several countries, including Ethiopia, where khat chewing remains popular at social gatherings, particularly among Muslim men. It is unclear whether khat chewing is associated with an excess risk of upper digestive tract cancer; additional research is needed to clarify this. © IARC/Joachim Schüz.**

A retrospective cohort study is being conducted on cancer mortality in chrysotile asbestos miners and millers (Schüz *et al.*, 2013). The world's largest open-pit chrysotile mine and its processing mills are located in Asbest, where approximately 20% of the world's chrysotile is currently produced (Figure 10). The overall aim of the study is to more precisely characterize and quantify the exposure–response relationship for total and site-specific cancer risks associated with exposure to chrysotile asbestos. The cohort is currently being enumerated and its expected size is approximately 30 000 workers.

Inter-individual variations in response to radiation after the Chernobyl nuclear accident suggest that genetic factors may also affect the risk of radiation-related papillary thyroid carcinoma (PTC). This was investigated by genotyping 83 cases and 324 matched controls sampled from children living near Chernobyl (Damiola *et al.*, 2013). Associations with PTC were found for rs1801516 (D1853N) in *ATM* (odds ratio, 0.34) and rs1867277 in the promoter region of *FOXE1* (odds ratio, 1.55). This suggests that both the DNA double-strand break repair pathway and the thyroid morphogenesis pathway are involved in the etiology of PTC, and that risk alleles and radiation dose act as independent multiplicative risk factors.

IARC has previously published data on cancer risk of workers in the nuclear industry. In an update, pooled follow-up data were analysed for nuclear workers from France, the United Kingdom, and the USA, which contained more refined adjustments for neutron doses compared with the previous studies. This will improve estimates of cancer risk related to radiation exposure within the workplace.

Cancer risk in adults after exposure to ionizing radiation in utero is currently being analysed in the cohorts of the exposed Southern Urals populations (SOLO project). The cohort consists of 11 000 persons exposed to radiation from releases of nuclear waste into the Techa River and 8000 persons born to workers of the Mayak nuclear facility, making it the largest data set worldwide to address this question. The highest doses were received by those born in the 1950s and mainly exposed through nuclear accidents, inappropriate waste dumping, and insufficient worker protection.

**Figure 10. About 20% of the world's chrysotile used today is from mines in the town of Asbest, Russian Federation. A retrospective cohort study was initiated to investigate the chrysotile-related cancer risk in workers. © IARC/Joachim Schüz.**

In April 2013, a feasibility study (SEMI-NUC) was initiated to assess the prospects of establishing a long-term, prospective cohort study of residents near the former Semipalatinsk nuclear test site (Figure 11). As study coordinator, ENV hosted a kick-off meeting inviting partners and experts from Kazakhstan, Norway, Japan, the Russian Federation, and the USA to discuss issues related to this project.

**Figure 11. The Semipalatinsk nuclear test site. Photograph courtesy of the Institute of Radiation Safety and Ecology, Kazakhstan.**

The Global Acute Leukaemia network (GALnet), a newly established network of paediatric oncologists and epidemiologists from 18 countries around the world, will conduct collaborative studies to better estimate the worldwide burden of childhood leukaemia, identify causes of the disease, and create an information exchange network to discuss treatment options. GALnet is the result of a pilot project led by IARC with a kick-off meeting held in Lyon in February 2013.

**ENV is grateful to the following for their collaboration:**

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Scientific Research Institute of Occupational Health of Russian Academy of Medical Sciences, Russian Federation
Supreme Council of Health, Qatar

# Section of Nutrition and Metabolism (NME)

**Section head**
Dr Isabelle Romieu

The Section of Nutrition and Metabolism (NME) is composed of three groups. Research conducted in the Biomarkers Group (BMA) and the Dietary Exposure Assessment Group (DEX) complements the research in the Nutritional Epidemiology Group (NEP).

Diet, nutrition, metabolic/hormonal imbalances, excess energy consumption, obesity, and physical inactivity are thought to be important contributors to increasing cancer incidence worldwide. The mechanisms of action of these factors remain poorly understood, and little is known about the influence of exposure in utero and during early infancy on risk of cancer and other noncommunicable diseases (NCDs). These factors are particularly relevant given the dietary and lifestyle transitions taking place in many low- and middle-income countries (LMICs), leading to an increased burden of obesity and malnutrition.

Thus, the main objective of NME is to address these issues by evaluating the association of diet, nutrition, physical activity, energy imbalance, and related environmental factors with cancer risk and survival rates in high-income countries and LMICs using cohort and case–control designs or human intervention studies. NME plays a leading role in the coordination and maintenance of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a large ongoing prospective cohort initiated by IARC, and is actively involved in the recently initiated Mexican teacher cohort (EsMaestras) study and in multicentre breast cancer studies in LMICs (in Latin America and Africa). NME participates in various consortia and large-scale projects and collaborates with international and national institutions, as well as several other IARC Groups/Sections.

New methodological approaches are being developed to improve the accuracy, understanding, and interpretation of dietary exposures in an international context (DEX), to measure the exposome using high-throughput analytical methods (BMA), and to study cellular, biochemical, and physiological changes considering genetic and epigenetic modulations (NEP). Ultimately, the translation of findings into public health recommendations and the development of appropriate cancer prevention and control strategies are of major importance to NME.

The more than 120 peer-reviewed articles published by NME, or accepted for publication, in 2012–2013 provide evidence of the Section's high productivity and many international collaborations.

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In cancer epidemiology, biomarkers are invaluable tools to improve the assessment of exposures to various environmental (diet, contaminants, pollutants) and endogenous factors (hormones, metabolic status) that may influence disease risk. However, most often only small sets of biomarkers are measured and this limited number cannot adequately describe the diversity of exposures contributing to cancer etiology. The goal of the Biomarkers Group (BMA) is to apply the most advanced analytical technologies to discover, validate, and implement biomarkers of environmental exposure and metabolism for cancer epidemiology. Emphasis is placed on the concept of the exposome, defined as the totality of environmental exposures faced by an individual during their lifetime, and on the use of powerful high-throughput metabolomic approaches to measure the exposome.

## Metabolomics for measuring the exposome

During the past biennium, significant effort has been devoted to the development of the BMA laboratory and the establishment of methods for measuring the exposome, complementing the well-established laboratory activities on fatty acids (collaboration with NEP) and hormones. Two rooms were fully renovated in the BMA laboratory to accommodate two new mass spectrometers. Computing capacity was increased and software was installed to allow storage and treatment of the large data sets generated with these high-throughput instruments. A virtual machine on a large central facility set up by ITS has been dedicated to mass spectrometry data analysis. Two researchers and a data manager with skills in mass spectrometry, chemometrics, multivariate statistics, and bioinformatics were recruited, and BMA staff members have been trained to run analyses on the new mass spectrometers. Both untargeted methods to measure thousands of metabolites and specific methods targeted at specific classes of metabolites, such as polyphenols, have been developed. A robust, organized, and standardized workflow for metabolomic analyses and data processing incorporating a series of standard operating procedures has been set up.

## Metabolic phenotypes and cancer

The exposome includes several thousand endogenous and exogenous metabolites that, together, define a metabolic phenotype characterizing a particular individual at a given time. This characterization should enable the identification of novel risk factors for cancers and the development of new hypotheses about the mechanisms of action involved. A customized and automated method using high-resolution mass spectrometry was developed that enables the detection of more than 2000 metabolites in plasma and the identification of up to 400 endogenous metabolites. Using this method, we will identify metabolic phenotypes associated with exposure to polluted air or contaminated water, as part of the EXPOsOMICS project (involving 12 partner institutions led by Imperial College London), in which BMA is responsible for metabolomic analyses. We will also use the method to detect metabolic phenotypes associated with cancer risk, in several nested case–control and case–control studies either under way or planned in EPIC and other cohorts on liver, colorectal, and breast cancer (collaboration with NEP).

Exogenous metabolites, part of the "food metabolome", resulting from the digestion of food-derived compounds, have also been analysed. They define a metabolic phenotype characteristic of the diet of an individual. The untargeted metabolomic workflow has been applied to urine samples from about 500 subjects from the cross-sectional study nested within EPIC. Highly detailed dietary data are available for these subjects, and this workflow enabled the identification of novel dietary biomarkers that can be used in future cancer epidemiological studies. Iterative regression and discriminant analyses led to the identification of a large number of signals characteristic of the 400 dietary variables (collaboration with DEX). The corresponding biomarkers are identified through the screening of customized databases developed by BMA during the biennium. These databases include FooDB, a database on all known food constituents (collaboration with the University of Alberta) (Wishart *et al.*, 2013), and Phenol-Explorer, a database on all known polyphenol metabolites (Rothwell *et al.*, 2012). In a first exploration of the data, approximately 100 polyphenol metabolites could be identified as putative novel biomarkers for some polyphenol-rich foods. This unique approach will be extended to the whole food metabolome, with special focus on dietary factors associated with cancer risk, such as coffee and dietary fibre. Various studies will be conducted to evaluate the reliability over time and validate the putative biomarkers.

BMA organized the 1st International Workshop on the Food Metabolome and Biomarkers for Dietary Exposure (Glasgow, 4–5 July 2013), which gathered 50 experts from Europe and North America. This workshop led to the definition of recommendations for future research in the field.

## Hormones and cancer

Over the past biennium, BMA has focused on the study of associations of thyroid stimulating hormone (TSH), thyroglobulin, thyroid hormones, growth factors, estrogens, insulin-related markers, cytokines, and inflammatory factors with cancer risk in large-scale epidemiological studies. In collaboration with the Section of Infections, the Group has undertaken a case–control study nested within EPIC to characterize associations between thyroid hormones and differentiated thyroid cancer risk on samples from 300 women and 57 men. This study showed a strong direct association between increasing circulating levels of thyroglobulin and differentiated thyroid cancer risk, and an inverse association with increasing TSH concentrations.

In collaboration with NEP, a cross-sectional study of 798 premenopausal and 1360 postmenopausal women undertaken in EPIC showed that increased physical activity levels were associated with lower concentrations of circulating androgens and estrogens, independent of body size. Several cross-sectional studies have also been carried out in a subsample of the large Mexican EsMaestras cohort (led by Dr Isabelle Romieu, NEP) to study the association between anthropometry, mammographic density, and circulating hormones,

insulin-related markers, cytokines, and inflammatory factors in premenopausal and postmenopausal women in this understudied population. Major results showed an inverse association between growth factor concentrations and dense tissue, which was, however, driven by adiposity. Single-nucleotide polymorphisms (SNPs) in specific genes were associated with circulating levels of growth factors but not with mammographic density features. Preliminary analyses also showed that circulating growth factors significantly increased with increasing height and leg length, and strongly decreased with increasing body mass index (BMI), weight, waist and hip circumferences, waist-to-hip ratio, and waist-to-height ratio, while circulating C-reactive protein, leptin, the leptin-to-adiponectin ratio, and C-peptide concentrations strongly increased. These results suggest a strong relationship between endogenous hormones, inflam-matory factors, and body size in this population of premenopausal Mexican women.

BMA scientists are involved in several cancer-related EPIC working groups (breast, ovarian, and endometrial cancer), are coordinating the activities of the EPIC thyroid cancer working group (in collaboration with the Infections and Cancer Epidemiology Group), and are leading studies on obesity, thyroid hormones, reproductive factors, and differentiated thyroid cancer risk. BMA also participates in an international consortium led by the United States National Cancer Institute to study the associations between obesity, reproductive factors, and thyroid cancer risk in cohort studies worldwide. In addition, the Group is involved in setting up case–control studies on breast cancer risk in Latin America and South Africa (studies led by NEP).

### Dietary polyphenols and cancer

Polyphenols constitute the most widely consumed class of dietary antioxidants. Their anti-carcinogenic effects have been well documented in many studies conducted in cell culture or experimental animals. Much less evidence exists on their anti-carcinogenic effects in humans as epidemiological data is still very limited. New tools are being developed in collaboration with DEX to assess exposure to the polyphenol metabolome and to identify those polyphenols most strongly associated with cancer risk. A food composition table for polyphenols is being developed based on food composition data from the Phenol-Explorer database. To increase the reliability of the polyphenol exposure measurements, 4600 values of retention factors, describing the amount of polyphenols retained after cooking and food processing, have been collected from the scientific literature and inserted into the Phenol-Explorer database (Rothwell *et al.*, 2013). This new food composition table will be used to assess associations with colorectal cancer in EPIC. In parallel, a highly sensitive and innovative method using differential stable isotope coding of the exposome is being developed to measure 40 different polyphenols by mass spectrometry in urine and blood. These biomarkers will be used in the first nested case–control studies on colorectal cancer in EPIC and to validate polyphenol intake measurements obtained with the new food composition table.

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# Dietary Exposure Assessment Group (DEX)

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

## International methodologies and web-based infrastructures to support large international nutritional studies

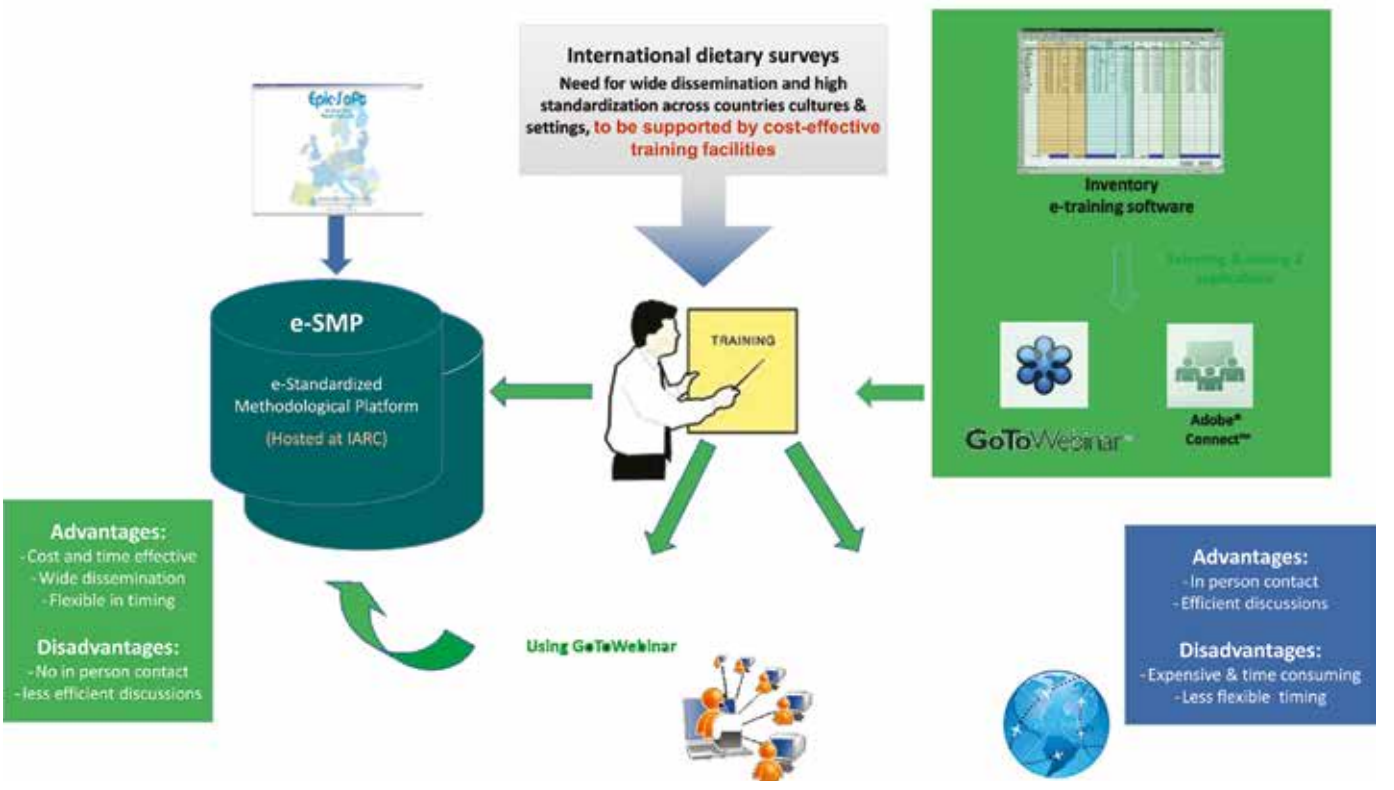
The standardized computerized 24-hour dietary recall method EPIC-Soft®-24-HDR, and its related tools, was initially developed by IARC within the framework of the EPIC study. Interest in its use has increased, particularly but not exclusively for international nutritional surveillance. Indeed, this international methodology was recommended by the European Food Safety Authority as the reference dietary methodology for pan-European dietary monitoring surveys (http://www.efsa.europa.eu/en/press/news/datex100212.htm). In view of the first pan-European dietary survey, EU Menu, various methodological and feasibility studies – such as EFCOVAL (http://www.efcoval.eu/), PANCAKE (http://www.efsa.europa.eu/fr/supporting/pub/339e.htm), and PILOT- and EMP-PANEU http://www.efsa.europa.eu) – were launched to adapt, test, and evaluate this methodology for nutritional surveillance and risk assessments.

Through these different projects, new software (EPIC-Soft Data Entry application®) designed for use in data entry of food consumption data among children (PANCAKE project) was successfully developed and field-tested. In addition, five new versions of EPIC-Soft®-24-HDR were developed, for Bulgaria, Finland, Hungary, Poland, and Portugal, and field-tested for use in adolescents, adults, and the elderly in four of the five countries (PANEU projects). Also, the newly developed web-based Interview Manager application for handling and management of collected interview data was field-tested.

Guidelines and e-training documents for the use of e-SMP are also under development. The EPIC-Soft®-24-HDR train-the-trainers course has been successfully implemented and evaluated as a conventional and e-learning course in the framework of the EMP-PANEU project (Huybrechts *et al.*, 2012). This e-training component was developed in collaboration with other IARC Groups/Sections (ETR, ASO, and ITS) to allow wider dissemination of the methods in a cost- and time- efficient way, which is particularly important for LMICs (Figure 1).

To disseminate these international tools and ensure their long-term maintenance and standardization, a comprehensive web-based infrastructure is needed to support nutritional studies, particularly in LMICs. Therefore, a web-based platform, the dietary e-Standardized Methodologies Platform (e-SMP), was designed to support the development and maintenance of EPIC-Soft®-24-HDR and other dietary tools. Although the development of e-SMP is ongoing and it is currently being tested in the pan-European dietary monitoring surveys, its implementation in other settings (e.g. cohorts and clinical trials) and regions worldwide has been initiated through different DEX initiatives and projects.

**Figure 1. Development and evaluation of the e-training train-the-trainers course.**



### Implementation of the DEX methodologies and infrastructure worldwide

Building on successful experiences in Europe where various countries – the Netherlands, Germany, Belgium, France, Switzerland, and Austria (under negotiation) – have already endorsed the DEX methodologies for their national monitoring surveys, DEX has initiated projects to expand the implementation to other regions worldwide, including Latin America, Asia, and Africa. The ultimate purpose is to better measure, monitor, and understand the nutritional transition observed in these regions and determine whether there is an association with cancer and other NCDs. DEX is following a stepwise approach, with several parallel projects – LaDieta (in Brazil and Mexico), a project in Asia (Republic of Korea), and AS-PADAM (in *n* = 22 African countries) – aimed at adapting, testing in real study conditions, and validating EPIC-Soft®-24-HDR and its web-supported infrastructure (e-SMP) for these regions. The planned next steps will be the expansion/adaptation of this software to other countries in these regions and its implementation, preferably in international nutritional surveillance settings and research studies. For Africa (AS-PADAM), the project started with an inventory on the availability, quality, and challenges of dietary and physical activity assessment methods available or currently being used in different African regions. This is a prerequisite to exploring the methodological infrastructure needed to improve nutritional research and monitoring in the continent within international frameworks.

### Evaluation of dietary measurement errors in multicentre studies

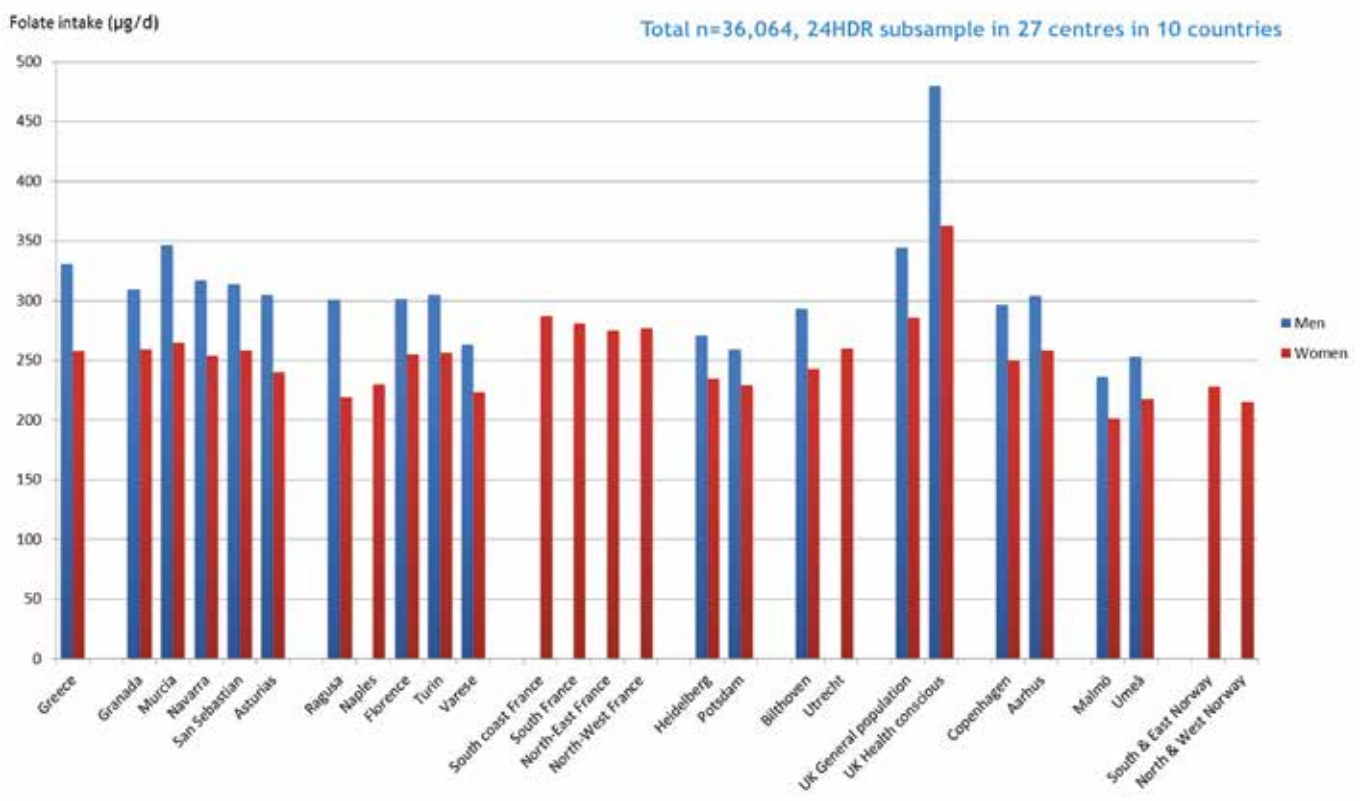
A better understanding of measurement errors is needed to improve the validity of dietary assessment tools. In the past biennium, three evaluation studies addressing complementary methodological questions were conducted. First, Freisling *et al.* (2012) confirmed that underreporting of protein and potassium intake is predicted by BMI and, for the first time, it was shown that underreporting is the same across countries. Second, Ferrari *et al.* (2013a) showed that acrylamide intake based on self-reported diet weakly correlates with biomarkers of acrylamide. Lastly, Crispim *et al.* (2012) concluded that group-level bias in protein and potassium intake collected with EPIC-Soft®-24-HDR does not vary across centres.

DEX also conducted an in-depth evaluation of measurement properties of new e-technologies in dietary assessment for large-scale epidemiological studies (Illner *et al.*, 2012).

### Studies on dietary exposure (including biomarkers of diet)

Descriptive analyses of dietary exposure have been published, such as the first standardized comparison of dietary folate intake across 10 European countries (Park *et al.*, 2012a) (Figure 2), and dietary acrylamide exposure in the EPIC study (Freisling *et al.*, 2013a) and their related biomarkers (Park *et al.*, 2013a).

**Figure 2. Mean intake of folate (µg/d) in men and women, stratified by centre ordered from south to north, adjusted for age, total energy intake, weight, and height, and weighted by season and day of recall. Source: Park *et al.* (2012a); reproduced with permission from Cambridge University Press.**



### 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 and INTERACT projects). A particular focus is on industrial foods (industrial trans fatty acids, acrylamide, energy-dense foods, and foods with high glycaemic index/glycaemic load). This work is in collaboration with other researchers in NME.

### Development and application of new methodologies to analyse dietary patterns

One of the Group's new research activities is dietary pattern analyses, which appear to be a promising approach for better depicting the complexities of diet and improving the understanding of its association with diseases, particularly cancer. DEX, in collaboration with other IARC researchers (in the Biostatistics Group and NEP) and external partners, has initiated a project on analysing nutrient and biological patterns in international studies; applications for supporting grants are being submitted and papers prepared for studies of colorectal cancer, breast cancer, and diabetes. Furthermore, a systematic review of peer-reviewed studies on diet quality indices applied to old age was recently published as an invited book chapter evaluating the impact of more than 40 factors from different domains (e.g. lifestyle, health, environment) on diet quality (Freisling *et al.*, 2013b).

### Goals and projects for the next biennium

DEX plans to develop its activities within the recently launched LPC-BBMRI project, which aims to federate the largest European cohorts with biobanks under the framework of the already existing Biobanking and Biomolecular Research Infrastructure (BBMRI) network. DEX will also collaborate as a task leader in the first Joint Programming Initiative, A Healthy Diet for a Healthy Life (JPI HDHL), on Determinants of Diet and Physical Activity Choice (DEDIPAC).

More broadly, DEX intends to contribute to the new global strategies on diet-related NCDs. Indeed, one of the main challenges in implementing these strategies is the lack of reliable and standardized dietary methodologies and their supporting research infrastructures for measuring, monitoring, comparing the nutritional transitions, and investigating their association with diseases.

To fill this gap, DEX intends, as part of its strategic plan, to support the establishment of a new worldwide network of nutritional surveillance, with a particular but not exclusive focus on LMICs. Within IARC, as an integrated part of WHO and building on its regional offices and other partnerships, DEX aims to provide standardized dietary methodologies and support for the collection of more comparable dietary exposure data worldwide. This comprehensive dietary framework should serve multiple research, prevention, and risk assessment purposes at the national, regional, and international level.

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# Nutritional Epidemiology Group (NEP)

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The overall objective of the Nutritional Epidemiology Group (NEP), in close interaction with DEX and BMA, is to determine the role of diet, under-/over-nutrition, hormonal factors, physical activity, and energy balance on cancer incidence and survival.

We recognize that the cancer process is a continuum, and that cancer and noncommunicable diseases (NCDs) share risk factors and underlying mechanisms with metabolic disorders, particularly metabolic syndrome and diabetes. Therefore, NEP works to implement a life-course approach to cancer etiology and to bring together information about early-life and mid-life exposures and determinants of healthy ageing. The Group uses modern epidemiological and statistical techniques tied to the use of biomarkers to explore metabolic alterations, along with the application of genetic, nutrigenomic, and epigenetic approaches.

## Studies in high-resource settings: the European Prospective Investigation into Cancer and Nutrition (EPIC)

NEP plays a key role in the coordination and scientific management of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. It ensures the cyclic end-point/vital status update of the EPIC database, with the centralization of the most recent information on incident cancer events and mortality from collaborating centres. NEP is setting up a larger centralized database to include additional chronic disease end-points and updated exposure information. NEP also ensures delivery of updated project-specific databases to the EPIC working group network, including the preparation of data sets for nested case–control studies. The Group also provides support to the Laboratory Information Management System for the retrieval of biological samples, in collaboration with the IARC Laboratory Services and Biobank Group.

## Nutritional and lifestyle predictors of cancer in EPIC

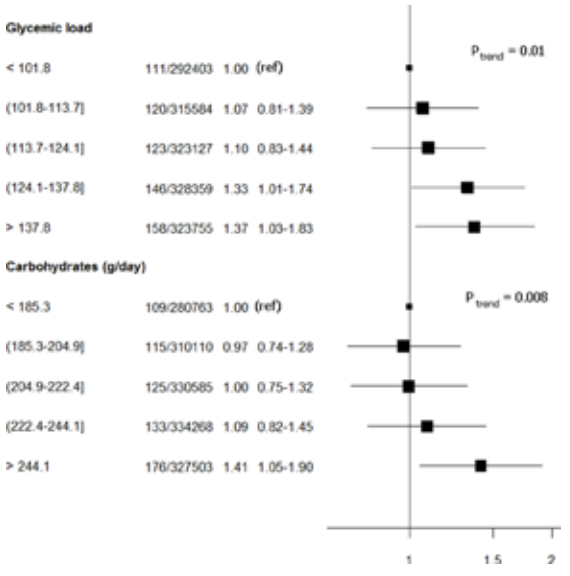
### Breast cancer

NEP considers that analysis of breast cancer phenotypes based on homogenous groupings by hormonal receptor status will lead to a clearer etiological understanding of dietary/metabolic risk factors. NEP has recently shown that: carbohydrate-rich diets are significantly related to increased breast cancer risk among postmenopausal women with estrogen receptor-negative (ER-) and ER-/progesterone-negative (PR-) tumours, but not those with receptor-positive tumours (Romieu *et al.*, 2012a) (Figure 1A); higher vegetable-source dietary fibre intake is significantly related to lower breast cancer risk in pre/postmenopausal women, with a stronger association in ER- and ER-/PR- tumours (Ferrari *et al.*, 2013b) (Figure 1B); dietary flavonoids/lignans and circulating vitamin D are not related to breast cancer risk (Zamora-Ros *et al.*, 2013b); and moderate to high levels of physical activity are strongly inversely associated with breast cancer risk, particularly in ER+/PR+ tumours (Steindorf *et al.*, 2013).

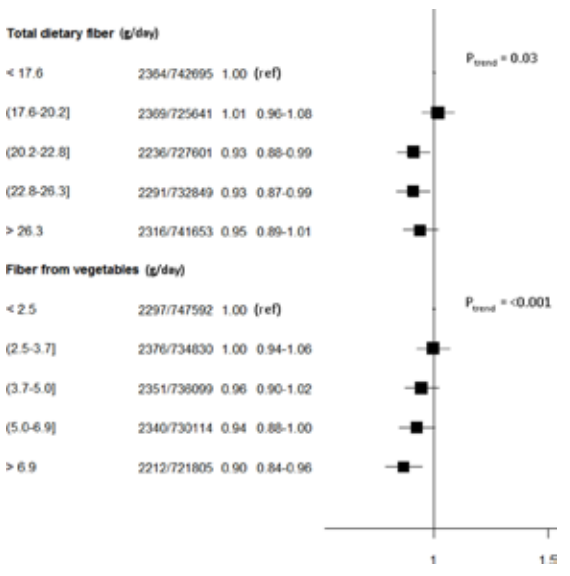
A nutrient of key interest is folate, which affects both genetic and epigenetic pro-carcinogenic processes (Teegarden *et al.*, 2012). NEP received funding (INCa/La Ligue Contre le Cancer/Fondation de France/WCRF) to determine the role of folate and other B vitamins on breast cancer risk using dietary information and biomarkers of one-carbon metabolism, and incorporating genetic factors and genome-wide DNA methylome profiling. Analyses are still under way, but preliminary results suggest a protective effect of dietary folate on breast cancer among women with high alcohol consumption.

**Figure 1. (A) Associations with risk of breast cancer in postmenopausal women with estrogen receptor (ER)-negative tumours, in the EPIC study: glycaemic load and carbohydrate intake. Figure compiled from Romieu *et al.* (2012a). (B) Associations with risk of breast cancer in postmenopausal women with ER-negative tumours, in the EPIC study: dietary fibre intake, total and from vegetable sources. Source: Ferrari *et al.* (2013b); reproduced with permission from the publisher.**

**(A)**




**(B)**



Another important group of nutrients are fatty acid biomarkers. Recent results from the E3N-EPIC cohort show a strong positive association between trans fatty acid isomers originating from industrial processes and breast cancer risk. In collaboration with BMA, NEP has extended this project to the full EPIC cohort (5000 breast cancer cases), using updated methodology to quantify 60 fatty acids, including 15 transisomers.

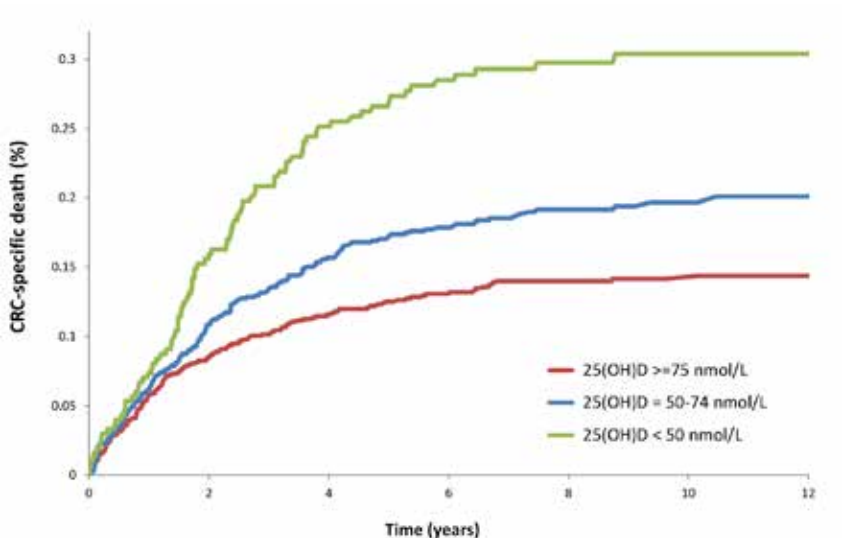
## Colorectal cancer

The Group has shown that maintaining healthy dietary habits, such as higher dietary fibre intake (Murphy *et al.*, 2012) and adherence to a Mediterranean diet (Bamia *et al.*, 2013), is associated with decreased colorectal cancer risk, whereas higher adult weight gain, particularly abdominal obesity, is positively associated (Aleksandrova *et al.*, 2013b). Accordingly, measures of selected circulating obesity markers showed decreased risk with higher concentrations of adiponectin (Aleksandrova *et al.*, 2012a) and soluble leptin receptor (Aleksandrova *et al.*, 2012b). A further analysis showed that these biomarkers, along with high-density lipoprotein (HDL), account for a large proportion of the association between abdominal obesity and colorectal cancer risk (Aleksandrova *et al.*, 2013a). Fatty acid biomarkers were analysed in the French E3N-EPIC cohort study, showing an increased risk of advanced adenoma with higher oleic acid levels, and a decreased risk with higher levels of long-chain polyunsaturated fatty acids (PUFAs), indicating altered fatty acid metabolism (Cottet *et al.*, 2013). Colorectal cancer analyses are currently under way, and NEP is also leading a project on determinants of colorectal cancer survival. The initial findings suggest longer survival in those with higher baseline vitamin D concentration (Fedirko *et al.*, 2012a) (Figure 2). Current projects include investigations of body iron status, advanced glycation end-products, and colonic barrier function.

## Hepatocellular carcinoma

Research showed that abdominal obesity (Schlesinger *et al.*, 2013a) and presence of diabetes (Schlesinger *et al.*, 2013b) are associated with increased hepatocellular carcinoma risks, as are lower intakes of dietary fibre (Fedirko *et al.*, 2013b), fish (Fedirko *et al.*, 2013c), and flavonoids and antioxidant nutrients (Zamora-Ros *et al.*, 2013a), and higher total sugar intake (Fedirko *et al.*, 2012b). Further detailed analyses, particularly with biomarker measures, are in progress.

**Figure 2. Adjusted cumulative incidence curve of colorectal cancer-specific mortality by pre-defined levels of pre-diagnostic 25-hydroxyvitamin D [25(OH)D] (< 50, deficient; 50–74, insufficient; ≥ 75 nmol/L, sufficient vitamin D status, on the basis of proposed levels of vitamin D deficiency/insufficiency). Source: Fedirko *et al.* (2012a); reproduced with permission from American Association for Cancer Research.**




## Pancreatic and other cancers

The Group has recently been funded by INCa/ARC/WCRF to analyse fatty acid biomarkers in association with risk of pancreatic cancer, a highly fatal tumour for which studies to date indicate a potential association with dietary fat and some fat subtypes.

NEP has adapted statistical models for dietary pattern analyses (Fahey *et al.*, 2012) and is applying the approach to measures of dietary/lifestyle quality (e.g. the Healthy Eating Index and the Oxidative Balance Score).

## Alcohol and cancer

NEP collaborated with the French Direction Générale de la Santé on an exhaustive evaluation of lifetime alcohol and tobacco use and overall/cause-specific mortality, using evidence from EPIC. Individuals consuming more than 5 drinks/day in men and more than 2.5 in women showed a 2–5 times higher risk of dying due to alcohol-related cancers (including cancers of the upper aerodigestive tract, liver, colorectum, and female breast) compared with subjects with lifetime consumption of less than one drink/week (Bergmann *et al.*, 2013). In the EPIC population, mortality rates were 1.5–3-fold larger for current smokers than never-smokers. Associations related to tobacco use were of similar magnitude for tobacco-related cancer, respiratory disease, and cardiovascular disease deaths (Bergmann *et al.*, 2013; Licaj *et al.*, 2013). Similar analyses on the incidence of NCDs are in progress. We also collaborated on a meta-analysis of low-dose alcohol consumption and cancer risk (Bagnardi *et al.*, 2013). NEP showed that genetic variability in alcohol metabolizing genes did not modulate the strong association between alcohol and colorectal cancer risk (Ferrari *et al.*, 2012a). For female cancers, no association was observed with alcohol intake and endometrial cancer (Fedirko *et al.*, 2013a); analyses on breast cancer and reproductive factors are in progress.

## Studies on breast cancer in low- and middle-income countries

Breast cancer incidence and mortality are rising rapidly in LMICs. In collaboration with the National Institute

of Public Health (INSP) and the National Institute of Cancerology (INCAN) in Mexico, NEP is using large cohorts (the EsMaestra cohort of Mexican teachers) and multicentre case–control studies (the CAMA study) to identify the role of diet, physical activity, obesity, and metabolic disorders on breast cancer incidence and survival. Findings from the CAMA study show lower breast cancer risk associated with higher circulating vitamin D levels (Fedirko *et al.*, 2012b) (Figure 3) and higher intake of n-3 PUFA (Chajès *et al.*, 2012) – a finding that is being pursued with fatty acid biomarker measures.

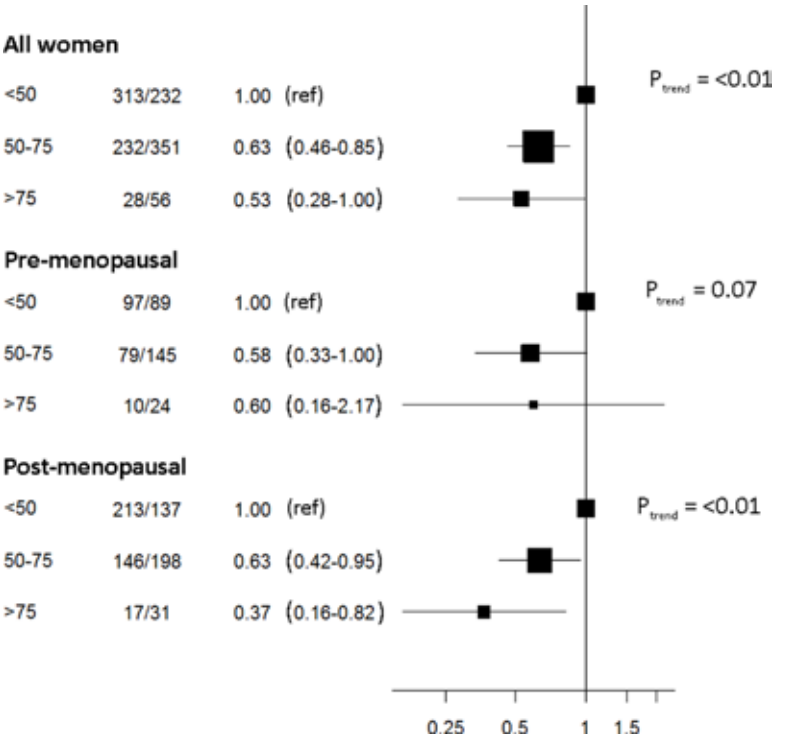
Higher breast cancer risks were observed in women reporting a diabetes diagnosis (Torres-Mejía *et al.*, 2012) and in women who reported increasing body shape silhouettes over their lifetime (Amadou *et al.*, 2013b). NEP plans to study interactions between fat distribution and genetics in breast cancer, following our recent meta-analysis that identified ethnicity as a key factor affecting the association of body size with premenopausal breast cancer (Amadou *et al.*, 2013b).

Since mammographic density is a strong predictor of breast cancer, understanding the link between breast cancer risk factors and mammographic density could provide better insight into mechanisms underlying breast cancer development and help identify women at higher risk. In the large EsMaestras cohort, mammographic density was positively related to metabolic syndrome (Rice *et al.*, 2013b) and early adult body fatness (Rice *et al.*, 2013a), but no association was observed with circulating levels of growth hormone.

### Molecular Subtypes of Premenopausal Breast Cancer in Latin American Women (PRECAMA): a multicentre population-based case–control study

Recently, the Group initiated a multicentre population study to determine risk factors for premenopausal breast cancer among Hispanic women, a culturally and genetically heterogeneous group. Detailed classification of tumour subtypes will help to refine the phenotype and improve the identification of specific endogenous and exogenous factors as well as to disentangle their interplay with regard to breast cancer. A feasibility study has been started with structured collection of individual, clinical, and pathological information and of biological specimens in four Latin American countries (Chile, Colombia, Costa Rica, and Mexico) in collaboration with national institutions, the Fred Hutchinson Cancer Research Center, and the Pan American Health Organization. Our efforts to establish the infrastructure for such a large, multicentre study in Latin America will enhance the potential of these countries to participate in international cancer research partnerships.

**Figure 3. Serum 25-hydroxyvitamin D [25(OH)D] blood levels and breast cancer risk in Mexican women. Figure compiled from Fedirko *et al.* (2012b).**




### Influence of diet, physical activity, and body size on breast cancer in South Africa: a study of African women in transition

NEP recently obtained WCRF funding to develop a study of dietary/lifestyle determinants of breast cancer in the understudied population of Soweto, Johannesburg, South Africa. The study includes structured collection of individual, clinical, and pathological information along with biological specimens and detailed information on anthropometry (DEXA/ultrasound). It will provide relevant information on tumour subtype frequencies and specific risk factors that affect breast cancer incidence and survival.

### Early environmental exposure, metabolic disorders, and cancer

NEP has established the Latin American Birth Cohort Consortium on Healthy Growth (LABCGD) composed of three cohorts from Brazil, Chile, and Mexico. We are evaluating the role of fetal and childhood exposures and the incidence of intermediate outcomes, child growth pattern, obesity and metabolic syndrome, and epigenetic changes. These outcomes are potentially relevant to future cancer risks. Thus, NEP intends to expand the consortium to other birth cohorts.

In collaboration with other IARC Groups (BMA, EGE, MMB), INSP (Mexico), and Emory University, recent NEP findings from the Mexican component

of the LABCGD show an influence of docosahexaenoic acid (DHA) supplementation on immune response and modulation of global methylation levels and Th1/Th2 response in infants of mothers who smoke (Lee *et al*., 2013a).

### Determinants of healthy ageing

NEP has a leading role in the CHANCES FP7 project, which brings together 14 cohorts for pooled analyses of determinants of cancer risk and survival in elderly populations. We initiated specific projects within CHANCES (socioeconomic status, body size, alcohol intake) and collaborate with groups in the CHANCES network on several other projects (dietary patterns, vitamin D levels, disability-adjusted life years). The Group is also exploring determinants of healthy ageing using the existing EPIC resources.

### Nutritional metabolomics

In collaboration with BMA and a leading nuclear magnetic resonance (NMR) metabolomics centre in Lyon http://www.ens-lyon.fr/crmn/crmn/index.html, NEP is conducting a series of metabolomic studies within EPIC on pancreatic, hepatocellular, and biliary tract cancers. Studies on other cancer sites are planned.

**NEP is grateful to the following for their collaboration:**

Alicia Matijasevich and Cesar Victora, Brazil; Robert W Bruce, Ahmed El-Sohemy, Gail McKeown-Eyssen, and Parminder Raina, Canada; Eva Bustamante, Eva Ana María Carrasco, Camila Corvalan, Maria Luisa Garmendia, and Ricardo Uayi, Chile; Carolina Echeverri, Miguel Roldan, and Gloria Sanchez, Colombia; Diego Guillén and Ana Cecilia Rodriguez, Costa Rica; Kim Overvad and Anne Tjønneland, Denmark; Pierre-Yves Bello, Marie-Christine Boutron-Ruault, Françoise Clavel-Chapelon, Beatrice Fervers, Martine Laville, and Fabienne Lesueur, France; Heiner Boeing, Rudolf Kaaks, and Tobias Pischon, Germany; Antonia Trichopoulou and Dimitrios Trichopoulos, Greece; Franco Berrino, Vittorio Krogh, Domenico Palli, Salvatore Panico, Rosario Tumino, and Paolo Vineis, Italy; David Hughes, Ireland; Hideyuki Hyogo, Japan; Isabel Alvarado Cabrera, Albino Barraza-Villareal, Martin Lajous, Alejandro Mohar, Ruy Lopez Ridaura, Juan Rivera, and Gabriela Torres-Mejia, Mexico; Bas Bueno de Mesquita and Petra Peeters, the Netherlands; Eiliv Lund, Guri Skeie, and Elisabete Wiederpass, Norway; Herbert Cubasch and Maureen Joffe, South Africa; Aurelio Barricarte, Carlos A. González, Miren Dorronsoro, Carmen Navarro, José Ramon Quirós, and María José Sánchez Pérez, Spain; Göran Hallmans and Jonas Manjer, Sweden; John E. Hesketh, Timothy J. Key, Kay-Tee Khaw, Elio Riboli, and Afshan Siddiq, United Kingdom; Elizabeth Donato, Veronika Fedirko, Andrew T. Gewirtz, Viktor Kipnis, and Peggy Porter, USA.

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Instituto Nacional de Salud Pública, Mexico
Le Comité du Rhône de la Ligue Nationale contre le Cancer
World Cancer Research Fund, London, United Kingdom

# Section of Genetics (GEN)

**Section head**
Dr Paul Brennan

The Section of Genetics (GEN) comprises the Genetic Epidemiology Group (GEP), the Genetic Cancer Susceptibility Group (GCS), and the Biostatistics Group (BST). The work of the Section combines large population-based studies with laboratory and bioinformatics expertise to identify specific genes that contribute to the development of cancer and elucidate how they interact with environmental and lifestyle factors in carcinogenesis. The Section also tries to identify individuals who are at high enough risk of developing cancer that they are likely to benefit from existing risk reduction strategies.

GEN projects usually involve extensive fieldwork in collaboration with external investigators in order to develop large-scale epidemiological studies with appropriate clinical and biosample collections. This typically occurs within GEP, which has a primary interest in the analysis and identification of common genetic susceptibility variants and their interaction with non-genetic risk factors. Genetic analysis comprises either candidate gene or genome-wide association studies (GWAS), as well as sequencing work. GEP studies also assess non-genetic exposures, partly in recognition of the importance of non-genetic factors in driving cancer incidence, and also to facilitate accurate assessment of gene–environment interactions. In contrast, GCS places more focus on identification of uncommon or rare genetic variants that may have a larger effect than common single-nucleotide polymorphisms but that are not sufficiently frequent to be captured by current GWAS genotyping arrays. The GCS approach has been to use genomic and bioinformatic techniques to complement more traditional approaches for the study of rare genetic variants. GCS also uses genomics to explore how the variants may be conferring genetic susceptibility to cancer. Thus, the research programme of GCS complements that of GEP, and also provides a facility for high-throughput genomic techniques and the related bioinformatics to support GEN's large-scale molecular epidemiology projects and other IARC genomics projects. BST interacts at all stages to provide overall statistical support.

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The role of the Biostatistics Group (BST) is multifaceted. It collaborates on projects with the other groups within GEN, exploring new methodologies and ensuring optimal use of existing techniques. BST also works closely with other Sections at IARC with specific methodological needs, as well as with external organizations. In addition, BST is involved in statistical education and facilitation across the Agency in cooperation with statisticians in other Sections.

## Increased cancer risk due to paediatric exposure to CT scans

BST played a major role in the analysis of the data from approximately 11 million children and young adults in Australia from a study on cancer risk due to paediatric exposure to computed tomography (CT) scans. The study was led by Professor John Mathews at the University of Melbourne, with Sarah Darby at the University of Oxford. The study demonstrated a 24% increased risk of any cancer after a CT scan before the age of 19 years (Mathews *et al.*, 2013). This risk was evaluated after excluding diagnoses in the year immediately after the scan, but was also seen after excluding the following 5 or 10 years. Moreover, the strength of the effect increased with a larger number of scans. There was also a significantly increased risk for many specific cancers, most strikingly brain cancers, but also for solid cancers of the digestive organs, melanoma, soft tissue, female genital, urinary tract, and thyroid, and for leukaemia, myelodysplasia, and other lymphoid and haematopoietic cancers. The effects were also significantly stronger for younger ages at exposure.

Other radiation-related research occurred in collaboration with the Section of Environment and Radiation and with GCS. These projects focused on the risk of thyroid cancers in Chernobyl clean-up workers (Kesminiene *et al.*, 2012) and the joint effect of radiation and genetic susceptibility, again on thyroid cancer (Damiola *et al.*, 2013)

## BST collaborations within GEN

BST has contributed to a variety of studies within GEN, notably combining RNA expression and genomic data to examine risk factors for kidney cancer (Wozniak *et al.*, 2013), and using prior information from the literature to prioritize genetic variants potentially associated with lung cancer (Johansson *et al.*, 2012a). Analysis of data from the Golestan Cohort indicated a strong increased risk of death from all causes associated with opium use (Khademi *et al.*, 2012a).

## Other BST research

BST provided important methodological input to other projects. Of note was an effort to quantify the burden of lung cancer attributable to asbestos use, making use of mesothelioma as a calibration factor (McCormack *et al.*, 2012, 2013b), and theoretical work on the development of breast cancer (Dowty *et al.*, 2013).

**BST is grateful to the following for their collaboration:**

John Mathews, James Dowty, John Burgess, Melbourne, Australia; Francesca Damiola, Pierre Hainaut, Lyon, France; Elisabeth Cardis, Barcelona, Spain; Sarah Darby, Oxford, United Kingdom.

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The Genetic Cancer Susceptibility Group (GCS) investigates genetic susceptibility to cancer through the application of high-throughput genomic techniques (including the related bioinformatics) to the biological samples stored within the extensive GEN biorepositories. In addition to implementing and maintaining genomic techniques to achieve our research goals, we also facilitate access to these techniques by IARC's other research groups through the Genetics Services Platform.

During the 2012–2013 biennium, GCS has studied the contribution of both common and rare variants to cancer susceptibility. We have also focused on the installation and optimization of massively parallel sequencing (MPS) and the development and implementation of bioinformatics tools to complement IARC's scientific activities; for example, IARC's Electronic Notebook programme.

## Genome-wide association studies (GWAS)

The genome-wide association studies (GWAS) approach has been very successful in the identification of genetic loci involved with complex genetic traits. GCS, in close collaboration with GEP and BST, is continuing to work within GWAS of lymphomas and kidney, cervical, lung, and nasopharyngeal cancers.

The size of the study appears to be a key factor to the success of a GWAS, with the application of increasingly larger sample sizes identifying progressively more susceptibility loci (Michailidou *et al.*, 2013). In the context of rare cancers, prioritized by IARC, assembling sufficiently large sample sizes for an appropriate GWAS presents a practical challenge. The GCS approach has been to explore the possibility of incorporating additional information to augment the potential of GWAS of relatively modest sample sizes. For example, we have undertaken an oral cancer GWAS consisting of 791 cases and 7012 controls (Johansson *et al.*, 2012a). We developed a Bayesian method (AdAPT) that allows prior probabilities for genetic variants to be considered in the ranking of GWAS results. Automated text screening of the medical literature was used to identify genes that might be more relevant to oral cancers. We placed higher prior probabilities on genetic variants near those genes and used them in the ranking of GWAS results. We then selected the top five genetic variants using the AdAPT ranking approach for validation. Only rs991316, located within the ADH gene cluster, displayed statistically significant association ($P_{replication}$ = 0.003), within a validation series of an additional 1046 oral cancer cases and 2131 controls. As we selected only five variants for validation, and rs991316 was ranked 77th using P-value ranking, we would not have selected this variant using that approach. Furthermore, if sufficient variants were selected for validation to allow the inclusion of rs991316 (more than 77), the statistical evidence in the validation stage would not be considered significant after correction for multiple testing, i.e. Bonferroni correction, $P$ = 0.23 (0.003 x 77).

GCS is now exploring the possibility of incorporating our laboratories' genomics techniques, through gene expression (eQTL) or somatic mutation profiles, as additional information sources for prior probabilities within our genetic studies.

## Nasopharyngeal cancer (NPC)

GCS, and the wider GEN Section, has committed to researching genetic susceptibility to nasopharyngeal cancer (NPC). Through studies in Malaysia, Thailand, and Singapore, GEN has assembled almost 2000 NPC cases and 2000 matched controls from South-East Asia. We have completed our first study within these biorepositories; the Thai arm highlighted the importance of tobacco smoking as a risk factor for NPC and the overlap of genetic NPC susceptibility alleles between the Chinese and Thai populations, and suggested the 5p15.33 locus containing the *TERT* gene as a novel NPC susceptibility locus (Fachiroh *et al.*, 2012).

In addition to the case–control studies, we have identified several pedigrees with an unusual reoccurrence of NPC. During the 2012–2013 biennium, we obtained extra-budgetary funds from the United States National Cancer Institute to enable the exploration of the genetic susceptibility to NPC within these pedigrees.

## Rare variants and breast cancer susceptibility

An exome sequencing study of families with multiple individuals affected by breast cancer identified two families with mutations in the homologous recombination-related DNA repair gene *XRCC2*, one protein-truncating mutation and one probably deleterious missense substitution (as predicted by in silico tools). To further investigate this gene, 689 families with multiple breast cancer cases were screened for mutations at the University of Melbourne, and 1308 breast cancer patients with an early age of cancer onset and 1120 controls were screened at IARC. The replication phase identified more deleterious variants in high-genetic-risk breast cancers than expected by chance, implicating *XRCC2* in breast cancer susceptibility and demonstrating the potential that MPS, in combination with appropriate study designs, has to discover new cancer susceptibility genes (Park *et al.*, 2012b). We have also investigated other genes in the homologous recombination repair pathway, although we found no evidence for association of rare variants in *RAD51* (Le Calvez-Kelm *et al.*, 2012).

## Genetics Services Platform (GSP)

By maintaining and further developing the Genetic Services Platform (GSP) and the related Laboratory Information Management System (LIMS), the GSP, nested within GCS, provides a suite of laboratory services to support multiple IARC genomics projects. The platform integrates several multipurpose liquid handling robots in combination with the use of a LIMS to track the progress of samples as they move through the laboratory workflows. Recent developments of GSP include the installation of two MPS (a Life Technologies SOLiD 5500XLW and an Ion Torrent PGM), and collaborative links have been established with local service providers for IARC researchers to access additional genomic techniques, such as Illumina (HiSeq/HiScan technology).

The main GSP capabilities are:

• Exome and targeted sequencing using massively parallel sequencing;

• SNP genotyping using TaqMan, High-Resolution Melting Curve Analysis, or Illumina microarrays;

• Gene expression, copy number variation, and whole-genome methylation profiling using Illumina microarrays.

GSP coordinates collaborative efforts with IARC Groups (GCS, GEP, Epigenetics [EGE], Infections and Cancer Biology [ICB], Molecular Mechanisms and Biomarkers [MMB]), the Section of Molecular Pathology (MPA), and external partners. Some examples of recent relevant projects are described below:

• Exome sequencing of NPC patients from an extended Malaysian pedigree (GCS);

• Exome sequencing of tumours from lung cancer patients and corresponding germline DNAs (collaboration with GEP);

• Whole-genome expression profiling of tumour/non-tumour renal tissue pairs (collaboration with GEP);

• Exome sequencing within families with a reoccurrence of multiple myeloma (in collaboration with Rockefeller University);

• Whole-genome expression profiling by RNA-Seq of total cellular RNA from Epstein–Barr virus-infected cells with pLXSN, anti-Np73 antisense oligonucleotide, and the sense oligonucleotide (collaboration with ICB);

• Exome sequencing of Schwannoma patients (collaboration with MPA);

• Exome sequencing of formalin-fixed, paraffin-embedded triple-negative breast cancers and corresponding germline DNAs (collaboration with MMB);

• Targeted deep sequencing of circulating free DNA in non-small cell lung cancer (collaboration with MMB);

• Whole-genome methylation profiling using Illumina 450K microarrays on blood samples from hepatocellular carcinoma patients exposed to aflatoxin (collaboration with EGE).

## Bioinformatics

During the 2012–2013 biennium, GCS has used a Linux-based, high-performance computing cluster to analyse MPS data produced in our laboratory and elsewhere. Bioinformatics pipelines, composed of pre-existing software packages and in-house custom tools, have been established for genetic variant detection (for Illumina HiSeq/MySeq and Life Technologies SOLiD5500/Ion Torrent) and RNA-Seq (Life Technologies SOLiD5500), allowing the raw sequencing data to be analysed to yield biologically exploitable results.

A total of 102 exomes and 15 RNA-Seq data sets have been generated by our SOLiD 5500XL sequencer and analysed in GCS; 18 of these exome analyses are GCS-related projects, and 84 exome analyses and RNA-Seq experiments are collaborative projects (GEP, MMB, MPA, ICB, EGE, and Centre Léon Bérard).

To complement our in-house data, GCS has also become an avid user of in silico data. Throughout the 2012–2013 biennium, we have accessed and analysed almost 1400 exome pairs from The Cancer Genome Atlas consortium (TCGA) for three cancer types (lung, head and neck, and kidney), which we now use to enhance our genetic analysis.

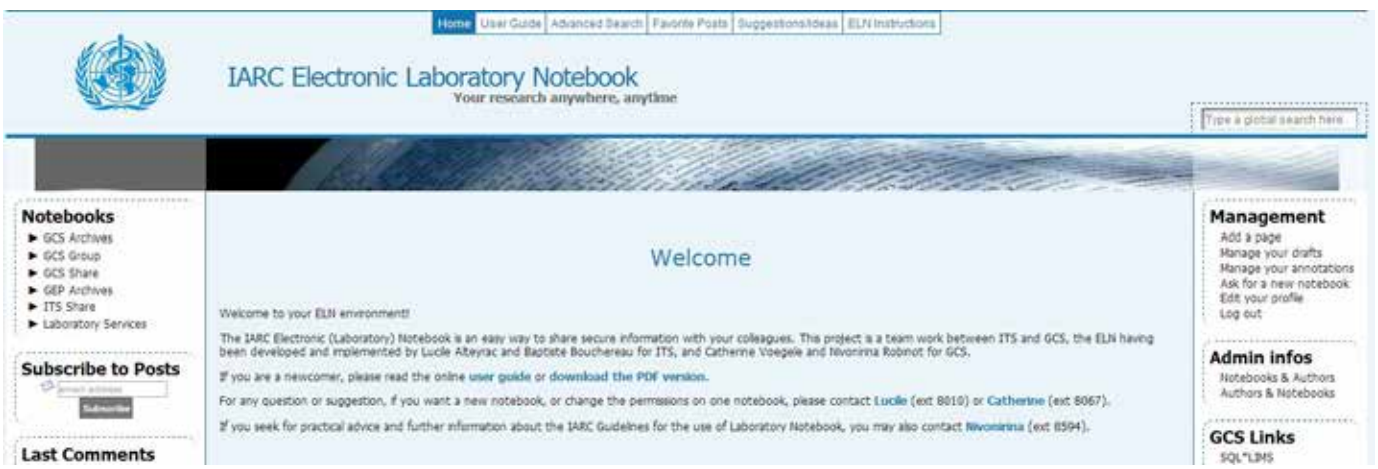
As bioinformatics becomes more important to IARC activities, GCS and ITS have led the formation of the Bioinformatics Steering Committee to monitor and facilitate cooperation among the Agency's bioinformatics and the related IT requirements.

## IARC's Electronic Laboratory Notebook (ELN)

Laboratory notebooks remain crucial to the scientific activities of research communities. With the increase in generation of electronic data within both wet and dry analytical laboratories, Electronic Laboratory Notebooks (ELN) are a practical tool to record experimental data while maintaining the legal recording functions of a paper laboratory notebook. Coupled with newer technologies, an ELN has the additional potential to provide more efficient means of communication and higher flexibility for data entry, record linkage, storage, and retrieval.

In recognition of this potential, GCS has worked with ITS on the implementation of an ELN tool adapted to the Agency's multidisciplinary research and adequate for data recording (as advised by IARC's

**Figure 1. Interface of IARC Electronic Laboratory Notebook.**



Laboratory Steering Committee and according to international standards). A prototype was developed by ITS and, after extensive piloting and refinement, was adopted Agency-wide in January 2013. IARC now has more than 100 users keeping track of their work using the ELN. In addition to laboratory staff, the ELN is also being used by epidemiologists, statisticians, and bioinformaticians (Voegele *et al.*, 2013).

**GCS is grateful to the following for their collaboration:**

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The overall goal for the Genetic Epidemiology Group (GEP) is to identify genetic susceptibility variants of various cancer sites and study their interaction with environmental and lifestyle factors. An additional objective 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 use and alcohol consumption, as well as rare cancers (e.g. nasopharyngeal cancer). Our main activities involve fieldwork with the goal of recruiting large numbers of cases and controls, comprising extensive questionnaire information and biological samples. Genetic analyses usually include a genome-wide approach initially, with subsequent large-scale coordinated replication studies in diverse populations. This latter aspect is aided 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, which are often conducted in collaboration with other IARC Groups. In addition to studies of genetic factors, GEP is conducting a wide range of studies 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 for data that have been collected during fieldwork.

## Lung cancer genetics

Genome-wide data are available on more than 15 000 lung cancer cases and 25 000 controls from eight different study groups (with IARC studies contributing about 25% of the data). A meta-analysis has provided increased support for previously identified risk loci at 5p15 ($P = 7.2 \times 10^{-16}$), 6p21 ($P = 2.3 \times 10^{-14}$), and 15q25 ($P = 2.2 \times 10^{-63}$) (Figure 2). Furthermore, we demonstrated histology-specific effects for 5p15, 6p21, and 12p13 loci. Subgroup analysis also identified a novel disease locus for squamous cell carcinoma at 9p21 (CDKN2A/p16INK4A) (Timofeeva *et al.*, 2012).

**Figure 1. Manhattan and quantile–quantile (Q–Q) plots for the meta-analysis of lung cancer genome-wide association studies (GWAS). (A,B) Manhattan plot and Q–Q plot for lung cancer overall. (C,D) Manhattan plots restricting to lung adenocarcinomas and squamous cell carcinomas, respectively. Source: Timofeeva *et al.* (2012), by permission of Oxford University Press.**

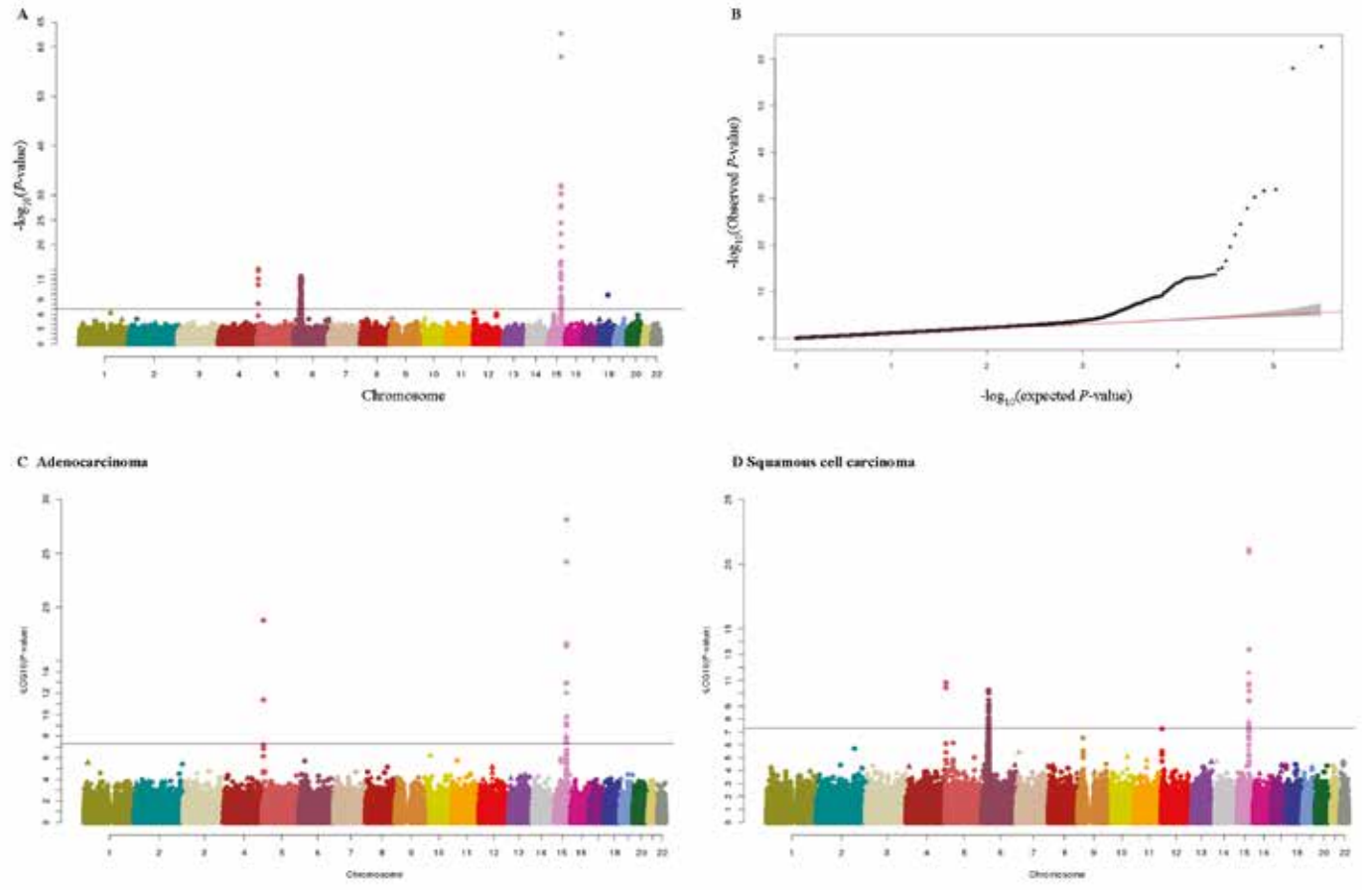
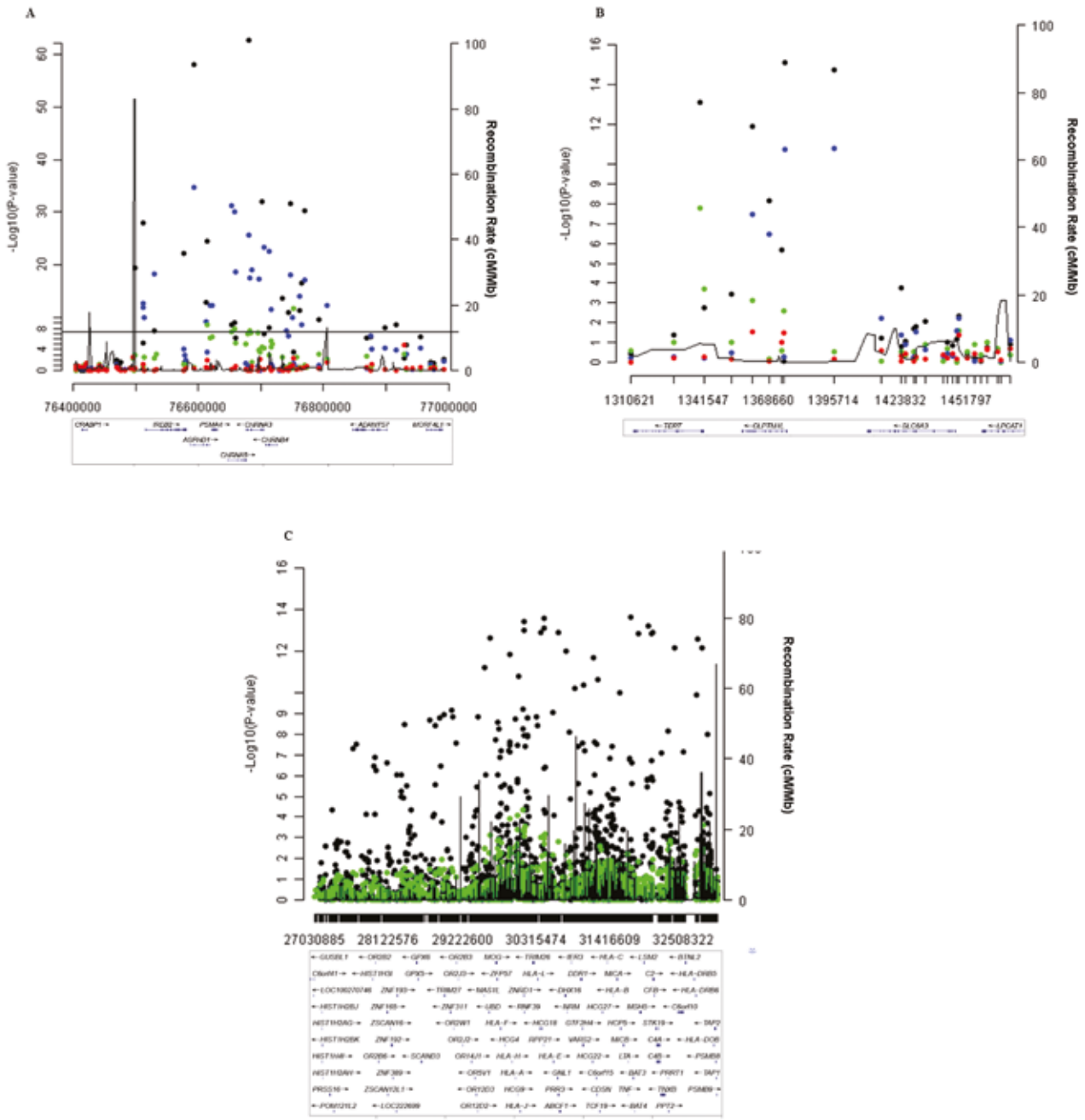


**Figure 2. Associations between lung cancer and genetic variants within the (A) 15q25, (B) 5p15, and (C) 6p21 susceptibility loci. Source: Timofeeva *et al.* (2012), by permission of Oxford University Press.**




## Genetics and genomics of renal cell carcinoma

The continuing recruitment of renal cell carcinoma cases and healthy controls in central and eastern Europe has been very successful. With the collaboration of seven centres in four countries (the Czech Republic, the Russian Federation, Romania, and Serbia), we have enrolled 2500 cases and twice as many controls who donated blood samples for genetic research. Tumour tissue samples were collected for the majority of cases and non-tumour renal tissue for approximately half of the cases. This represents a very large and comprehensive RCC biorepository with detailed questionnaire and clinical data. Follow-up of cases for disease outcome is performed biannually, and pathological characterization of the renal samples is under way.

This biorepository participates in a large genome-wide scanning effort co-led by GEP scientists and the United States National Cancer Institute (US NCI). GEP scientists have coordinated the genotyping of the IARC biorepository together with other study collections (the French CeRePP study; the European EPIC study; the Swedish COSM, SMC, and Umea studies; and the Australian MCCS study), and the US NCI has led the United States component. Genotyping using very dense marker chips is under way, with a goal of reaching 10 000 cases and 16 000 controls in early 2014.

In parallel, we have performed whole-genome expression profiling of tumour/non-tumour renal tissue pairs. Through our initial analysis based on 100 sample pairs collected in the Czech Republic, we identified 630 upregulated and 720 downregulated genes, showing a large overlap with our analysis of the United States public data available for 65 cases (Wozniak *et al.*, 2013). This work is continuing with a plan to correlate expression profiles of 800 cases with germline polymorphisms.

GEP also has a central role in the CAGEKID study (part of the International Cancer Genome Consortium), which has whole-genome sequenced 100 tumour/germline DNA pairs collected through the IARC study and in the United Kingdom. The interpretation of whole-genome data is being finalized, and the replication in 400 cases from the same centres has started. Whole-genome sequencing data are complemented by an examination of gene expression through RNA sequencing and epigenetic changes. CAGEKID represents the renal component of the International Cancer Genome Consortium and, as such, data will soon be available to the scientific community.

### Head and neck cancers and human papillomavirus infection

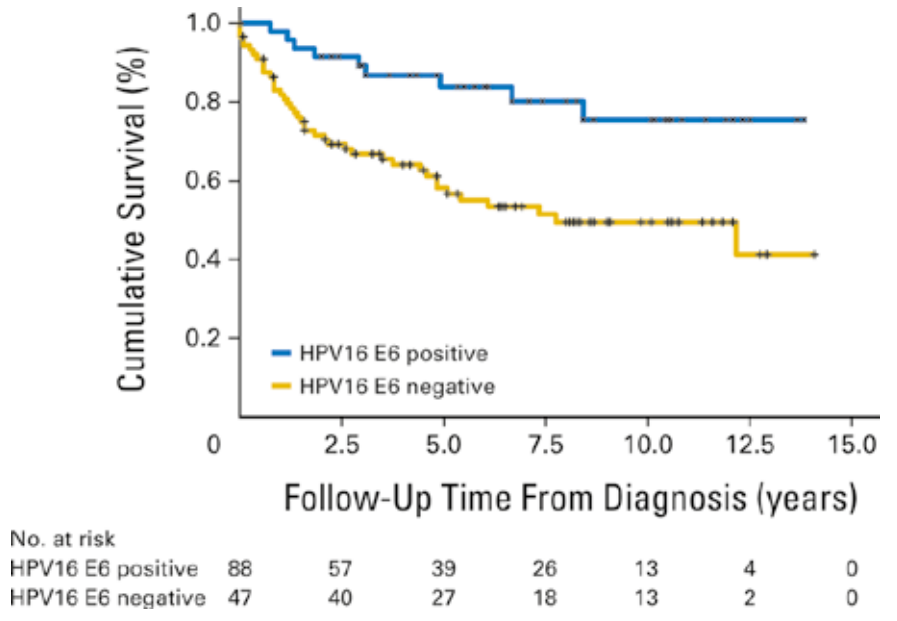
GEP will continue to investigate the role of human papillomavirus (HPV) in head and neck cancers, and potential genetic modifiers. Recently, in a large western European study, we found that HPV16 E6 antibodies were specific to HPV16-related cancer (present in 30% of oropharyngeal cancers, compared with < 1% of 1400 controls) (Anantharaman *et al.*, 2013). Subsequent analysis in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort demonstrated that HPV16 E6 antibodies were detectable 10 years before diagnosis in 35% of cases, again with very few false-positives (< 1% of controls were positive) (Kreimer *et al.*, 2013). Subsequent survival analysis also showed that HPV16 E6 seropositive oropharyngeal cancers had approximately 3 times better survival rates than those that were negative (hazard ratio, 0.3; 95% confidence interval, 0.13–0.67). In particular, 5-year survival rates were 58% among HPV16 E6 seronegative cases and 84% among seropositive cases (Figure 3). We plan to extend our findings within the large cohort consortium, currently being set up, to examine the utility of circulating antibodies to HPV16 as a predictive biomarker for head and neck cancer. GEP is also leading Work Package (WP) 4 of the HPV-AHEAD consortium, which is supported by a major grant from the European Commission (FP7; coordinator, Massimo Tommasino, IARC). The aim of this WP is to investigate the epidemiology of HPV-positive and -negative head and neck cancer, and, as part of this initiative, tumour samples are being retrieved from the previously completed western Europe study. In addition, GEP is also coordinating a multicentre cancer case–control study in South America (InterCHANGE). These new initiatives will help clarify the sensitivity and specificity of HPV16 E6 antibodies, as well as the association of viral infection with cancer response and relapse. Centralized assessment of a large series of samples from Brazil, the USA, and Europe is under way to further evaluate the geographical differences in HPV prevalence.

### Large population cohorts

Research conducted within prospective cohorts constitutes an important part of the scientific activities within GEP. These studies focus on risk predictors that require measurement before diagnosis to establish robust associations, with complementary genetic work used primarily to establish causality along the lines of Mendelian randomization, as well as in risk prediction modelling. In the past, these studies were typically conducted within the EPIC cohort, but over the past year we have expanded to also include multiple additional European and non-European cohorts.

We will also continue to assist in the coordination of two large population cohorts that GEP initiated in collaboration with other non-IARC scientists. The first is a prospective cohort of 200 000 adults from three cities in Siberia, Russian Federation, in collaboration with the Cancer Research Centre, Moscow, and the Clinical Trials Services Unit, Oxford, United Kingdom. Analysis has focused on the role of alcohol consumption on all-cause mortality. The second is the Golestan Cohort study of 50 000 individuals from north-eastern Islamic Republic of Iran, being conducted with colleagues from Tehran and the US NCI. Analyses within GEP are focused on the effects of opium, obesity, and hypertension on all-cause and cause-specific mortality.

**Figure 3. Cumulative survival of oropharyngeal cancer cases by prediagnostic HPV16 E6 serostatus. Source: Kreimer *et al.* (2013). Reprinted with permission. © 2013 American Society of Clinical Oncology. All rights reserved.**



### The European Prospective Investigation into Cancer and Nutrition (EPIC)

EPIC remains an important focus for GEP, in terms of both governance and research projects. The Group head, Paul Brennan, and a staff scientist, Mattias Johansson, are members of the EPIC steering committee, and Mattias Johansson is also leading the lung cancer working group within EPIC. Notable scientific highlights include the above-mentioned study of HPV serology in head and neck cancer (Kreimer *et al.*, 2013). Other examples include several studies on circulating vitamins in renal cell carcinoma and head and neck cancers. Of note is a study of renal cell carcinoma where subjects with elevated levels of vitamin B6 had a clearly higher incidence, as well as improved survival after diagnosis (see further details below).

### The Lung Cancer Cohort Consortium (LC3)

As a comprehensive follow-up on a previous lung cancer study, we initiated the Lung Cancer Cohort Consortium (LC3) in 2011 and received support from the US NCI. The project aims to conduct biochemical and genetic analyses on more than 5000 case–control pairs from 24 prospective cohorts recruited in Europe, the USA, Asia, and Oceania. The first 2 years of the project have been committed to gathering biosamples, laboratory analysis, and administration. Scientific results are expected in early 2014. Similar projects are planned to follow up the EPIC studies on HPV and head and neck cancer, as well as vitamin B6 and renal cell carcinoma.

### The European Biobanking and Biomolecular Research Infrastructure-Large Prospective Cohorts (BBMRI-LPC)

GEP is a leading partner of the BBMRI-LPC project, which is supported by a major grant from the European Commission (FP7; coordinator, Markus Perola, Finland). The overall aim is to join prospective cohorts across Europe and facilitate collaborative transnational studies. The specific aim of WP 10 is to coordinate calls for scientific proposals and select proposals that will receive financial and administrative support to access biosamples and data from multiple European cohorts.

### Novel analysis on one-carbon metabolism biomarkers

We have recently expanded our work on biomarkers of the one-carbon metabolism, with a particular focus on renal cell carcinoma and head and neck cancers. For example, the renal cell carcinoma analysis conducted within the EPIC study strongly indicated that subjects with higher concentrations of vitamin B6 had substantially lower renal cell carcinoma risk, as well as reduced mortality after diagnosis. Subjects with plasma vitamin B6 in the top quartile had less than half the risk of renal cell carcinoma than those in the bottom quartile. In addition, elevated plasma B6 was also related to reduced all-cause mortality in EPIC. The associations between vitamin B6 and risk of renal cell carcinoma, as well as mortality, were subsequently validated in the independent Melbourne Collaborative Cohort Study (MCCS). A manuscript outlining these preliminary results is currently being reviewed. Plans are under way for additional analysis within the context of a large-scale consortium in collaboration with cohorts participating in the US NCI cohort consortium.

**GEP is grateful to the following for their collaboration:**

Marta Vilensky, Buenos Aires, Argentina; Gianluca Severi, Victoria, Australia; Gyl Ramos, Curitiba, José Carlos de Oliveira, Goiania, Sergio Koifman, Rio de Janeiro, Marcelo Benedito Menezes, Luis Paulo Kowalski, José Eduardo Levi, Victor Wünsch-Filho, São Paulo, José Roberto Vasconcelos de Podestà, Vitoria, Brazil; Mark Lathrop, Montreal, Rayjean Hung, Toronto, Canada; Ariana Znaor, Zagreb, Croatia; Lenka Foretova, Brno, Vladimir Janout, Olomouc, Vladimir Bencko, Ivana Holcatova, Prague, Czech Republic; Markus Perola, Helsinki, Finland; Olivier Cussenot, Jean-François Deleuze, Paris, France; Wolfgang Ahrens, Bremen, Michael Pawlita, Heidelberg, Erich Wichmann, Munich, Germany; Pagona Lagiou, Athens, Greece; Rajesh Dikshit, Mumbai, India; Reza Malekzadeh, Tehran, Islamic Republic of Iran; Claire Healy, Dublin, Ireland; Renato Talamini, Aviano, Lorenzo Simonato, Padova, Stefania Boccia, Roma, Franco Merletti, Turino, Italy; Beena Devi, Kuching, Malaysia; Per Magne Ueland, Bergen, Arnulf Langhammer, Levanger, Kristina Kjaerheim, Oslo, Norway; Beata Swiatkowska, Lodz, Jolanta Lissowska, Warsaw, Poland; Dana Mates, Jinga Viorel, Bucharest, Romania; Alexander Boroda, Anush Mukeriya, Egor Prokhortchouk, David Zaridze, Moscow, Russian Federation; Miodrag Ognjanovic, Simona Ognjanovic, Belgrade, Serbia; Tam Ha, Singapore; Eleonora Fabianova, Banska Bystrica, Slovakia; Jonas Manjer, Malmö, Lars Egevad, Alicja Wolk, Stockholm, Göran Hallmans, Börje Ljungberg, Umeå, Sweden; Sulee Sangrajrang, Bangkok, Thailand; Tatiana Macfarlane, Aberdeen, Hisham Mehanna, Birmingham, David Conway, Glasgow, Alvis Brazma, Hinxton, Rosamonde Banks, Leeds, Elio Riboli, Paolo Vineis, London, Caroline Relton, Max Robinson, Newcastle, Angus Roberts, Sheffield, United Kingdom; Mauricio Cuello, Montevideo, Uruguay; Victoria Stevens, Atlanta, Kala Visvanathan, Baltimore, Stephen Chanock, Aimee Kreimer, Lee Moore, Mark Purdue, Nathaniel Rothman, Bethesda, Jiali Han, Boston, Chris Amos, Dartmouth, Loic Le Marchand, Honolulu, Qiuyin Cai, Xiao-Ou Shu, Wei Zheng, Nashville, Alan Arslan, New York, Jian Min Yuan, Pittsburgh, Ross Prentice, Seattle, Jon Wakefield, Washington, USA.

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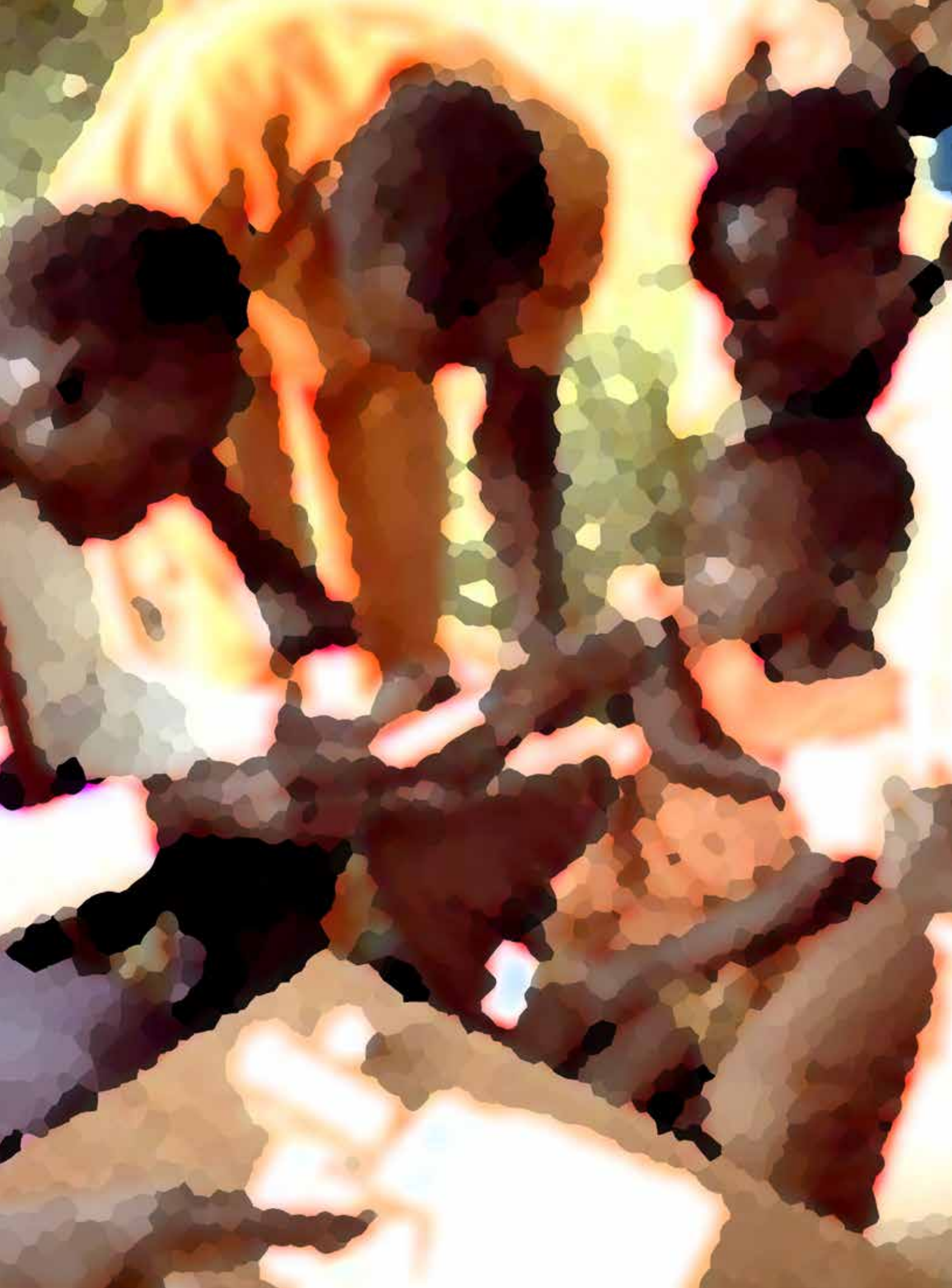
World Cancer Research Fund, London, United Kingdom



# Section of Early Detection and Prevention (EDP)

**Section head**
Dr Rengaswamy Sankaranarayanan

Prevention and early detection, including screening and early clinical diagnosis, are major interventions in cancer control that decrease the burden of cancer and improve quality of life. The Early Detection and Prevention Section (EDP), composed of the Prevention and Implementation Group (PRI), the Quality Assurance Group (QAS), and the Screening Group (SCR), focuses on research activities that contribute to the development of resource-appropriate public health policies, approaches to quality assured cost-effective prevention programmes, and early detection strategies for the control of common cancers such as breast, cervical, colorectal, oral, oesophageal, and stomach cancers globally, with particular emphasis on low- and middle-income countries (LMICs). It is evident that prevention offers the most cost-effective long-term strategy for the control of cancer. As such, prevention initiatives within EDP include the development and implementation of safe, affordable, and effective vaccination schemes for human papillomavirus-related cancers, and the evaluation of the impact of *Helicobacter pylori* eradication on stomach cancer incidence and mortality. The focus of early detection research within the Section includes assessing new technologies and alternative screening approaches, as well as evaluating the impact of improved awareness and access to health care services for the early detection of major cancers such as breast, cervix, oral, and colorectal.

To achieve the above-mentioned objectives, the Section initiates and implements studies in collaboration with investigators in national cancer organizations, national health services, state health agencies, and other key groups within and outside the Agency. EDP works closely with international organizations such as the International Atomic Energy Agency and the Union for International Cancer Control to develop, implement, and promote effective strategies for preventing and controlling cancer in the context of national cancer control programmes. There is continued emphasis on developing, updating, and expanding training resources for cancer prevention and early detection initiatives in LMICs, and enhancing prevention and early detection services by contributing to the development of local health care systems within the context of our research studies. Our motto is not research unto research, but research to improve cancer prevention and early detection services in limited-resource settings.

# Prevention and Implementation Group (PRI)

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**Postdoctoral fellow**
Dr Jin Young Park

The Prevention and Implementation Group (PRI) conducts studies to evaluate the efficacy, population impact, and feasibility of interventions aimed at the primary and secondary prevention of cervical, anal, oral, and gastric cancers, particularly in low- and middle-income countries where these cancers are common. In addition, we collaborate with public health institutions and governments to implement and evaluate effective interventions for cancer prevention. The main focus of PRI has been the development and implementation of safe and effective vaccines against human papillomavirus (HPV)-related cancers and the evaluation of the potential impact of *Helicobacter pylori* eradication on gastric cancer incidence and mortality. In addition, we are conducting a large-scale multicentre evaluation of methods to triage HPV-positive women in the context of cervical cancer screening and promoting the implementation of organized cervical cancer prevention and control programmes in Latin America and other areas of the world.

## Cervical cancer studies in Guanacaste, Costa Rica

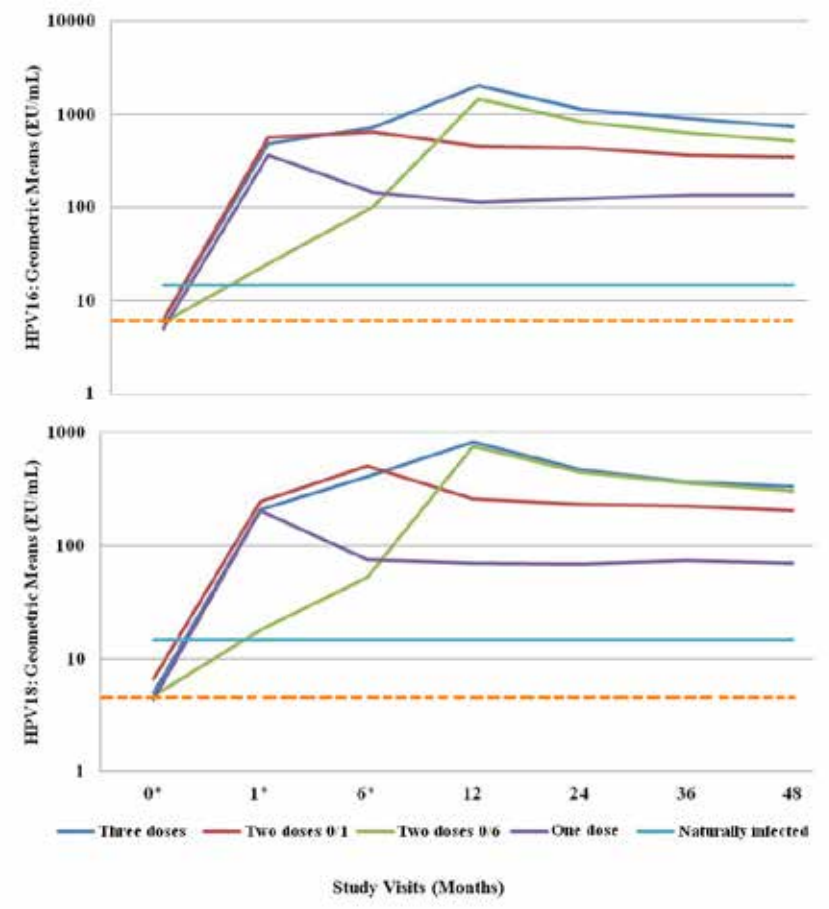
The Guanacaste Project (PEG) is a long-term collaboration with the United States National Cancer Institute (NCI) and Costa Rican researchers to investigate the natural history of HPV infections and associated neoplasia, in addition to new preventive strategies. The Costa Rica Vaccine Trial (CVT) is part of this effort. In 2004 and 2005, CVT recruited approximately 7500 women aged 18–25 to participate in a randomized controlled trial of the bivalent HPV vaccine (HPV 16/18) to evaluate its efficacy against cervical infections and cervical intraepithelial neoplasia (CIN2+). PRI previously published on the efficacy of the vaccine to prevent persistent cervical HPV infections with HPV 16/18 and phylogenetically related HPV types. We also reported on the impact of vaccination on cervical cytology screening, colposcopy, and treatment in the first 4 years after vaccination. Colposcopy referral and treatment were reduced by 21% ($P$ = 0.01) and 45.6% ($P$ = 0.08), respectively, among women with no evidence of previous exposure to HPV 16/18 at the time of vaccination (Rodríguez *et al.*, 2013). Furthermore, 4-year vaccine efficacy against 12-month HPV 16/18 persistent infection was similarly high among young women who received one dose, two doses, or the recommended three doses of the vaccine. We have now evaluated the magnitude and 4-year durability of immune responses to the vaccine after administration of one, two, or three doses. HPV 16/18 geometric mean titers (GMTs) were, respectively, at least 24 and 14 times higher among women receiving two doses of the vaccine and 9 and 5 times higher among those receiving one dose, compared with the GMTs among naturally infected women. The one-dose GMTs remained stable from month 6 through month 48 (Figure 1), raising the possibility that even a single dose of HPV virus-like particles will induce long-term protection (Safaeian *et al.*, 2013a).

Follow-up of the vaccinated cohort continues mainly to evaluate long-term protection (10 years), safety, immunogenicity, and HPV type-replacement.

## Epidemiology and prevention of anal and oral HPV infection

At the 4-year visit in the CVT, we obtained anal specimens for HPV testing from sexually active women. We detected 22% of anal oncogenic HPV infection in this group of relatively young women with clear indication of an association with sexual activity, including anal sex (Castro *et al.*, 2012). Previously we reported on the efficacy of the vaccine to prevent anal HPV infection 4 years after recruitment. Current plans include long-term follow-up of anal HPV-positive

**Figure 1. HPV 16 (top) and HPV 18 (bottom) specific antibody geometric means, by number of vaccine doses and study visit. *Vaccination period: 0/1/6 months. Solid lines represent HPV 16/18 specific geometric means. The line for the natural infection is from enrolment only and does not represent longitudinal samples. Dashed orange line is the laboratory-determined seropositivity cut-off (HPV 16 = 8 EU/mL; HPV 18 = 7 EU/mL). Source: Safaeian M *et al.* (2013a); reprinted by permission from the American Association for Cancer Research.**



women with HPV testing, anal cytology, and anoscopy, to define the natural history of these infections and assess long-term efficacy.

In addition, PRI is investigating oral HPV infections and the efficacy of the bivalent vaccine to prevent them. We tested oral specimens from 5838 participants in the trial for α mucosal HPV types (SPF10/LiPA25 version 1). HPV infection was rare, and in the control arm (*n* = 2926) 1.9% of women had an oral α mucosal HPV detected, 1.3% had carcinogenic HPV, and 0.4% had HPV 16. HPV infection was predominately associated with sexual behaviour (Lang Kuhs *et al.*, 2013). Recently, we demonstrated for the first time a 93% efficacy of the bivalent vaccine to prevent oral HPV 16/18 infections 4 years after vaccination in the CVT (Herrero *et al.*, 2013). Follow-up is under way to investigate the natural history of these infections (Table 1).

**Table 1. Protection against human papillomavirus (HPV) 16/18 infection by anatomical site in different cohorts[a] within the Costa Rica vaccine trial**

| Site | Arm | Number of women | Number of events | Rate per 100 | Efficacy (95% confidence interval) |
|---|---|---|---|---|---|
| Cervix (incident 12-months persistent infection) | HPV | 2635 | 8 | 0.3 | 91% (82–96) |
| | Control | 2677 | 89 | 3.3 | |
| Anus (prevalent infection ~48 months after vaccination) | HPV | 1003 | 8 | 0.8 | 84% (67–93) |
| | Control | 986 | 48 | 4.9 | |
| Oral cavity (prevalent infection ~48 months after vaccination) | HPV | 2910 | 1 | 0.0 | 93% (63–100) |
| | Control | 2924 | 15 | 0.5 | |

[a] For the cervix, data are from the according-to-protocol cohort (protocol-compliant women negative for HPV at enrolment); for the anus, data are from the restricted cohort of cervical HPV negative and HPV 16/18 serology negative; and for the oral cavity, data are from the intention-to-treat cohort (all women vaccinated with HPV results). Table compiled from Herrero *et al.* (2013); Herrero *et al.* (2011). *Cancer Discov,* 1:408–419. http://dx.doi.org/10.1158/2159-8290.CD-11-0131 PMID:22586631; Kreimer *et al.* (2011). *Lancet Oncol,* 12:862–870. http://dx.doi.org/10.1016/S1470-2045(11)70213-3 PMID:21865087

## Multicentre study of HPV screening and triage (ESTAMPA)

We have organized a group of Latin American investigators to conduct a large multicentre study including more than 50 000 women to evaluate multiple triage techniques among HPV-positive women. Women aged 30–64 years will be recruited at centres in at least seven Latin American countries and screened with an HPV test. All HPV-positive women and a sample of HPV-negative women will be referred for colposcopy, biopsy, and final diagnosis, with follow-up at 18 months. Visual, cytological, and molecular triage methods will guide the formation of specific strategies to select women requiring more intensive follow-up and treatment. Recruitment has begun in two sites in Colombia and is expected to expand shortly to Honduras, Paraguay, and Mexico and later to other countries in the region. An important objective of the study is to evaluate different strategies for implementation of organized cervical cancer screening in Latin America, as well as to provide extensive training (Figure 2) on the different aspects of the programme and transfer new technologies, including the use of molecular risk markers.

**Figure 2. ESTAMPA study: cervical pathology training course participants, Instituto Nacional de Cancerología, Bogotá, Colombia, 5–7 September 2013. Photograph courtesy of Adrián Moreno.**

### Clinical trial of *Helicobacter pylori* infection in Latin America

We have completed the initial follow-up phase of our Latin American randomized clinical trial to evaluate efficacy of three different treatment regimens against *H. pylori* in seven centres in Latin America, conducted in collaboration with the South West Oncology Group of the USA. A total of 1463 *H. pylori*-positive participants aged 21–65 years were treated with different antibiotic regimes and observed between September 2009 and July 2011. The results of eradication at 6 weeks after treatment have been published, and we have now completed analysis of the 1-year follow-up data.

Recurrence risk was 11.5% (95% CI, 9.6–13.5%) at 1 year, and it was significantly associated with study site, non-adherence to initial therapy, and number of children in the household. Overall effectiveness at 1 year was 79% (95% CI, 77–82%) with no difference by treatment regime (Morgan *et al.*, 2013). Plans are under way to extend follow-up to investigate long-term *H. pylori* recurrence.

### Medellin, Colombia, ASCUS trial

In collaboration with the University of Antioquia, we are participating in a randomized trial to evaluate different strategies for clinical management of women with atypical squamous cells of unknown significance (ASCUS) cytology. The trial is well under way with 2700 women recruited.

### Support of HPV vaccination and screening programmes in Latin America

The National Screening Program of Argentina has implemented an HPV-based screening programme. In order for the first province to implement the programme (Jujuy), extensive political and educational meetings took place, guidelines and educational materials were developed, and laboratories were set up, among other things. A protocol to evaluate the acceptability and performance of self-collected specimens was recently completed, with excellent results that are now under analysis. Plans to extend the programme to new areas in the country are under way. The materials developed and the experience should be useful for other programmes in the region.

We have also participated in meetings with local authorities from Mexico, Costa Rica, Guatemala, Nicaragua, Chile, Colombia, Peru, and Paraguay and with the Network of Latin American Cancer Institutes, to promote implementation of new cervical cancer screening approaches and HPV vaccination programmes.

**PRI is grateful to the following for their collaboration:**

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National Cancer Institute, National Institutes of Health, USA
Reproductive Health and Research Department, World Health Organization, Geneva, Switzerland

# Quality Assurance Group (QAS)

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Dr René Lambert
Dr Nereo Segnan
Dr Eero Suonio
Dr Martin Wiseman
(until September 2013)

**Students**
Mr Simon Ducarroz
Mr Douglas Puricelli Perin
(until September 2013)

Several years are required to establish effective and affordable cancer prevention programmes across a country. Knowledge of how to assure the quality of such long-term efforts is essential if they are to achieve their potential impact in cancer control. The main goal of the Quality Assurance Group (QAS) is to expand and effectively disseminate such knowledge. This is achieved primarily through international collaborative projects that develop, update, and implement multidisciplinary quality-assurance guidelines for cancer screening, and through application of the lessons learned to other approaches in cancer control, such as primary prevention. Distribution of the guidelines is achieved through publications and training and through the exchange of experience and collaboration between programmes and countries. Our collaboration with WHO, the European Union (EU), and Participating States of the Agency plays a key role in these efforts.

The principal activities of QAS are conducted in the framework of international collaborative projects with large numbers of experts in a wide range of health care settings, primarily in high-income countries but increasingly also in low- and middle-income countries. Key projects during the biennium included the development and piloting of the first comprehensive training course of the European Schools of Screening Management; development and updating of the European guidelines for quality assurance in breast, cervical, and colorectal cancer screening; evidence-based updating of the European Code Against Cancer; and collaboration with the WHO, the International Atomic Energy Agency, the EU, and national health authorities in guideline development, implementation, and dissemination.

## Guideline development and dissemination

In a project coordinated by QAS, the individual chapters of the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis (Figure 1) were published as open access articles in a high-profile peer-reviewed journal, Endoscopy, in 2012, and an overview with updates of key evidence was published in 2013 (von Karsa *et al.*, 2013a). More than 100 experts from 49 countries in four continents participated, primarily in Europe, but also in North and South America, Asia, and Australia.

Supplements to the fourth edition of the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis have been produced in 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). The supplements deal with histopathology, physico-technical quality control, and digital mammography and were recently published by the European Commission (Figure 2). Supplements on HPV testing and vaccination have also been prepared for the second edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening, with publication expected in the near future. This project was coordinated by QAS and co-financed by the EU Health Programme (European Cooperation for Development and Implementation of Cancer Screening and Prevention Guidelines). QAS has also participated in projects to update the WHO guidelines on cervical cancer prevention and to develop recommendations on breast cancer screening. Publication of the updated cervical cancer prevention guidelines is expected in 2014.

**Figure 1. Cover of the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis. First edition.**

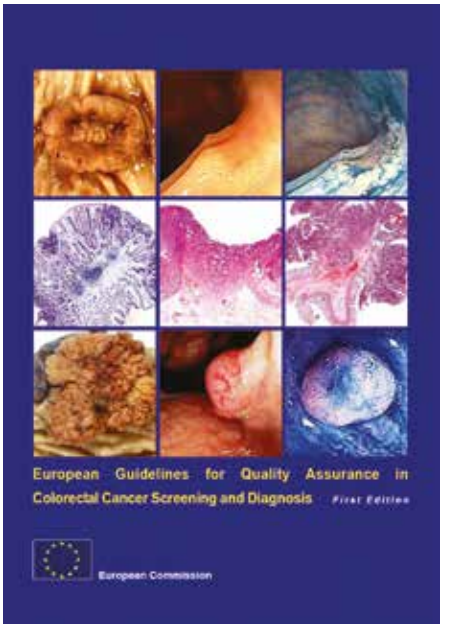
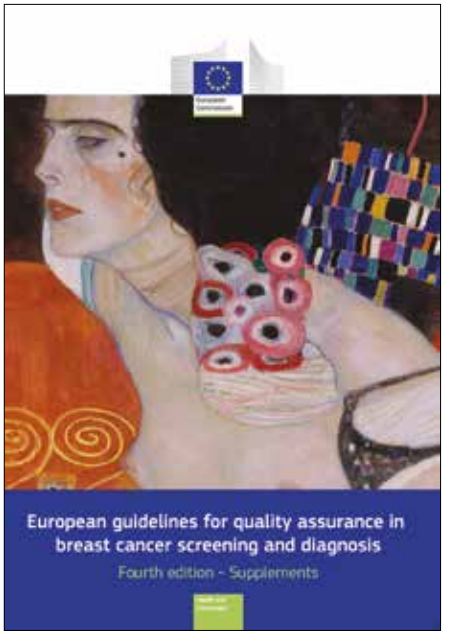



**Figure 2. Cover of the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. Fourth edition - Supplements.**




In another project co-financed by the EU, QAS is updating the report on implementation of cancer screening in the EU, an essential tool for monitoring the progress and evolution of screening programmes. This update will include information on the extent to which key parameters in the European quality assurance guidelines are achieved. This will permit benchmarking and comparison of programme performance between EU Member States and countries in other regions of the world, which is important due to the increasing interest of other countries in establishing cancer screening programmes that fulfil the comprehensive European standards. For the same reason, recent publications of the Group explain the approach to programme implementation that has been most successful in Europe: international collaboration in coordinated planning, followed by feasibility testing, piloting, and phased rollout across the country, enabling the responsible authorities to control the pace of the implementation process and assure the quality of a programme as it unfolds (von Karsa *et al.*, 2012a; Lynge *et al.*, 2012; von Karsa and Arrossi, 2013). QAS has also participated in a comprehensive review of the performance of population-based breast cancer screening programmes in

Europe. The results were published in 2012 in eight articles in a supplement of the *Journal of Medical Screening*. They provide an authoritative appraisal of the balance between benefit and harm that shows that for every case of overdiagnosis, at least one breast cancer death is avoided (Paci, 2012).

### Update of the European Code Against Cancer

Quality assurance of cancer screening programmes requires expertise in areas common to successful implementation of primary prevention programmes, such as the behavioural aspects of motivation, communication, and the reinforcement of activities designed to prevent cancer. Therefore, in collaboration with the IARC Section of Environment and Radiation, QAS is coordinating a project to revise the European Code Against Cancer (ECAC). The code was established as a package of recommendations for the general public that, if followed, should significantly reduce an individual's risk of developing cancer. The principal aim of the ECAC is to encourage lay people to take appropriate action. The fourth edition will therefore be worded in a manner that lay people can easily understand; other aspects of communication for the general public will also be taken into account. This is a collaborative effort involving the IARC Sections of Infections, Cancer Information, Monographs, Nutrition and Metabolism, and the Office of the Director, including the Communications Group, and all of the groups in the Section of Early Detection and Prevention (QAS, PRI, and SCR). Co-financing is provided by the European Partnership for Action Against Cancer, a current initiative of the EU Health Programme.

### European Schools of Screening Management (ESSM)

The European Schools of Screening Management (ESSM), a network of reference and training centres, has been established in Europe. This network is developing and piloting comprehensive training courses for planning, implementation, quality assurance, and evaluation of population-based cancer screening programmes (Anttila *et al.*, 2013). The intent is to expand the ESSM network into a platform for direct collaboration between more and less developed countries as they implement cancer screening programmes, and ESSM is intended to become a model for other regional networks that collaborate with IARC. Decision-makers and professionals involved in the planning, implementation, or evaluation of cancer screening programmes in eight EU countries (Estonia, Latvia, Lithuania, Poland, Romania, Slovenia, Spain, and Sweden) and six non-EU countries (Albania, Croatia, Georgia, Morocco, Serbia, and Turkey) attended both of the 1-week modules of the course that were held at IARC in November 2012 and March 2013 (Figure 3). The training was conducted in close collaboration with a project led

**Figure 3. Participants in Module 1 of the pilot course of the European Schools of Screening Management, 19–23 November 2012: Left to right, front row: Snežana Žujković, Maria Fernan, Loubna Abousselham, Luciana Neamtiu, Paola Armaroli, Ahti Anttila, Lawrence von Karsa, Jozica Maučec Zakotnik, Dunja Skoko-Poljak, Müjdegül Zayıfoğlu Karaca, Miriam Elfström, Daiga Santare, Kozeta Filipi. Second row: Rugile Ivanauskiene, Tracy Lignini, Mejreme Maloku, Isabelle Soerjomataram, Aleksandra Jaric, Yulia Panayotova, Isabel Portillo Villares, Elena Pérez Sanz, Melita Jelavic, Vaida Momkuviene, Kirstin Grosse Frie. Back row: Eero Suonio, Nereo Segnan, Giuseppe Salamina, Elvis Ahmedi, Sven Törnberg, Levan Jugeli, Stephen Halloran, Ondrej Majek, Andrzej Czuba, Arkadiusz Chil, Jolanta Kotowska, Piret Veerus, Stefan Lönnberg, Lennarth Nyström. © Roland Dray/IARC.**

by the Italian Ministry of Health and supported by WHO headquarters and the WHO regional offices in Europe, the Middle East, and Africa, and the governments of France and Spain (Cancer Screening and Early Detection in Mediterranean Countries).

### Collaboration with WHO in developing and implementing the global and European action plans on noncommunicable diseases (NCDs)

The head of QAS also served as rapporteur for the indicator on cervical cancer screening at the Regional Technical Consultation on NCD Surveillance, Monitoring and Evaluation convened by the WHO Regional Office for Europe in Oslo, Norway, in February 2012. The proposals and feedback provided at the meeting were used to shape the European contribution to the WHO Global Monitoring Framework for control of noncommunicable diseases (NCDs) and assisted in monitoring and evaluating the 2012–2016 Action Plan for implementation of the European Strategy for the Prevention and Control of NCDs. The results of the Oslo meeting were also considered in the development of regional targets and indicators under the umbrella of the European Health Policy, Health 2020. QAS collaborated with the WHO Regional Office for Europe in the preparation of the European Ministerial Conference on the Prevention and Control of NCDs that will take place in Ashgabat, Turkmenistan, in December 2013. The Ashgabat Declaration on the Implementation of the Global and European Actions on NCDs is expected to be adopted at the conference. The conference report will include an evaluation of early detection of breast cancer in Turkmenistan coordinated by QAS, the first such evaluation conducted in the country.

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# Screening Group (SCR)

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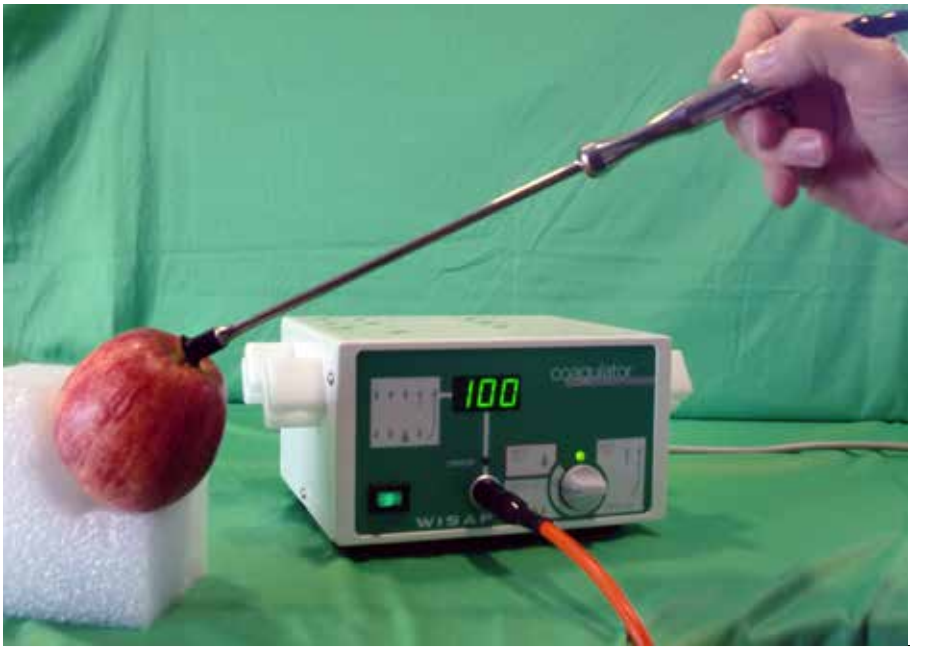
The objective of the Screening Group (SCR) is to evaluate the accuracy, effectiveness, and feasibility of a variety of early detection approaches and to accelerate the development of resource-appropriate screening, early diagnosis policies, and health care systems to reduce premature mortality from cancer and improve quality of life in low- and middle-income countries (LMICs). SCR conducts a variety of field studies to evaluate the performance characteristics, effectiveness, and service delivery aspects of early detection interventions for control of breast, cervical, colorectal, and oral cancers that could be scaled-up through routine health systems in LMICs. Also addressed are population and service delivery determinants that influence participation in early detection programmes, and the development of different training resources to catalyse and augment the training of personnel. The Group provides technical support to planning and implementing national early detection programmes in selected LMICs. A brief overview of major SCR studies, findings, and their impact on cancer control is provided below.

## Cervical cancer prevention and screening

A variety of screening approaches for cervical cancer prevention were evaluated by SCR. With antiretroviral therapy, HIV-infected women live longer and therefore effective screening methods are needed to prevent cervical cancer, for which they are at high risk. We addressed the accuracy and clinical utility of visual screening with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), Pap smear, and HPV testing in detecting high-grade cervical intraepithelial neoplasia (CIN 2 and 3) among 1128 HIV-infected women in Pune, India. Our results showed that sequential testing with VIA and VILI is the most feasible method until affordable HPV tests are available (Joshi *et al.*, 2013). The value of VIA and VILI in settings where HPV testing is not feasible was demonstrated in a large cross-sectional study (Deodhar *et al.*, 2012a). Affordable and effective treatment methods are vital for treating CIN 2 and 3 lesions. In a meta-analysis and field study, we demonstrated that cryotherapy results in an effective, safe, and acceptable treatment for CIN (Sauvaget *et al.*, 2013; Wesley *et al.*, 2013). We showed in another meta-analysis that cure rates exceeding 90% are achieved by cold coagulation treatment of CIN (Figure 1). Following a cross-sectional study to evaluate the performance of visual screening for cervical cancer, VIA and VILI screening services and treatment of CIN and early invasive cancer were sustained and scaled-up in Bamako and surrounding villages in Mali (Teguete *et al.*, 2012). Phase 1 of an organized Pap smear screening programme in Thailand during 2005–2009, involving approximately 5 million women aged 35–60 years, was evaluated. The feasibility of introducing organized cervical screening programmes through routine health services in higher middle-income countries, such as Thailand, was documented, and constructive suggestions for improving quality and coverage for the second phase during 2010–2014 were introduced (Khuhaprema *et al.*, 2012). We continue to provide technical support to national and regional screening programmes and initiatives in Angola, Argentina, Bangladesh, China, Congo, Guinea, India, Mali, Morocco, Nepal, Sri Lanka, and Thailand. SCR also continues to document cervical cancer incidence and mortality among the 230 000 women in the Osmanabad and Dindigul district cervical screening trials in India, addressing the impact of a single round of screening with HPV testing, cytology, or VIA and the risk of cervical cancer in more than 200 000 screen-negative women, in women who had treatment for CIN, and in women who defaulted treatment.

HPV vaccination is a major strategy for controlling cervical cancer by preventing persistent HPV infection. The use of less than three doses, if found effective, can substantially reduce HPV vaccine delivery costs and can accelerate the integration of HPV vaccination into national immunization programmes. In a multicentre clinical-trial-turned-observational-study in India, 4955 girls who received one dose (by default), 3963 who received two doses on days 1 and 60 (by default), 4920 who received two doses on days 1 and 180 or later (by design), and 4337 who received three doses on days 1, 60, and 180 or later (by design) are being followed up for immunogenicity, persistent HPV infection, and frequency of CIN caused by vaccine-included and -non-included HPV types. There have been no medically significant events related to HPV vaccination in this study. The immunogenicity after the two doses on days 1 and 180 or later was non-inferior to the three-dose regime; the immunogenicity among girls aged 15–18 years was non-inferior to that of girls

**Figure 1. Simulating hands-on training in cold coagulation treatment using an apple and a cotton swab. © IARC/Evelyn Bayle and Krittika Guinot.**



aged 10–14 years. The immunogenicity of one dose and of two doses on days 1 and 60 were significantly inferior to that of three doses over 6 months. Analysis of the 24- and 36-month plasma samples will be carried out in November 2013.

## Breast cancer screening

In a randomized controlled screening trial involving 116 000 women in Trivandrum District, India, the second round of screening by clinical breast examination (CBE) is complete and the third round has been initiated. A total of 720 000 person-years have been accrued over 6 years. Interim results indicate significantly higher early detection in the intervention group: 21% and 46% of breast cancers are diagnosed in stage I and stages I and II compared with 13% and 35%, respectively, in the control group. However, there is no difference in breast cancer mortality between the two groups yet, indicating the significant impact of adequate treatment in preventing breast cancer mortality. A qualitative study addressing the factors influencing participation in the various levels of the screening trial has been initiated. A cross-sectional study comparing the diagnostic performance of mammography and near-infrared imaging in triaging women with breast lumps has been completed in Cheng Du, China; similar diagnostic accuracy of the two approaches was indicated. The diagnostic performance of tactile imaging in triaging women with breast lumps is currently under way in Thailand (Figure 2). The role of breast awareness in improving early detection of breast cancer and survival of breast cancer patients is currently being investigated in Mumbai and through routine health services among the general population in Coimbatore District, India. We reported a 5-year survival of 76% among an industrial cohort in Mumbai after improved awareness and adequate access to diagnostic and treatment services, which is 25 percentage points higher than reported breast cancer survival estimates in India (Gadgil *et al.*, 2012).

## Oral cancer screening

Long-term results, after 15 years of follow-up, of the 192 000 participants in the randomized trial of oral visual screening in Kerala, India, showed a 25% reduction in mortality among users of tobacco or alcohol or both, a 38% reduction in oral cancer incidence, and an 81% reduction in mortality in those who complied with all four rounds of screening (Sankaranarayanan *et al.*, 2013a). The cumulative reduction in oral cancer incidence and mortality are shown in Figure 3. A detailed manual to guide primary care practitioners and health workers on early detection of oral cancer has been published (Ramadas *et al.*, 2013). We are currently evaluating the effectiveness of a "social marketing" programme to increase awareness for early detection in Sri Lanka.

## Colorectal cancer screening

Along with the National Cancer Institute (Bangkok) and the Thai Health Authorities, we successfully implemented a pilot colorectal cancer (CRC) screening programme using immunochemical focal

**Figure 2. Digital image, from a tactile imaging device, showing a firm round mass that was subsequently confirmed as neoplasia. Courtesy of Thanasitthichai Somchai.**

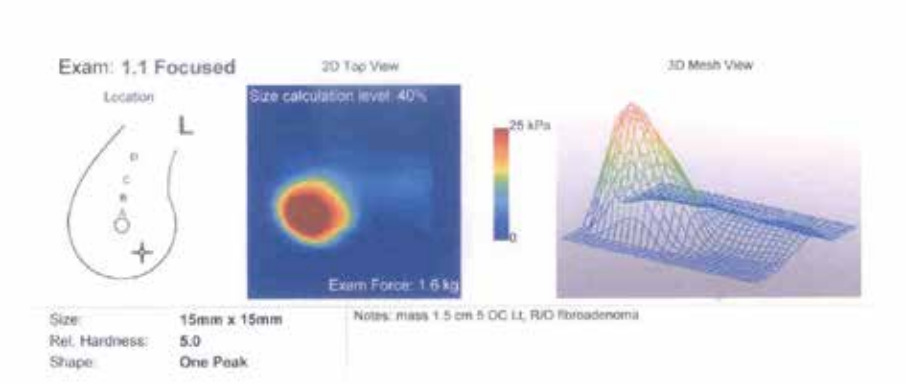
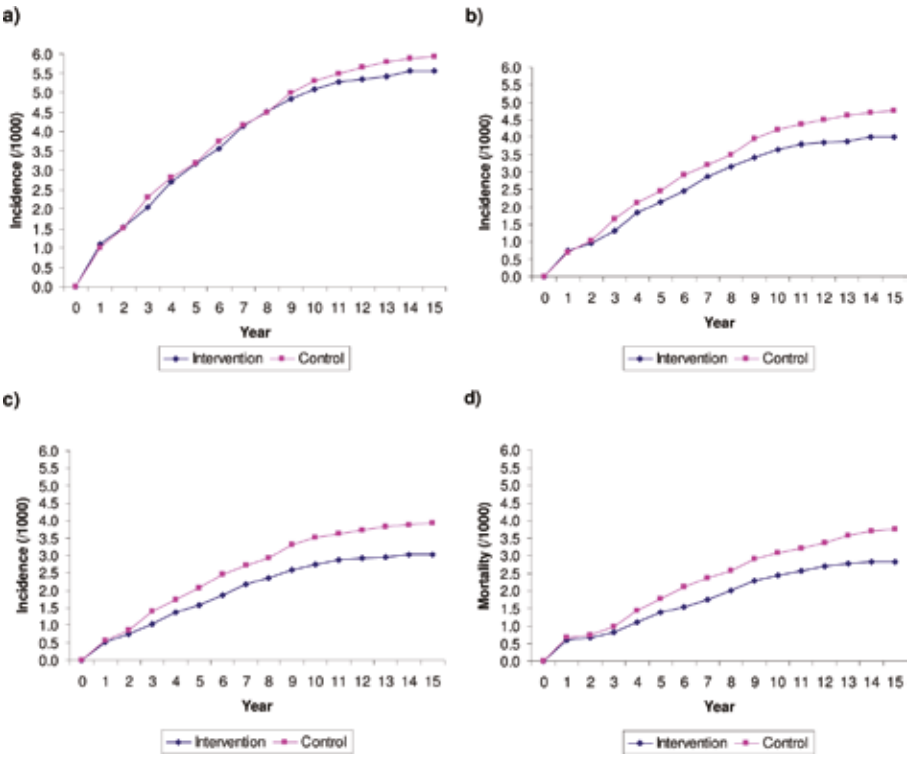



**Figure 3. Cumulative incidence of (a) overall, (b) stage 2 or worse, (c) stage 3 or worse, and (d) mortality from oral cancer among individuals who used tobacco or drank alcohol, or both. Source: Sankaranarayanan *et al.* (2013a); reproduced with permission from Elsevier.**



blood testing (iFOBT) and colonoscopy for test-positives through the routine government health services in Lampang Province, Thailand. Of the target population of 127 301 participants, 80 012 (62.9%) were screened using iFOBT. Participation was higher among women (67.8%) than men (57.8%) and lower in those aged 50–54 years than those aged 60–65 years. Of those screened, 873 (1.1%) were found iFOBT-positive; 627 (72.0%) screen-positive persons had a colonoscopy; 187 (29.8%) were diagnosed with adenomatous polyps, and 119 (63.6%) of them had advanced adenoma; and 30 (4.8%) were diagnosed with CRC, of which 53% (*n* = 16) had stage I disease. This project substantially improved the capability of local health services in colonoscopy, treatment of polyps and CRC, and histological assessment of colorectal neoplasia. The successful implementation of the pilot CRC screening, with satisfactory process and intermediate outcome measures, informed the feasibility of scaling up organized CRC screening through existing health services and paved the way for the government in Thailand to implement CRC screening more widely.

**Figure 4. Colonoscopy in Lampang colorectal cancer screening programme in Thailand; a large bowel polyp is being removed during colonoscopy. © IARC/Rengaswamy Sankaranarayanan.**

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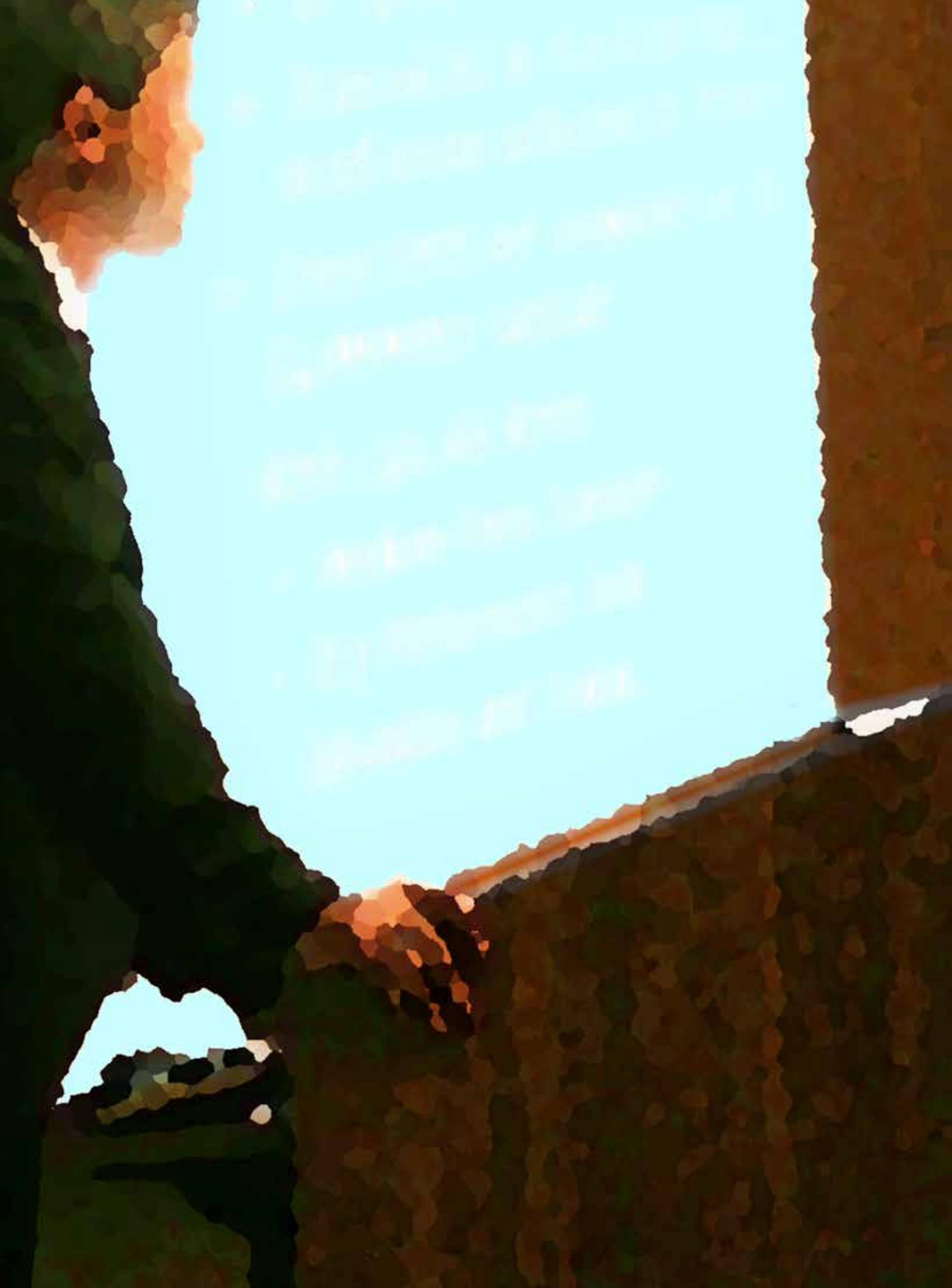

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**Special advisor (NCD)**
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The Office of the Director comprises a small team that supports the Director in the implementation of the vision and strategy for the Agency, as outlined in the IARC Medium-Term Strategy developed in conjunction with the Scientific and Governing Councils. The key functions are to develop strategic partnerships to support the mission of the Agency; to assist in the coordination of the Agency's scientific programme, particularly for projects that integrate activities across multiple Sections or Groups; and to maintain and develop relations with IARC's network of partners. As well as the support team, three Groups are within the Director's Office: Communications (COM), Education and Training (ETR), and Laboratory Services and Biobank (LSB, reflecting the fact that these Groups provide support to scientists across the Agency. In addition, the Gambia Hepatitis Intervention Study (GHIS), a long-term specialized project of the Agency, is managed by the Director.

The Director's Office assists in the coordination of relations and contacts with institutional partners, both governmental or nongovernmental research organizations and funding agencies, to support IARC's research programmes, and with key partners in global policy development for cancer prevention and control, including WHO Headquarters and Regional Offices, the International Atomic Energy Agency's Programme of Action for Cancer Therapy (IAEA-PACT), the United States National Cancer Institute's Center for Global Health (NCI-CGH), and the Union for International Cancer Control (UICC). In October 2013, IARC joined with WHO and UNESCO to support a meeting on Cancers of the Oesophagus held at the UNESCO Headquarters in Paris. In November 2013, IARC and WHO were sponsors of the World Cancer Leaders' Summit organized by UICC in Cape Town, South Africa. In addition to these international partners, the Director's Office supports the Director in liaising with current Participating States and in maintaining and developing official contacts in prospective new Participating States.

In the 2012–2013 biennium, the Director's Office coordinated or assisted in the organization of two key strategic scientific meetings. The first was the IARC-Latin America Collaboration Meeting in Lyon in March 2012, attended by leaders of national cancer centres from 16 Latin American countries and supported by La Red de Institutos Nacionales de Cáncer (RINC), which helped ensure that the priorities for the region were reflected in the Agency's future planning. The second was a meeting held in Doha in October 2013, organized jointly by IARC and the WHO Regional Office for the Eastern Mediterranean (EMRO) and hosted with the assistance of the Supreme Council

of Health, Qatar. This meeting identified the priorities for cancer control and cancer research across the countries covered by EMRO and reflected the recent presence of Qatar as one of the Participating States of IARC.

The Director's Office organized several high-level meetings with key partners from leading national cancer centres. Dr Silvia Franceschi was assigned a new role as Special Advisor to the Director on the topic of noncommunicable diseases. In addition, the Director hosted the visit of Dr Margaret Chan, WHO Director-General, in February 2013 on the occasion of World Cancer Day. Dr Chan addressed all staff on IARC's contribution to the work of WHO on cancer. This visit was followed by two high-level meetings (in February 2013 and December 2013) between senior IARC scientists and the WHO Assistant Directors-General, Deputy Director-General, and Dr Chan to identify priorities and set a joint programme of work across both organizations in relation to the Global Action Plan for Noncommunicable Diseases (2013–2020).

As part of its role in supporting scientific and coordination activities across the Agency, the Director's Office provides secretariat to several internal committees and ad hoc advisory groups. Most notable are 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 the implementation of the scientific strategy and on management issues, and the IARC Ethics Committee (IEC), which reviews all IARC projects and ensures that research is conducted in accordance with the most stringent ethical standards (for details of the composition and activities of the IEC, see page 138).

# Section of Support to Research (SSR)

## Office of Director of Administration and Finance

**Director of administration and finance**
Mr David Allen

**Administrative officer**
Ms Virginie Vocanson

**Secretary**
Ms Anne-Magali Maillol

**Assistant (Documents)**
Ms Agnès Meneghel

## Administrative Services Office

**Administrative services officer**
Ms Elisabeth Françon

**Administrative assistant**
Ms Sophie Servat

**Assistants (Supplies)**
Ms Fabienne Lelong
Mr Didier Louis (Temporary Assistant, Procurement)
Ms Sandrine Macé

**Assistant (Registry)**
Mr François Deloche

**Support staff**
Ms Odile Drutel (Clerk) (until December 2012)
Mr Antoine Hernandez (Driver)
Mr Michel Javin (Reproduction equipment operator)
Ms Rita Kibrisliyan (Receptionist) (until June 2013)
Ms Nicole Lagneau (Temporary Receptionist) (until July 2013)
Mr Ludovic Ripert (Storekeeper)
Ms Valérie Rut (Secretary)
Ms Séverine Sarboni (Clerk, Reception)

**Support staff (Building maintenance)**
Mr Patrice Barbieux (Electrician) (until December 2012)
Mr José Cardia Lima (Technician)
Mr William Goudard (Carpenter)
Mr Hafed Lamouchi (Electronics)
Mr Jean-Alain Pedil (Security)

## Grants, Budget and Finance Office

**Administration and finance officer**
Ms Angkana Santhiprechachit

**External relations officer (IARC Grants Office)**
Dr Olaf Kelm

**Budget officer**
Ms Editta Odame

**Finance officers**
Ms Julie Goux
Mr Rommel Nidea

**Budget assistants**
Mr Thomas Odin
Ms Madeleine Ongaro
Mr Franck Rousset

**Finance assistants**
Ms Françoise Florentin (Accounts) (until April 2013)
Ms Laurence Piau (Accounts)

**Support staff**
Ms Belinda Annibaldi (Temporary Clerk, Finance)
Mr Pascal Binet (Clerk, Accounts)
Ms Lobna Boulegroun (Secretary, Finance)
Ms Nathalie Lamandé (Secretary, Grants)
Ms Adèle Séguret (Clerk, Accounts)

## Human Resources Office

**Human resources officer**
Ms Dina D'Amico

**Junior professional officer**
Ms Sara Allkämper (until February 2013)

**Assistants (Human Resources)**
Ms Isabelle Battaglia
Ms Maud Bessenay

**Secretary**
Ms Sophie Sibert

**Central Secretarial Services (CSS)**
Ms Carole Durieux
Ms Marieke Dusenberg
Ms Carole Lastricani

**Secretary to IARC Staff Association Committee and Staff physician**
Ms Isabelle Poncet

**Social adviser**
Ms Christine Astier

**Staff physician**
Dr Michel Baduraux
Dr Dorothée Cuche (until December 2012)

## Information Technology Services

**Programmer analyst**
Mr Philippe Damiecki

**IT officers**
Mr Philippe Boutarin
Mr Christopher Jack

**Support staff**
Ms Lucile Alteyrac (Assistant, Informatics)
Mr Cédric Barrancos (Temporary Programming Technician)
Mr Nicolas Hernandez (Temporary Assistant, Informatics) (until November 2012)
Mr Nicolas Tardy (Assistant, Informatics)

During the 2012–2013 biennium, the Division of Administration and Finance was renamed the Section of Support to Research (SSR) in recognition of its role in the achievement of IARC's scientific objectives through efficient and effective management of the Agency's resources and provision of administrative services, ensuring accountable risk mitigation and implementing strategies to strengthen IARC's capacities.

The Section is made up of specialized administrative units that manage and provide services intrinsic to the successful implementation of IARC's scientific programme in the areas of: Grants, Budget, and Finance; Human Resources; Conference, Office Administration, and Buildings; and Information and Communications Technology. SSR ensures that the Agency's activities uphold the highest standards of management, efficiency, and accountability in the use of the funding made available by its Participating States and donors.

At the beginning of the reporting period, SSR teams implemented an ambitious 2-year work plan that had been reviewed and agreed upon by the Director and the Senior Leadership Team. Highlights of the results achieved include full implementation of the International Public Sector Accounting Standards (IPSAS), modernization and augmentation of the IT infrastructure, the launch of several staff recognition and career development programmes, several large-scale infrastructure interventions on the premises, and substantive progress in efforts to house the Agency in more suitable premises in the near future. In collaboration with colleagues across other Sections, SSR teams made considerable strides in revamping IARC's administrative policies and procedures with the aim of streamlining and simplifying, including automating several such processes.

In the face of continued escalating costs, the Agency remains committed to finding innovative approaches to ensure that delivery of the scientific programme is not adversely affected. SSR leads these efforts through careful resource planning and management, as well as advising the Director on a regular basis about potential areas of concern and remedial actions. In efforts to diversify the revenue stream for the Agency, SSR spearheaded efforts towards a corporate Resource Mobilization Strategy to be launched during the 2014–2015 biennium. During the current biennium, SSR achieved cost savings of approximately €150 000 through rationalization of recurrent contracts and reduced its projected operating budget by more than €325 000 for the 2014–2015 biennium in order to support the objectives of the scientific programme.

# Communications Group (COM)

**Group head**
Dr Nicolas Gaudin

**Secretary**
Ms Bernadette Geoffre

**Editor**
Dr Karen Müller

**Scientific officer**
Dr Rachel Purcell

**Institutional webmaster**
Ms Maria de la Trinidad Valdivieso Gonzalez

**Librarian**
Ms Sharon Grant (until July 2013)

**Press officer**
Ms Véronique Terrasse

**Technical assistants**
Mr Antoine Bellon (until October 2013)
Ms Latifa Bouanzi
Mr Roland Dray
Ms Sylvia Lesage
Ms Solène Quennehen

An integral part of the Director's Office, the Communications Group (COM) is responsible for the presentation of a homogeneous image 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.

## Restructuring

As part of an Agency-wide effort to streamline processes and increase efficiency, in line with the IARC Medium-Term Strategy, COM presented an IARC Communications Strategy, which was endorsed by the Senior Leadership Team and agreed upon by the Director. After an internal review, COM was reorganized into a four-team unit, whose collective objective is to enhance the Agency's external profile, both institutionally and scientifically.

• The Knowledge Management Centre has the overall objective of integrating services and resources that support the creation, preservation, and dissemination of IARC research and knowledge. This team is responsible for the functions of the IARC Library as well as enhanced support to the Agency's Publications Programme. The new position of Knowledge Manager is supported by a Librarian Assistant and a Publishing Assistant, whose terms of reference have been upgraded, to help the Knowledge Manager discharge the central publications functions.

• A Press Officer position was established to strengthen the Agency's external communications capacity and enhance media presence globally, and the position was filled earlier this year. The Press Officer is supported by a Multimedia Assistant.

• To best meet and coordinate the editing requirements across the Agency, a Technical Editor position has been moved from the Molecular Pathology Section to COM to support in part the English-language Editor.

• The Web team continues to improve IARC's presence on the Internet and to coordinate and manage the Intranet content. Currently, the Web services are carried out by the Institutional Webmaster with the support of a Web Assistant.

## Knowledge management services

Reporting to the Head, COM, the Knowledge Manager is responsible for the Knowledge Management Centre components: the IARC Library and Publications Programme. As the manager of the Library team, the Knowledge Manager coordinates the delivery of a wide range of information resources and services, and also manages the IARC Publications Programme, overseeing and coordinating the publication cycle from conception through to actual publication and dissemination.

• 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 growing rapidly. The Library works closely with local libraries in Lyon and with WHO Libraries and Information Networks for Knowledge to provide additional means for IARC users to access information. Furthermore, the Library's highly efficient Document Delivery Service ensures a quick turnaround time between requests and delivery of documents. The IARC Library provides access to its

collections and services to institutions and individuals.

• The Publications Programme supports all IARC publication projects by using a cross-cutting approach to streamlining processes, establishing standard tools (e.g. automated manuscript submission software and applications) and formats (e.g. print version and ePub), and stepwise submission of projects, through the Advisory Committee on Publications. This approach caters both to publications produced by individual Sections, namely the WHO Classification of Tumours and the IARC Monographs series, and to the more general IARC Scientific Publications series and non-serial publications.

• The Knowledge Management Centre team also addresses IARC's contractual agreement with WHO Press for the dissemination of IARC publications to ensure higher efficiency and better return on investment. Therefore, COM, along with the Administration, has been seeking the support of an external consultant to explore various approaches to commercial development and market positioning for IARC publications and other data products (such as the PubCan integrated database, which is under development).

During the 2012–2013 biennium, IARC published several key reference publications:

### WHO Classification of Tumours

WHO Classification of Tumours of the Breast, fourth edition; and
WHO Classification of Tumours of Soft Tissue and Bone, fourth edition.

### IARC Monographs

Volume 100 – A Review of Human Carcinogens (including a six-volume boxed set):

- Volume 100A (2012) Pharmaceuticals
- Volume 100B (2012) Biological Agents
- Volume 100C (2012) Arsenic, Metals, Fibres, and Dusts
- Volume 100D (2012) Radiation
- Volume 100E (2012) Personal Habits and Indoor Combustions
- Volume 100F (2012) Chemical Agents and Related Occupations.

In addition to these printed and electronic volumes, the Monographs Section published the following titles in free-access PDF format on the IARC web site:

- Volume 101 (2012) Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water
- Volume 102 (2013) Non-Ionizing Radiation, Part 2: Radiofrequency Electromagnetic Fields
- Volume 103 (2013) Bitumens and Bitumen Emissions, and Some *N*- and *S*-Heterocyclic Polycyclic Aromatic Hydrocarbons
- Volume 104 (2013) Malaria and Some Polyomaviruses (SV40, BK, JC, and Merkel Cell Viruses).

### IARC Scientific Publications

**In print exclusively:**

- Improving Public Health through Mycotoxin Control, IARC Scientific Publication No. 158 (2012).

**In electronic format exclusively:**

- Air Pollution and Cancer, IARC Scientific Publication No. 161 (2013).
- Cancer Incidence in Five Continents, Vol. X (electronic version) (2013)

(The printed version of this volume, IARC Scientific Publication No. 164, will be available in 2014.)

**IARC CancerBases:**

- IARC CancerBase No. 11, GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide (2013)

**IARC Working Group Reports (PDF publication only):**

- Current Status and Future Directions of Breast and Cervical Cancer Prevention and Early Detection in Belarus, Working Group Reports, Volume 6 (2012).

**IARC Technical Publications:**

- A Digital Manual for the Early Diagnosis of Oral Neoplasia, IARC Technical Publication No. 42 (2012).

Following in the footsteps of the seminal *World Cancer Report* published in 2003, and five years after the previous edition of this landmark publication, production of *World Cancer Report* 2014 began in 2012. This landmark volume is expected to be published early in 2014, both in print and e-book format. The result of a major effort, which mobilized dozens of IARC scientists, many collaborators worldwide, and the whole COM team to various degrees, this book should become an indispensable resource for scientists and public health professionals.

### Editing, language, and translation services

COM provides English and technical editing services to all IARC Groups for publication of papers in peer-reviewed journals and book chapters, or for publication in one of the established IARC Publications series. Additional support was added in 2013 when a Technical Editor position was moved from the Molecular Pathology Section to COM, to support in part the English-language Editor and thereby provide additional centralized resources to this key Agency-wide service. Further, the administration of external English-to-French translation services (mainly for large documents for IARC's governing bodies) has now been transferred to the English-language Editor. Day-to-day translation requirements are handled by COM for articles, technical documents, correspondence, memoranda, and other texts for all the scientific and administrative Groups. COM also organizes successful language courses for the Agency's staff in both working languages, plus Spanish beginning in 2012.

### Media services

The IARC Communications Strategy identified the need for reinforcing media presence and heightened activity in this area. Therefore, a professional position of Press Officer was established, which was filled in 2013. This activity has already shown that it is key to the development of IARC's image in the scientific community, the media, and the general public. Branding is now emphasized throughout the Agency (web, graphics support, media training, etc.). Two major press conferences, to announce the results of the evaluation of Diesel Engine Exhaust in June 2012 (Group 1 carcinogen) and of Outdoor Air Pollution in October 2013 (Group 1 carcinogen), demonstrate the usefulness of enhanced presence and cooperation with the WHO Media team. The IARC Media team rolled out six press releases in 2012 and nine in 2013 to a large network of more than 4500 correspondents all over the world. In addition, dissemination of more specific

news releases was made through the publication of 61 IARC News items in 2012 and an equal number to date in 2013.

### Web services

To promote an effective corporate image, COM's Web services team ensures that presentation of all of IARC's research available through the web and IARC subsites is standardized. As part of the Agency's communications and web strategy, a redesigned IARC web site was launched on 16 May 2012 and a mobile-optimized version was made available on 17 May 2013 to reach a wider audience. Also to increase accessibility, a special effort has been made to align the majority of the IARC research projects to also become available on such mobile platforms (http://www.iarc.fr/en/websites/researchprg.php).

COM's Web services team also helps to analyse the web needs of the IARC Groups, to conceptualize and guide the process of development (e.g. content definition, design, and launch), and to maintain web sites for various Groups. During the 2012–2013 biennium, the Web services team developed and successfully launched the following web sites:

#### Public web sites:

The International Paediatric CT-scan Study
The Global Acute Leukaemia network (GALnet)
The Human Papillomavirus Infection and Head and Neck Cancer Study (HPV-AHEAD)
The IARC Biobank (IBB)
The InterCHANGE Study
The INTERPHONE Study
The Study of HPV and Precancerous Lesions In the Tonsil (SPLIT) Project
The WHO/IARC Classification of Tumours

#### Meeting web sites:

Emerging Oncogenic Viruses
Emerging Issues in Head and Neck Cancer

#### Internal web site:

IARC Laboratory Services

The Web services team ensures greater visibility of the key IARC activities through the home page and feeds key performance indicators (KPIs) (particularly as relates to information access through the www.iarc.fr portal) to the Head of the Group and to the Director. The substantial impact of the media efforts is evident from the news coverage of the major releases mentioned above, which made global headlines. The profile of the media impact is being monitored by news monitoring services, led by COM. The media impact correlates closely to major media launches, and the IARC home page offers real-time IARC media coverage.

This team also maintains the Intranet service, which provides staff with many administrative resources and information for internal use (e.g. library, language classes [English, French, and Spanish], Occupational Health and Safety Committee, laboratory activities).

# Education and Training Group (ETR)

**Group head**
Ms Anouk Berger

**Acting head**
Dr Eduardo Seleiro
(until May 2012)

**Responsible officer, fellowship programme**
Dr Zdenko Herceg

**Senior visiting scientist**
Dr Rodolfo Saracci

**Assistant, fellowship programme**
Ms Eve El Akroud

**Assistant, courses programme**
Ms Susan Anthony

Education and training in cancer research is one of the statutory functions of the Agency. For more than four decades, IARC's Education and Training programme has made a substantial contribution to the development of cancer research in many countries, with special emphasis on low- and middle-income countries (LMICs), through the training of cancer researchers, particularly in the field of cancer epidemiology. This has in turn contributed to shaping the Agency's research strategy and to widening the network of collaborators, as well as promoting and enhancing IARC's reputation and worldwide standing as an international organization.

Recognizing the importance of education and training activities within the Agency's mission, and after internal consultation and guidance from an ad hoc Advisory Group meeting in 2009, the ETR Group was established in 2010 as a distinct structure within the Office of the Director. The mission of ETR is to coordinate the various IARC training initiatives and promote them both internally and externally. The Group is under the direction of an education and training officer, with two senior programme assistants managing the Fellowship and Courses Programmes.

The following sections present key achievements of ETR in 2012–2013. It should be noted that although the ETR Group oversees the activities of the Agency in these matters, many initiatives are led by the research Groups.

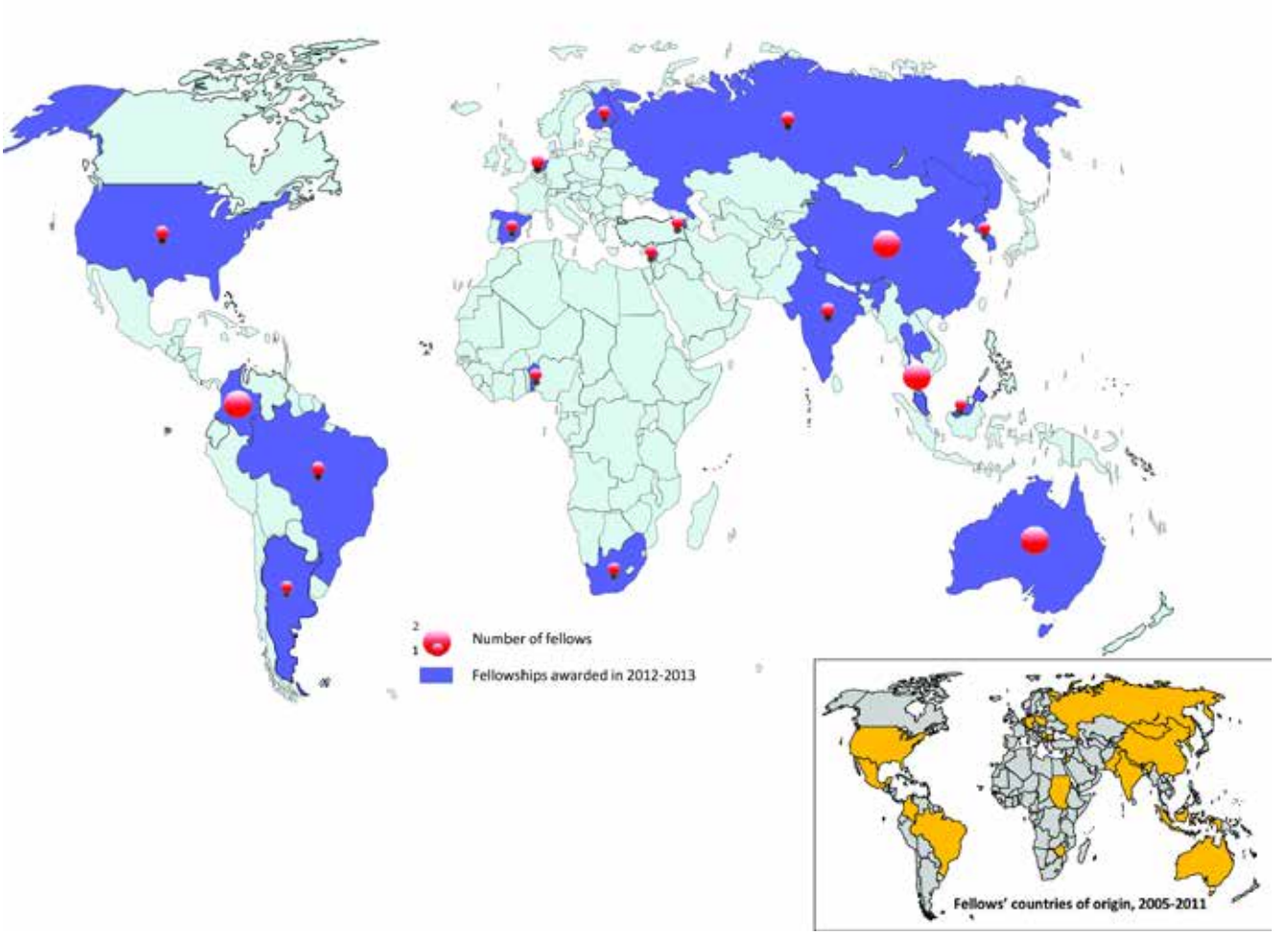
## Postdoctoral Fellowships

Since 2005, IARC Postdoctoral Fellowships have been uniquely tenable at the Agency. They target scientists from LMICs, or with research projects relevant to these countries, in areas related to IARC's own programme and with an emphasis on interdisciplinary projects.

The number of applicants to the Postdoctoral Fellowship Programme has increased in recent years, testifying to the growing interest in the programme. Fellowships are awarded after a highly competitive process with interviews and an evaluation by an international panel of experts comprising the IARC Fellowship Selection Committee.

Fellowships were awarded to 12 postdoctoral fellows in 2012 and to 8 in 2013, coming from 16 different countries. The Agency hosted 18 or 19 fellows per year during this period, as the majority of awards were extended for a second year after a review by the Fellowship Selection Committee. Of the fellows, 70% were from LMICs; 45% were epidemiologists and 55% laboratory scientists; almost half were women (45%). A research Return Grant was awarded to three fellows from LMICs to establish their research activity in their own country. Although modest, this represents a significant boost for the initiation of such projects.

**Figure 1. IARC Postdoctoral Fellowships awarded in 2012 and 2013, by country of origin.**



ETR successfully obtained a second competitive grant from the EC-FP7 Marie Curie Actions-People-COFUND, which will contribute 40% of the postdoctoral fellowship costs for the next 5 years.

The bilateral agreements concluded with Cancer Council Australia in 2010 and with the Irish Cancer Society in 2011 to establish the IARC-Australia and the IARC-Ireland Postdoctoral Fellowship, respectively, allowed two additional fellows to be supported during the biennium. Other similar partnerships are currently under discussion with several institutions in Participating States.

A survey was carried out in 2012 to assess the outcomes of the programme since 2005. The online questionnaire was completed by 87% of former fellows: 77% of respondents returned to their home country; 81% have remained active in cancer research in public institutions; half considered that the fellowship had a direct impact on successfully obtaining grants after leaving IARC, and most of those benefiting from a Return Grant considered it beneficial to their career as well as to their institution; and all respondents felt that the fellowship was either "helpful" or "decisive" for their career.

**Table 1. Senior Visiting Scientist Awards and Expertise Transfer Fellowships awarded in 2012 and 2013**

| | |
|---|---|
| **2012** | |
| Professor Isabel Dos Santos Silva | London School of Hygiene & Tropical Medicine, London, United Kingdom |
| Professor Terrence Dwyer | Royal Children's Hospital, Parkville, Australia |
| Professor Steven Rappaport | University of California, Berkeley, USA |
| **2013** | |
| Professor Leticia M. Fernandez Garrote | National School of Public Health, La Habana, Cuba |
| Professor John D. Groopman | Johns Hopkins University Bloomberg School of Public Health, Baltimore, USA |
| Professor Groesbeck P. Parham | Center for Infectious Disease Research in Zambia, Lusaka, Zambia |
| Professor Christopher J. Portier | Agency for Toxic Substances and Disease Registry, Atlanta, USA |
| Dr Esther De Vries [a] | Erasmus University Medical Center, Rotterdam, The Netherlands |

[a] Expertise Transfer Fellowship: 12 months at the National Cancer Institute, Bogotá, Colombia, to improve the use of population-based cancer registries in Colombia and other Latin American countries.

## Senior Visiting Scientist Award and Expertise Transfer Fellowship

The Senior Visiting Scientist Award gives IARC the opportunity to host eminent researchers for up to 1 year, providing a significant boost to the Agency's research activities and collaborations, as well as an excellent opportunity for the development of early career scientists within IARC. The Expertise Transfer Fellowship enables an established and experienced investigator to spend 6–12 months in an appropriate host institute in a LMIC to share knowledge and expertise in a research area relevant to the host country and related to IARC's programme.

Seven Senior Visiting Scientist Awards and one Expertise Transfer Fellowship were awarded in 2012–2013 (Table 1). Additional funding, made available by the Governing Council in 2011 and 2012, allowed the granting of all the Senior Visiting Scientist Awards recommended by the IARC Fellowship Selection Committee. In addition, the Swiss Federal Office of Public Health in Berne made a generous contribution to support the Senior Visiting Scientist Award programme.

## New opportunities for training at IARC

ETR further explored the expansion of the Fellowship Programme to include short-term stays at IARC (3–4 months) with the intention of transferring basic skills for cancer research to promising candidates from LMICs. In 2012 and in collaboration with the Union for International Cancer Control (UICC), the UICC-IARC Development Fellowship was successfully launched during the IARC Summer School. This initiative allowed two of the most promising participants of the 2012 and 2013 courses to return to IARC for a period of 3 months to receive further training and to set up research collaborations.

## Hosting environment

In addition to the IARC Fellows described above, the Agency hosts junior and senior scientists supported by project funds from the research Groups. A total of 240 trainees, graduate students, postdocs, or visiting scientists funded by the Fellowship Programme or IARC Groups worked at IARC during the reporting period. A framework for hosting trainees, graduate students, postdocs, and visiting scientists, funded either by the Fellowship Programme or directly by the IARC Groups, has been developed and managed to ensure the quality of the hosting environment.

The Postdoctoral Fellowship Charter, implemented in 2011, has been extremely successful. It allows a more structured approach to postdoctoral training at IARC by defining expectations and providing opportunities for generic training to equip young scientists with essential skills to enhance career prospects. To

this end, 19 courses were organized at IARC during the biennium within four categories of generic skills: research skill development, responsible conduct of research, communication skills, and leadership and management (Table 2).

A related initiative, the creation of the IARC Early Career Scientists Association (ECSA), was encouraged. ECSA, which was launched in July 2013, aims to bring together students of all levels, as well as postdoctoral scientists and fellows, for training and career development in collaboration with ETR, for social activities, and to facilitate dialogue with ETR and IARC management. ECSA's mission and guidelines were defined by its members, with guidance and support from ETR and senior management.

**Table 2. Generic courses for early career scientists, 2012 and 2013**

| |
|---|
| **Research skill development** |
| Principles of oncology (twice) |
| Epidemiology for non-epidemiologists: a short introduction (twice) |
| Biostatistics: data preparation and formatting |
| Biostatistics: generalized linear models using Stata |
| Basic UNIX for handling large data sets |
| **Responsible conduct of research** |
| Biomedical research ethics (twice) |
| **Communication skills** |
| Publishing in scientific journals |
| **Leadership and management** |
| Project management (three times) |
| Grant writing (four times) |
| Financial management |
| Task management |

## IARC Summer School in Cancer Epidemiology

As a core activity of the IARC Education and Training programme, the IARC Summer School on Cancer Epidemiology is held every year at IARC in June–July, with the goal of improving methodological and practical skills of cancer researchers and health professionals. Both a Cancer Registration module (week 1) and an Introduction to Cancer Epidemiology module (weeks 2 and 3) were organized each year. The target audience is epidemiologists, statisticians, physicians and oncologists, public health specialists, and others with a direct interest in cancer epidemiology or registration. Priority is given to researchers from LMICs. A balance is sought between leaders in research and more junior staff, and between institutions or groups involved in cancer monitoring, in the evaluation of care practices and preventive interventions, or in etiological research.

**Figure 2. IARC Summer School 2013: Introduction to Cancer Epidemiology. © IARC/R. Dray.**

**Table 3. Specialized and advanced courses, 2012 and 2013**

| Course title | Location | Number of participants | External collaborations |
|---|---|---|---|
| **2012** | | | |
| Course on cancer registration and survival: principles and methods | Mumbai, India | 28 | Tata Memorial Centre, UICC |
| PROLIFICA virology training workshop | Lyon, France | 5 | PROLIFICA, INSERM |
| Quality improvement and basic analysis of information in population - based cancer registries in Latin America | Cali, Colombia | 36 | Instituto National de Cancerologia Colombia, Registro poblacional de cancer de Cali, Universidad del Valle, UICC, PAHO, RINC |
| Role of infections in human cancers | Trivandrum, India | 30 | HPV-HEAD consortium |
| Training course on principles, organization, evaluation, planning and management of cancer screening programmes (module 1) | Lyon, France | 26 | FCS, EPAAC |
| EPIC-Soft® 24-HDR | Online course | 13 | PILOT-PANEU consortium EFSA project |
| CanReg5 | Webinar cycle | 91[a] | GICR, IACR |
| Cervical and breast cancer prevention training | Jaffna, Sri Lanka | 20 | Regional Cancer Treatment Center, Jaffna<br>WHO SRL |
| **2013** | | | |
| EPIC-Soft® Train the trainers | Lyon, France and online learning | 22 | EU-MENU |
| EPIC-Soft® Train the trainers | Online learning | 30 | EU-MENU |
| Training course on principles, organization, evaluation, planning and management of cancer screening programmes (module 2) | Lyon, France | 26 | FCS, EPAAC |
| Training course to screen for (by visual inspection with or without colposcopy) and treat (by cold coagulation/cryotherapy) cervical cancer | Sikkim, India | 32 | Sikkim State Government<br>STNM Hospital, Gangtok, Sikkim |
| Training course on colposcopy and LEEP procedures in the management of cervical cancer | Pattaya, Thailand | 29 | National Cancer Institute Bangkok and Thai Colposcopy Society |
| Statistical practice in epidemiology with R | Lyon, France | 40 | Bendix Carstensen, University of Copenhagen, Denmark; Krista Fischer, University of Tartu, Estonia; Esa Läärä, University of Oulu, Finland |
| 1st pathology training course – ESTAMPA study | Bogota, Colombia | 18 | Instituto Nacional de Cancerologia de Colombia |
| IARC regional hub course on cancer registration and epidemiology | Bangkok, Thailand | 45 | Tata Memorial Centre, US CDC, UICC |
| IARC regional hub course on cancer registration & epidemiology | Jakarta, Indonesia | 40 | Tata Memorial Centre, UICC |
| Cancer registry training course | Izmir, Turkey | 44 | European Network of Cancer Registries, US NCI, MECC, EU- Joint Research Centre, Izmir Cancer Registry, University of California Irvine |
| Training course for cancer registry staff: from population-based cancer registry data to a scientific publication | Buenos Aires, Argentina and online learning | 8 | Erasmus MC University Medical Center, Rotterdam, The Netherlands, IACR, UICC |
| Training course on cervical colposcopy – ESTAMPA study | Buenos Aires, Argentina | 16 | Argentinean Society of Lower Genital Tract Pathology and Colposcopy |
| CanReg5 | Webinar cycle | 120[a] | GIRC, IACR |
| Paediatric oncology for cancer registries | Lyon, France | 40 | ENCCA, ENCR |

[a] Participated in one or more of the 6 webinars that were offered each year.

The application rate for the course has been consistently high (up to 250 applicants), with an average of 45 participants attending each module. During the biennium, the Summer Schools enabled the training of a total of 124 researchers and health professionals from 60 countries, 103 of them (83%) from 45 different LMICs.

The Summer School modules have been very well received by the participants, who expressed their appreciation of the quality of the content, the teaching, and the learning environment. As indicated by the results of a course outcomes evaluation carried out in 2012, the vast majority of responding participants were able to apply what they had learned directly to their work. The course also promotes the development of collaborations with other participants, as well as with IARC groups and partners. Finally, most participants remain active in cancer research in public institutions and reuse training material for their own learning or to train others.

### Specialized and advanced courses

Specialized and advanced courses are sometimes organized by IARC's scientific Groups, often with the support of ETR. The majority of these courses are associated with collaborative research projects, where IARC is transferring skills necessary for the conduct of the projects. This will subsequently enable the implementation of the research findings in the countries concerned. Specialized methodological courses held at IARC include Statistical Practice in Epidemiology with R, in collaboration with members of the R development team, and courses on the EPIC-Soft® 24-hour dietary recall and the CanReg5 software (see eLearning below). In some instances, specialized courses are co-organized with external partners and held at diverse locations throughout the world (Table 3). Over the biennium, specialized and advanced courses enabled the training of a total of approximately 700 scientists and health professionals.

**Figure 3. IARC Summer School 2013: Measures of occurrence and association. © IARC/R. Dray.**

### e-Learning

IARC has sought to develop distance learning projects to complement and expand the initiatives described above. Some specialized courses were offered completely as distance learning courses. For example, the Cancer Information Section organized a cycle of six webinar sessions on the use of CanReg5 during 2012. Each session combined a live lecture with a Q&A session and was attended by participants from all regions of the world. The sessions were recorded and posted as teaching and learning material on the web site of the Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries (GICR; http://gicr.iarc.fr/index.php? page_id = 4&lang_id = 1). Both high attendance of the virtual sessions and the large number of downloads of material underline the value of this approach. A similar successful experience was conducted by the Dietary Exposure Assessment Group with a 3-day course on the EPIC-Soft® 24-hour dietary recall software conducted 100% at distance over a period of 2 weeks.

ETR reshaped its web site as an online single entry point to all IARC education and training initiatives, including, for example, a database that links to existing online IARC learning and training resources such as the digital training manuals for cervical screening and treatment published by the Screening Group (http://training.iarc.fr).

Finally, the Agency initiated partnerships to develop e-Learning material that can be used in different contexts. In particular, IARC contributed content and expertise for the development of the International Atomic Energy Agency-Programme of Action for Cancer Therapy (IAEA-PACT) Virtual University for Cancer Control network (VUCCnet) demonstration module on cervical cancer prevention that was successfully tested by the Institut Català d'Oncologia (ICO) in 2011 and 2012. Further negotiations with IAEA-PACT are under way to develop an e-Learning module on cancer registration in 2014. Other collaborations set up during the biennium have led to the planning of a joint IARC/ICO online course in cancer epidemiology targeting Latin American countries, as well as to the contribution to the contents of an e-Learning session, Introduction to Cancer, developed by the London School of Hygiene & Tropical Medicine.

# The Gambia Hepatitis Intervention Study (GHIS)

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**Cancer registrar**
Mr Lamin Giana

**Tumour registration officers**
Mr Modou Musa Sisawo
Mr Yusupha Bah
Mr Lamin Sanneh
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The Gambia Hepatitis Intervention Study (GHIS), now in its third decade, 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 vaccination in childhood for the prevention of infection, chronic liver disease, and hepatocellular carcinoma in adulthood in a high-risk population. Led by the Director's Office, GHIS is a high-profile project of the Agency. At the beginning of GHIS, a population-based National Cancer Registry (NCR) was established. Cancer cases are identified through public health facilities and private clinics.

Dr Ramatoulie Njie, the hepatologist managing the project, together with a team of tumour registration officers, carries out enhanced surveillance of chronic liver disease and cancer in hospitals and health centres around the country. She is assisted by junior doctors from the local Edward Francis Small Teaching Hospital (EFSTH) whom she has trained in ultrasonography and liver biopsy techniques. Suspected cases of liver cancer are assessed by ultrasonography, by quantitative α-fetoprotein assays, and, in many cases, by histological confirmation from liver biopsy samples. Histopathology reporting is carried out by two independent pathologists: in The Gambia by Professor O. Khalil at EFSTH and in London by Professor Rob Goldin at Imperial College. All confirmed cases of liver cirrhosis and cancer are recorded in the NCR.

## Current status

• There have been sufficient numbers of confirmed liver cancer/liver cirrhosis cases to allow us to start testing the record linkage with the original GHIS vaccination database. This is being undertaken with Sir Andrew J. Hall, now a senior visiting scientist at IARC.

• To further strengthen the histological diagnoses, consideration is being given to sending slides for validation by the histopathology team at IARC.

• Improving the quality of the NCR remains a priority, through recruitment and training of additional tumour registration officers, improving the quality of cancer diagnoses, and providing histopathology support to GHIS.

# Laboratory Services and Biobank Group (LSB)

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**Secretary**
Ms Sally Moldan

**Laboratory services**
Ms Brigitte Chapot
Ms Nicole Farina
Ms Maria Maranhao
Ms Marcelle Essertel

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

Established in 2010, the Laboratory Services and Biobank Group (LSB) is responsible for managing the IARC Biobank facility and the common laboratory platform. The LSB Group works closely with the Laboratory Services Committee (LSC) and the Biobank Steering Committee (BSC) to ensure that its activities are adapted to the needs of the Sections and Groups across the Agency. To make information related to all laboratory services readily available and easily accessible, an intranet web site was developed and launched in mid-2013.

In the current biennium, LSB's main focus has been on operational and quality control issues that are important in shaping the future of the Agency's laboratories and the Biobank. LSB led the development of an Access Policy for biospecimens stored in the IARC Biobank. This policy is published on the IARC web site and provides clear guidance on how potential collaborators should approach the Agency with proposals for new studies using existing resources. The centralization of IARC's biological samples, consisting of more than 5 million biospecimens, is being conducted according to principles of best practice, using a common sample management database, developing a Minimum Recommended Data set for biobank data collection, and ensuring optimal storage through investment in new equipment and systems.

A significant initiative in 2012 was the creation of the Technician Discussion Group (TDG). In recognition of the important role played by laboratory technicians in research at IARC, the TDG brings together the technicians, the LSC Chair, and the LSB Head on a regular basis to discuss ongoing laboratory issues and opportunities. The TDG serves as an important medium of communication between LSC, LSB, and laboratory staff.

### Cataloguing, reviewing, and reorganization of biobank resources and infrastructure

The database used for sample archiving and management, SAMI (Sample Management for IARC), has provided the opportunity to centralize the IARC Biobank resources. Prior to entry into the centralization programme, collections undergo inventory and inspection for apparent discrepancies between records in existing databases versus actual storage location. The ultimate aim of the inventory is to create and maintain a comprehensive catalogue and up-to-date information on IARCs biological resources. So far, out of the estimated ~1.5 million samples that constitute the IARC-based collection (excluding European Prospective Investigation into Cancer and Nutrition [EPIC] samples, which are stored in a separate database), more than 500 000 (~30%) have been inventoried; close to 400 000 of the inventoried samples have been uploaded, and another 165 000 are in databases ready for migration into SAMI.

To deal with the acute shortage of storage space, samples were reorganized to take up less space, aged freezers were replaced, and back-up equipment was acquired to accommodate the increasing number of samples received (19 000 samples/year) and to prepare for emergencies and breakdowns. In addition, the IARC Biobank facility was expanded to accommodate additional freezers and a separate facility for ambient-temperature storage.

An automatic temperature monitoring system was installed in 2012 to provide real-time monitoring of the storage facilities. This ensures timely interventions that minimize the risk of unexpected breakdowns and thus maintain a stable and secure environment for samples.

### Introduction of IARC's Minimum Recommended Data set for standardized data collection for IARC stored samples

The SAMI database is supported by an integrated IT system and enables users to upload, monitor, and trace sample movement. The original version of SAMI provided a structure for importation of basic information on the origin of the biospecimens and sample location.

Historically, the IARC Biobank has not had direct links to the field and clinical settings where the pre-acquisition and acquisition stages of biospecimens took place. Since it is important that tools and mechanisms are available to collect vital information on sample quality, from the point of acquisition to transportation to IARC, the Minimum Recommended Data set (MRD) was developed to collect standard data and provide information for the broad use of the stored samples, so as to increase sample value and utility and align the IARC Biobank with other international repositories. The MRD items are extracted from MIABIS (Minimum Information About Biobank Data Sharing: http://bbmri-wiki.wikidot.com/en:dataset) and SPREC[2] (Standard PREanalytical coding for biospecimens: defining the sample PREanalytical code). In implementing MRD, project, patient, and sample information are provided through the completion of a registration form for incorporation into SAMI. The original programme has been upgraded to deal with the heterogeneity of the Biobank samples already in storage, but it will require further upgrading to accommodate the attributes of the MRD.

### Sample Access Policy and revision of Material Transfer Agreement and shipment procedures

LSB contributes to IARC's mission to promote cancer research internationally by ensuring that the sample collections stored in the IARC Biobank are used for research in a way consistent with IARC's scientific goals and the applicable legal and ethical standard practices. Therefore, in collaboration with BSC, an Access Policy was developed to manage requests for collaborative studies using samples within the Biobank. Information about how to access the resources is available on the newly designed Biobank web site (http://ibb.iarc.fr/).

Revisions of the Material Transfer Agreement (MTA) and shipment procedures were initiated during the biennium, in collaboration with the Section of Support to Research (SSR), to bring the documents in line with WHO procedures. In addition, a central Biobank archive system has been created for referencing and archiving fully executed MTAs, informed consent templates, and documents related to shipping and sample exchange.

## Biobank services platform and quality assurance

The IARC Biobank maintains high-quality sample collections from international collaborative studies; provides safe storage facilities; acts as custodian for collections from collaborators in low- and middle-income countries (LMICs); and operates a service platform for sample retrieval, DNA extraction, and shipment of biological material to international collaborators worldwide, according to international guidelines and protocols. During the biennium, a total of 24 projects were conducted relating to 37 requests from international institutions, resulting in a total of more than 16 000 sample retrievals from liquid nitrogen, 16 000 DNA extractions, more than 18 800 DNA aliquots, and shipment of 94 parcels to 17 different destinations worldwide. In addition to activities in evidence-based research (Caboux *et al.*, 2012), emphasis has been on stringent quality control protocols being introduced in the pre-analytical processing services.

## Implementation of good laboratory practice tools, including standardization of laboratory standard operating procedures

Good laboratory practice (GLP) is an essential component of laboratory-based research. To facilitate research conducted at IARC, and in alignment with the Agency's mission of providing leadership in cancer research, several GLP tools were introduced. One is the Electronic Laboratory Notebook (ELN), which replaces the conventional paper notebook as the method of documenting experimental records. In addition to being a safe and secure method of documentation, ELN makes it possible to include multimedia (audio/video clips), electronic files, and hyperlinks to laboratory-based records. Also, captured information can be organized, shared, and easily searched in ELN.

Along the same lines was the introduction of a uniform format for the preparation of laboratory standard operating procedures across the Agency. The template ensures the accurate and up-to-date documentation of laboratory procedures to enhance the smooth running of laboratory activities.

**Figure 1. Activities in the IARC biobank pre-analytical services platform. © IARC/R. Dray.**

An Agency-wide service of checking and performing basic maintenance on laboratory pipettes was introduced to help researchers and technicians better control their experiments.

## Support of common laboratory platforms, facilities, and equipment

In line with IARC's 2010–2014 Medium-Term Strategy, which highlighted the paramount importance of performing interdisciplinary research, efforts have been made in the past two years to reinforce the interaction between laboratory-based and epidemiological research. Constant upgrading, updating, and acquisition of state-of-the-art scientific instruments are essential to support this effort.

IARC upgraded the Biobank platform in 2012 by replacing an ageing high-throughput DNA extractor and acquiring an electrophoresis and gel documentation system and DNA volume inspection system. During this same period, a DNA/RNA extractor and a digital slide scanner were obtained for the common laboratory facilities. To respond to the increasing workload associated with the development of large-scale projects, the Agency purchased four specialized robots for sample preparation and extraction to provide high-quality data at a reduced labour cost. IARC also funded the replacement of the ageing pyrosequencing system, an essential tool for the conduct of high-throughput DNA methylation analysis.

A reliable and efficient maintenance programme is now in place to ensure that equipment is kept in good condition for optimal use of all available resources. In addition, LSB maintains the common laboratory reagents and consumables store, which provides laboratory staff with easy access to commonly used items.

## Health and safety

Health and safety issues are addressed in close collaboration with the Staff Physician and the Occupational Health and Safety Committee (OHSC). LSB acts as technical adviser to OHSC and organizes regular training sessions to keep laboratory staff informed and to provide reminders on safety issues.

## Low- and middle-income countries biobank support

Even though there is a strong international trend towards the development of biobanking, there has been relatively little emphasis on this in LMICs, despite the opportunities for important research projects with partners from these regions. In LMICs, population cohorts and biobanking facilities are either underdeveloped or non-existent, and many of these countries have yet to develop standard sample management protocols and guidelines or to regulate

the exchange of biological samples for research purposes.

Therefore, IARC is exploring the development of an LMIC Biobank and Cohort Network (BCNet). The network will create opportunities for LMICs to work together in a coordinated and effective manner, and jointly address the shortfalls in biobanking infrastructure and other shared challenges such as ethical, legal, and societal issues. A situational analysis on infrastructure and facilities was conducted, followed by a BCNet International Working Group meeting in Lyon in September 2013, organized in collaboration with the United States National Cancer Institute Center for Global Health. Representatives from international societies, networks, and organizations, including ISBER, ESBB, RINC, NCRI, AORTIC, and $P^3G$, met with LMIC partners to identify potential areas and opportunities for cohort building, define specific aims and objectives for the network, determine short- and long-term goals, and advise IARC on next steps, including the specific role the Agency might play in this initiative.

IARC is also participating in some specific national developments in biobanking – for example, supporting initiatives in Egypt (Academy of Scientific Research and Technology, Cairo) and India (Tata Memorial Hospital, Mumbai). Site visits were conducted in 2012–2013 in support of the Agency's involvement in the planning of both these biobank projects.

**Figure 2. Participants at the BCNet International Working Group meeting. © IARC/R. Dray.**


## International collaborations

LSB participated in the following research activities: The Gambia Hepatitis Intervention Study, the EU-FP7-Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) effort (Fye *et al.*, 2013; Mendy *et al.*, 2013a), and the EU-FP7-EPIC-CVD study. LSB is a co-applicant in the recently funded EU-FP7 BBMRI-LPC Grant. The Agency is exploring the possibility of joining BBMRI-ERIC under the category of international organization as an observer.

IARC acts as the custodian for biological samples collected from three national recruitment sites involved in the PROLIFICA project. As a member of international biobanking societies, IARC has been asked to serve on the conference programme committees for ESBB (2012) and ISBER (2013) and is a member of the biorepository independent expert committee for the Wellcome Trust and NIH-funded Human Heredity and Health in Africa (H3Africa) Common Fund Biorepository programme. An important achievement during the biennium is the contribution as lead author for the biobanking and biosampling chapter in the *Handbook on Cancer Research in Africa.* This volume, which is commissioned by AORTIC, will be published at the end of 2013 and is being translated into French and Portuguese by WHO.

# Committees

## Laboratory Steering Committee (LSC)

The combination of laboratory-based and epidemiological research at IARC offers unique opportunities to conduct interdisciplinary research to identify the causes and mechanisms of cancer and translate these findings into better disease prevention. Laboratory research directly involves seven Groups or Sections at IARC (BMA, EGE, GCS, ICB, LSB, MMB, and MPA) and implements highly sophisticated techniques and methods. These techniques are as diverse as high-throughput DNA sequencing, single-nucleotide polymorphism (SNP) genotyping, mutation scanning, infectious agent detection, hormone and nutrient measurement, metabolome analysis, and biomolecular imaging.

The IARC Laboratory Steering Committee (LSC) oversees the IARC core laboratory facilities and advises the Director on their most efficient use. LSC meets every one or two months to discuss issues related to the acquisition or replacement of laboratory equipment, the development and renovation of laboratory facilities, the maximization of cost recovery, and the development of external collaborations.

Over the past two years, LSC has been instrumental in the installation of new mass spectrometers for the analysis of the human metabolome, the acquisition of a digital slide scanner for pathology confirmation of tumour material, the establishment of Electronic Laboratory Notebooks, the initiation of a new series of Laboratory Technical Watch seminars, the organization of regular meetings of the laboratory technical staff, and the launch of a new intranet site for laboratory activities.

## Biobank Steering Committee (BSC)

The number of biological specimens stored in IARC's Biobank facility is now close to 6 million, and this number continues to grow with our ongoing scientific activities. The IARC Biobank Steering Committee (BSC) oversees biobanking at the Agency and advises IARC's Director regarding the strategic development of the biobank and the advantages and challenges associated with the heterogeneous nature of IARC's biobanking needs.

The key development of BSC in the 2012–2013 biennium was the creation and implementation of a sample Access Policy for the Agency. The goal of this policy is to ensure that the Agency's samples are put to their best possible use in cancer research by providing clear guidelines through which qualified researchers are able to apply for access. BSC has also supported the day-to-day logistic challenges of biobanking at IARC and the continued implementation of IARC sample management systems, particularly debating the ideal data variable contents needed to standardize data across studies.

The IARC Ethics Committee (IEC) is composed of eight external members, one WHO member, and four IARC staff members.

IEC holds five meetings each year at IARC. In 2012–2013, IEC met eight times (up to July 2013). During these meetings, 60 applications were evaluated; 47 were approved after ethical review, eight were requested to resubmit or provide additional information before approval, four were given conditional approval pending submission of further information, and one study was not approved.

The IARC Ethics Advisory Group (EAV), composed of three international experts, supports the work of IEC by providing expertise in ethical issues when necessary. During the biennium, EAV was consulted on the management of incidental findings in genomic studies. Further information about IEC and EAV can be found on the IEC web site (http://ethics.iarc.fr/role.php).

## Occupational Health and Safety Committee (OHSC)

The IARC Occupational Health and Safety Committee (OHSC) focuses on issues in close collaboration with the Staff Physician and the IARC administration to provide a safe and comfortable work environment for all IARC staff.

Educational activities offered include a general safety introduction for new employees, 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.

In the 2012–2013 biennium, the main OHSC activities included: an inspection of all IARC radioactivity-based procedures by the French Autorité de Sûreté Nucléaire, which resulted in the application of new surveillance methods for radioisotope users; submission of a renewal request for our Genetically Modified Organisms authorization to the Commission de Génie Génétique of the Ministère de l'Enseignement Supérieur et de la Recherche; and an updated medical follow-up procedure for staff working in laboratories, adapted to their potential exposures.

# 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. The Agency's research programme is regularly reviewed by a Scientific Council. The Governing Council elects IARC's Director for a five-year term. The Council re-elected Dr Christopher Wild in May 2013 to serve for a second five-year term that will start on 1 January 2014.

## 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 to, among other things, advise the Director, make periodic evaluations of IARC's activities, make recommendations on the programme of permanent activities, and 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, both national and international. The regular budget level for the 2012–2013 biennium was approved in May 2011 at a level of €39 419 315.

# Participating States and Representatives at IARC Governing Councils
## Fifty-Fourth Session, 17–18 May 2012

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# IARC Staff Publications 2012–2013


Abbas S, Linseisen J, Rohrmann S *et al.* (2013a). Dietary intake of vitamin D and calcium and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Nutr Cancer,* 65:178–187. http://dx.doi.org/10.1080/01635581.2013.752018 PMID:23441605

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