

BIENNIAL REPORT



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2014–2015

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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INTRODUCTION



Dr Christopher Wild. © Jason Harris.

I AM PLEASED TO PRESENT THIS BIENNIAL REPORT, WHICH PROVIDES A SUMMARY OF THE ACTIVITIES OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) OVER THE PERIOD 2014–2015. THIS HAS BEEN A HISTORIC PERIOD, MARKING 50 YEARS SINCE THE CREATION OF THE ORGANIZATION IN 1965.

Several events marked the 50th anniversary, starting with a celebration at the City Hall in Lyon on 15 May 2015 in the presence of Her Royal Highness Princess Lalla Salma of Morocco, Her Royal Highness Princess Dina Mired of Jordan, and Mr Gérard Collomb, Mayor of Lyon, Senator, and President of the Lyon Métropole, together with other dignitaries. Agency personnel were joined by former IARC staff members as well as colleagues and collaborators from the city and region, and from across France and worldwide. The celebration was the occasion to launch a new publication, *International Agency for Research on Cancer: The First 50 Years, 1965–2015*, which charts the creation of IARC and the Agency's activities over the past five decades.

The 50th anniversary also marked a turning point in relation to several other key aspects of the Agency's future. The Governing Council adopted the IARC Medium-Term Strategy for 2016–2020, which is built on three major themes: describing the occurrence of cancer, understanding the causes, and evaluating preventive interventions and their implementation. Training new generations of cancer researchers remains as a core responsibility. Catalysing international collaboration is an underlying principle that is as relevant today as ever before.

In addition, the opportunities for interdisciplinary research, notably integrating laboratory science into epidemiological research, continue to grow. The 50th anniversary also coincided with a major commitment from the local and national governments of our host country, France, to provide a new, purpose-built centre for the Agency, confirming its presence in Lyon for the coming decades. Morocco became the first country from the African continent to join IARC as a Participating State, a further important step in expanding the geographical representation on the Governing Council as the demands on the Agency continue to grow along with the increasing cancer burden globally.

Fifty years on from 1965, IARC is an internationally recognized centre of excellence, respected and appreciated for its mission, its research, its independence, its leadership, and its cooperation. While some core commitments have remained, the Agency has constantly adapted to the changing knowledge about cancer and the evolving international cancer research landscape. Its unique role as the cancer agency of the World Health Organization (WHO) provides the foundation both to conduct novel research and to produce the authoritative evidence base for cancer control, which is provided by programmes such as the IARC Monographs, the IARC Handbooks of Cancer Prevention, the

WHO Classification of Tumours, and the global cancer statistics contained in *Cancer Incidence in Five Continents* and GLOBOCAN. The Agency's overall research portfolio has increasing relevance to policy, with implementation research becoming a theme across a number of the research Sections.

The current Report presents a spectrum of research contributing in different ways to cancer control. It is an ambitious programme in line with the ambitions expressed in the new IARC Medium-Term Strategy. However, through the list of collaborators recorded herein, the Report reveals the secret of how IARC is able to achieve so much with so little: by joining with the international cancer research community to achieve common goals.

Generosity in collaboration, working in partnership with others as equals, is surely one major reason why there remains a strong desire of scientists across the world to work with IARC. Coupled with excellent science, this is a powerful model for success – through cooperation rather than competition, through emphasis on the group rather than the individual. That much has not changed over the past 50 years and is unlikely to over the next 50.

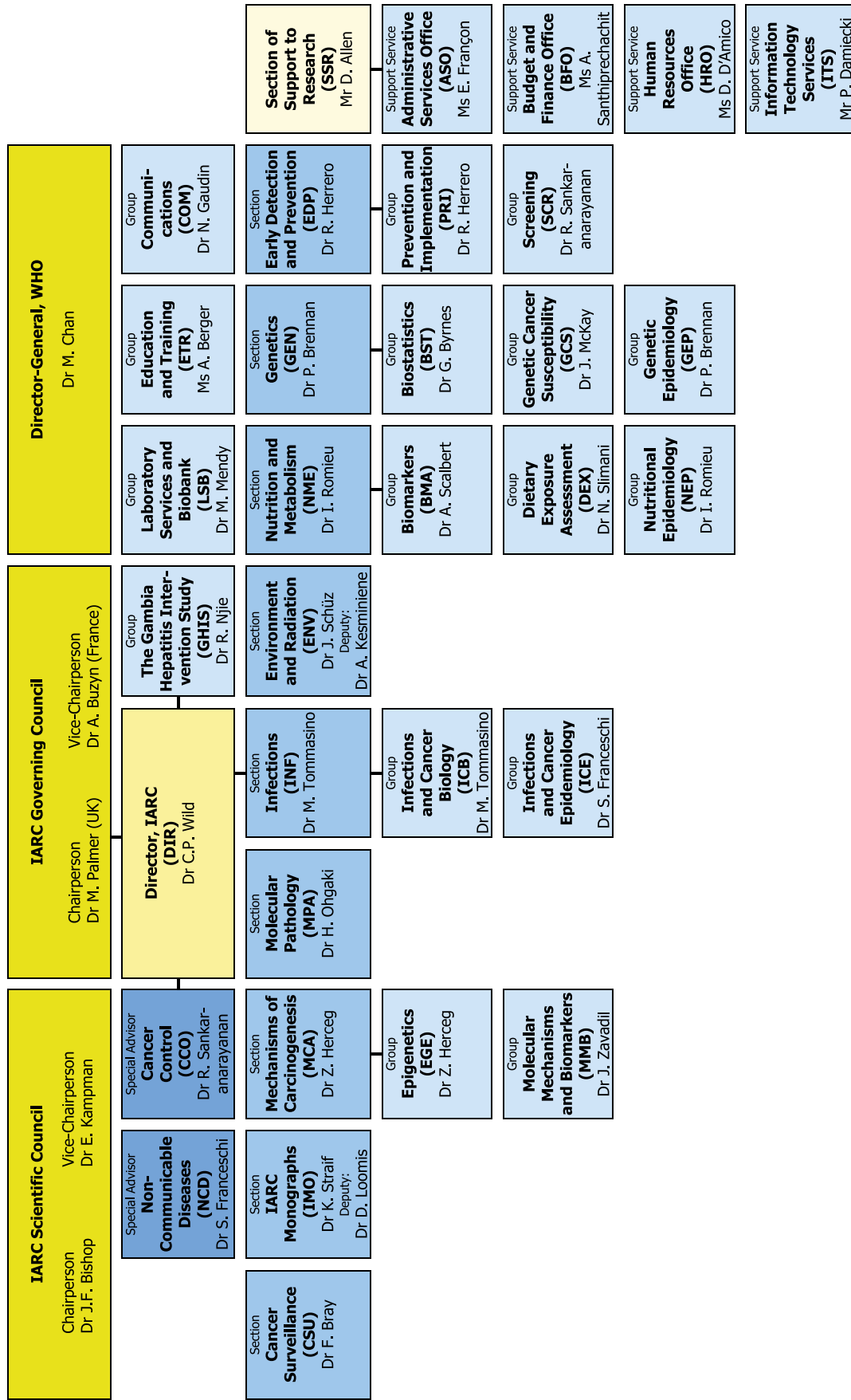
The Agency's year of celebrations will conclude with a major scientific conference in Lyon on 7–10 June 2016, structured around the main areas of IARC's research strategy: Global Cancer: Occurrence, Causes, and Avenues to Prevention. This conference will serve to launch the next phase of IARC's work.

In addition, it will feature the IARC "50 for 50" initiative, whereby the Agency will invite 50 future leaders in cancer research from low- and middle-income countries to attend the conference and participate in an associated programme of leadership training. We hope this will be an additional legacy of the vision shown by the leaders who, 50 years ago, had the foresight to create an international cancer agency to "fight for life".

I commend the work of all IARC personnel to you and trust that the contents of this Biennial Report provide a clear illustration of the value of the Agency's research as it seeks to fulfil its mission to reduce the global burden of cancer.

International Agency for Research on Cancer World Health Organization

1 July 2015





IARC MEDALS OF HONOUR

THE IARC MEDALS OF HONOUR ARE AWARDED TO ACKNOWLEDGE AND REWARD THE WORK OF SCIENTISTS WHOSE RESEARCH HAS MADE AN OUTSTANDING CONTRIBUTION TO ADVANCING OUR UNDERSTANDING OF THE BIOLOGY OR OF THE EPIDEMIOLOGY OF CANCER.



Her Royal Highness Princess Dina Mired of Jordan



Her Royal Highness Princess Lalla Salma of Morocco

On the occasion of the celebrations of the 50th anniversary of the establishment of IARC, on 15 May 2015, the IARC Medals of Honour were awarded to Her Royal Highness Princess Dina Mired of Jordan and to Her Royal Highness Princess Lalla Salma of Morocco. The awards were made in recognition of their outstanding leadership and advocacy for cancer control worldwide. Princess Dina Mired presented a speech on “Caring for cancer patients in developing countries”, and Princess Lalla Salma presented a speech on “La lutte contre le cancer en Afrique du Nord”.

The Agency also invites outstanding speakers to present the IARC Cancer and Society Lecture to address the ways in which cancer research has a broad relevance for society, in a style that is accessible to all IARC personnel, both scientists and non-scientists. Professor Sir Michael G. Marmot (University College London, United Kingdom) presented the second IARC Cancer and Society Lecture, on “Fair society, healthy lives”, on 4 February 2014 (World Cancer Day). Professor W. Philip T. James (London School of Hygiene & Tropical Medicine, United Kingdom) presented the third IARC Cancer and Society Lecture, on “Cancer prevention: the challenge of dietary change and obesity”, on 5 February 2015, again timed to mark World Cancer Day.

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, United Kingdom) – Avoidance of premature death
- 1996 Dirk Bootsma (Erasmus University, Rotterdam, The Netherlands) – DNA repair: maintaining nature's perfection
- 1997 Luca Cavalli-Sforza (Stanford University, USA) – Gènes, peuples, langues, cultures
- 1998 Charles Weissmann (University of Zurich, Switzerland) – Biology and transmission of prion diseases
- 1999 Jan Pontén (Uppsala University, Sweden) – Sunlight and skin cancer: new insights
- 2000 Richard Klausner (National Cancer Institute, Bethesda, USA) – The war on cancer: where we are and where research is taking us
- 2001 Oliver Brüstle (Institut für Neuropathologie, University of Bonn, Germany) – Embryonic stem cells: basic concepts and therapeutic applications
- 2002 Jeffrey Koplan (Centers for Disease Control, Atlanta, USA) – Bioterrorism and public health preparedness
- 2003 Paul Kleihues (Director, IARC) – Poverty, affluence and the global burden of cancer
- 2004 Umberto Veronesi (European Institute of Oncology, Milan, Italy) – Breast cancer management and care: current results and future perspectives
- 2005 David Lane (University of Dundee, United Kingdom) – p53 and human cancer: the next 25 years
- 2006 Georg Klein (Karolinska Institutet, 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 Center, 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
- 2013 Harold Varmus (National Cancer Institute, Maryland, USA) – Promoting the discovery and application of knowledge about cancer

RICHARD DOLL LECTURE

- 2004 Richard Doll (London, United Kingdom) – 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 etiology to prevention: the case of cervical cancer
- 2010 Julian Peto (London School of Hygiene & Tropical Medicine and the Institute of Cancer Research, United Kingdom) – 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) – The gastric precancerous cascade

IARC LECTURE

- 2005 Tadao Kakizoe (National Cancer Center, 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

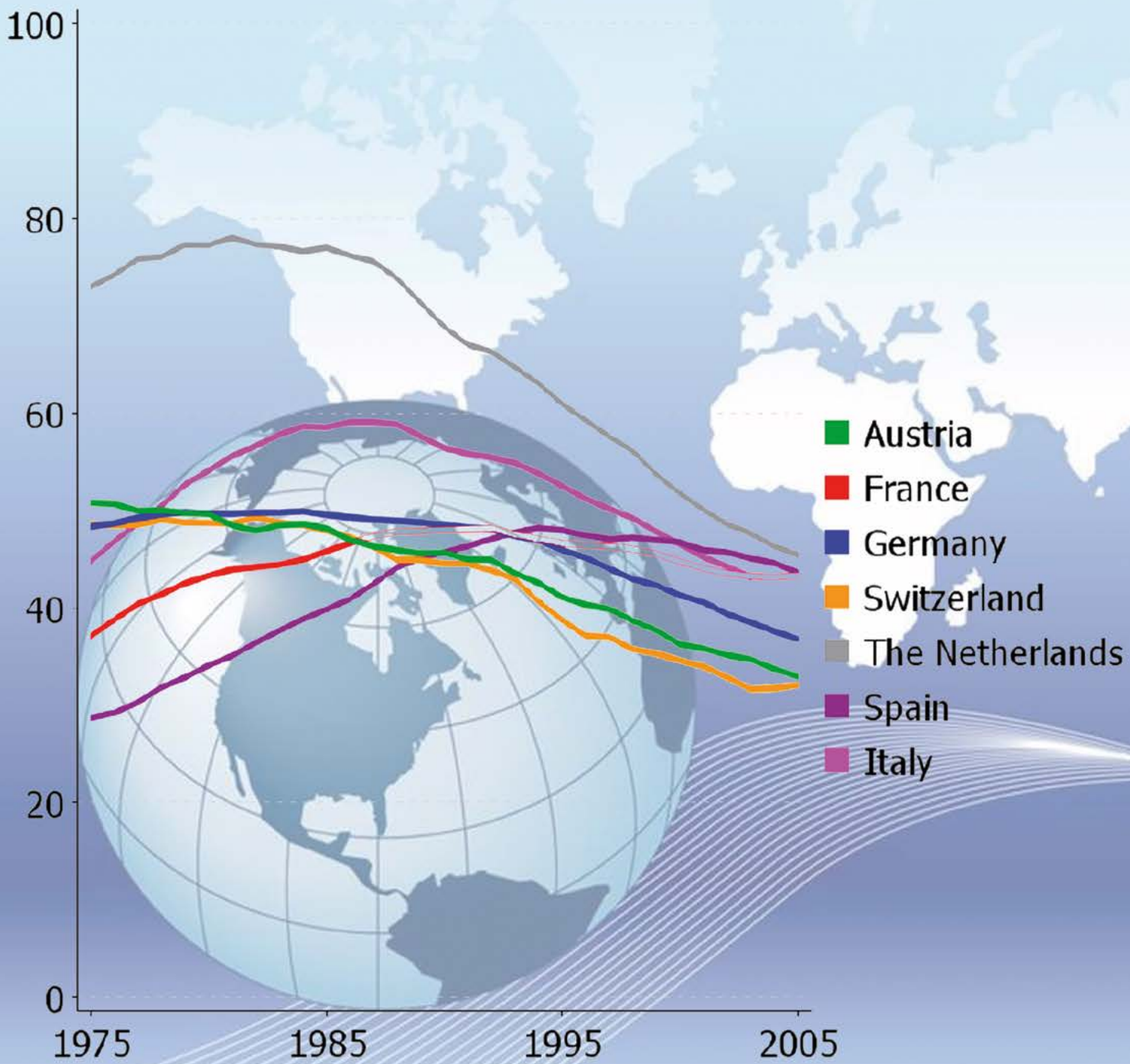
IARC CANCER AND SOCIETY LECTURE

- 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
- 2014 Michael G. Marmot (University College London, United Kingdom) – Fair society, healthy lives
- 2015 W. Philip T. James (London School of Hygiene & Tropical Medicine, United Kingdom) – Cancer prevention: the challenge of dietary change and obesity

IARC 50TH ANNIVERSARY CELEBRATIONS, 15 MAY 2015

Her Royal Highness Princess Dina Mired of Jordan (King Hussein Cancer Center, Jordan) – Caring for cancer patients in developing countries

Her Royal Highness Princess Lalla Salma of Morocco (Fondation Lalla Salma, Morocco) – La lutte contre le cancer en Afrique du Nord



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THE SECTION OF CANCER SURVEILLANCE (CSU) COMPILES, ANALYSES, INTERPRETS, AND DISSEMINATES GLOBAL CANCER INDICATORS THAT DOCUMENT THE CHANGING SCALE, PROFILE, AND IMPACT OF THE DISEASE WORLDWIDE. THREE CORE AREAS OF INTERRELATED ACTIVITY AIM TO SUPPORT NATIONAL AS WELL AS GLOBAL CANCER PLANNING.

CANCER REGISTRY SUPPORT AND DEVELOPMENT

Close cooperation with population-based cancer registries (PBCRs) worldwide is an essential aspect of the Section's work, and CSU serves as the secretariat for the International Association of Cancer Registries (IACR), working closely with the umbrella organization and individual registries in collaborative studies, including *Cancer Incidence in Five Continents* (C15). With cancer incidence set to rise to 20 million by 2025, and increasing by 70% in low- and middle-income countries (LMICs), cancer planning is critical but is currently impeded by the fact that only one third of countries (mostly high-income countries) are able to report high-quality cancer incidence data. The clear need for investment in PBCRs in LMICs led to the launch of the Global Initiative for Cancer Registry Development (GICR, <http://gicr.iarc.fr>). The goal is to inform cancer control through defined improvements in the coverage, quality, and usage of PBCRs worldwide. Operating to integrate activities at the global, regional, and national levels, partners share

Table 1. GICR IARC Regional Hubs

IARC Regional Hub (year established)	Area of coverage	Principal investigator	Main collaborators
Mumbai (2012)	South, East, and South-East Asia	Dr Rajesh Dikshit, Tata Memorial Hospital, India	Tata Memorial Hospital, Mumbai, India
African Cancer Registry Network (2012)	Sub-Saharan Africa	Dr Max Parkin, University of Oxford, United Kingdom	International Network for Cancer Treatment and Research
Izmir (2013)	North Africa, Central and West Asia	Dr Sultan Eser, Izmir Cancer Registry, Turkey	Cancer Control Department, Ministry of Health, Turkey Center for Global Health, National Cancer Institute, USA
Argentina (2014)	Latin America	Dr Graciela Abriata, National Cancer Institute, Argentina	National Cancer Institute, Buenos Aires, Argentina Brazil National Cancer Institute, Rio de Janeiro, Brazil Colombia National Cancer Institute, Bogotá, Colombia Uruguay Cancer Registry, Honorary Commission for the Fight Against Cancer, Montevideo, Uruguay
Caribbean (2015)	Caribbean	To be determined	Caribbean Public Health Agency, Port of Spain, Trinidad and Tobago Center for Global Health, Centers for Disease Control and Prevention, USA Center for Global Health, National Cancer Institute, USA
Pacific Islands (2015)	Oceania	To be determined	Cancer Institute New South Wales, Australia Cancer Council Victoria, Australia Cancer Council Queensland, Australia South Australian Health and Medical Research Institute, Australia

knowledge and adopt proven methods effectively across settings. Six IARC Regional Hubs have been established to deliver localized programmes of training, consultancy support, research, and advocacy (Table 1). Collectively, the IARC Regional Hubs target more than 6 billion people (85% of the world's population) in more than 150 underserved countries in Africa, the Americas, Asia, and Oceania. IARC Technical Publication No. 43, which is available in English, French, and Spanish, serves as a reference for health planners seeking to plan and develop PBCRs in LMICs.

During 2014–2015, several key activities of the GICR were achieved. Globally, the commitment of international partners to work together was secured, resulting in a unified solution to address disparities in cancer registration. The resulting GICR strategic plan was endorsed by the World Health Organization (WHO) as an official tool to support Member States in addressing cancer-related targets and indicators within the Global Monitoring Framework for the Prevention and Control of Noncommunicable Diseases (NCDs). Building on this, a group of initial focus countries have been identified to develop a mutual programme of activities

among GICR global partners to increase the effectiveness of capacity-building in cancer registration. Highlights of the regional and national activities are listed in Table 2; key GICR collaborative partners are listed below.

GLOBAL CANCER INDICATORS: DEVELOPMENT AND DISSEMINATION

CSU's two-tiered approach to global estimation involves validating estimates against recorded data of high quality where available and, where not, supporting in-country investments in data collection through the GICR, where feasible. The reporting of cancer statistics is generated through flagship projects, including CI5 and GLOBOCAN. After the computation of national estimates in 184 countries for 2012 and the launch of the GLOBOCAN 2012 website at the end of 2013, the 2014–2015 biennium has been devoted to documenting the source disparities, methods, and results (Ferlay et al., 2015a) and extending the use of GLOBOCAN to high-profile international collaborations. These include chapters in *World Cancer Report 2014*, the second edition of *The Cancer Atlas* (Jemal et al., 2014), and the cancer volume of the third edition of

Disease Control Priorities (DCP3) (Bray and Soerjomataram, 2015), alongside peer-reviewed articles, including the Lancet Oncology Commission on Global Radiotherapy (Atun et al., 2015) and a JNCI Commentary on the importance of integrating primary prevention into cancer control strategies worldwide (Bray et al., 2015b).

Validation exercises include a comparative study of estimates derived from the nine methods used in GLOBOCAN versus high-quality recorded incidence data in Norway. The results broadly emphasize the high performance of trends-based estimation approaches and the need for population-based data to accurately estimate incidence. The development of national estimates that capture the uncertainty in source information is also a priority for the next iteration of GLOBOCAN, and collaborative work with the University of Washington (USA) is ongoing; a study examining the derivation of credible intervals using Bayesian models in estimating national breast cancer in Europe is under way.

GLOBOCAN estimation relies heavily on the collaboration of PBCRs worldwide

Table 2. GICR activities by region, 2014–2015

Activity	Total number	Region [number] ^a			
		Africa	Asia	Caribbean	Americas
Site visits ^b	36	Algeria, Angola, Egypt, The Gambia, Madagascar, Malawi, Mali, Morocco, Namibia, Réunion, Senegal, Uganda, Zimbabwe [13]	Cambodia, India, Indonesia, Islamic Republic of Iran, Kyrgyzstan, Lao People's Democratic Republic, Philippines, Turkey, West Bank and Gaza Strip [9]	Aruba, Barbados, Grenada, Trinidad and Tobago [4]	Argentina, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru [10]
Courses	28	Côte d'Ivoire (Abidjan, August 2014); Egypt (Cairo, September 2014); Ethiopia (Addis Ababa, August 2015); Guinea (Conakry, August 2014); Kenya (Eldoret, March 2015); Kenya (Nairobi, August 2015); Mozambique (Beira, July 2014); Mozambique (Maputo, July 2014); Namibia (Windhoek, June 2014); Namibia (Windhoek, February 2015); Sudan (Khartoum, November 2014); Uganda (Kampala, June 2014) [12]	Cambodia (Phnom Penh, February 2014); China (Shanghai, September 2014); India (Chennai, March 2014); India (Chennai, October 2014); India (Mumbai, July 2014); Kazakhstan (Astana, September 2014); Myanmar (Yangon, September 2014); Russian Federation (Saint Petersburg, September 2015); Thailand (Bangkok, June 2015); Turkey (Ankara, October 2014); West Bank and Gaza Strip (Gaza City, July 2015); West Bank and Gaza Strip (Ramallah, July 2015) [12]	—	Canada (Ottawa, June 2014); Chile (Santiago, July 2014); El Salvador (San Salvador, October 2014); Panama (Panama City, November 2015) [4]
Signed agreements ^c	17	Congo, Côte d'Ivoire, Kenya, Mauritius, Mozambique, Senegal, South Africa, Uganda, Zimbabwe [9]	India, Islamic Republic of Iran, Turkey [3]	—	Argentina, Colombia, Guatemala, Mexico, Uruguay [5]

^a Classified into continents according to IARC Regional Hub involvement; activities in Oceania will commence in 2016.

^b Only initial visits to countries are listed.

^c Includes agreements signed by the African Cancer Registry Network to provide the IARC Regional Hub for Sub-Saharan Africa.

and the high-quality registry data compiled in successive CI5 volumes. Volume X, released in late 2014, comprises cancer incidence data from 290 registries in 68 countries for 2003–2007. The increase in the number of high-quality PBCRs included in Volume X is offset by challenges in ensuring that data from more registries in LMICs are accepted in subsequent volumes. A recent paper documented the status of PBCRs worldwide (linking the registry capacity-building approaches of the GICR) and the techniques used in CI5 to evaluate quality (Bray et al., 2015a). The paper also highlighted the variability in cancer risk: a ratio of 3 to 45 was observed in the lowest versus highest rates for specific cancers worldwide (Figure 1). The call for data for the next volume (Volume XI) has been launched.

Childhood cancer surveillance is a major component of CSU's activities, and preparation of the third volume of *International Incidence of Childhood Cancer* (IICC3, <http://iicc.iarc.fr/>) is

nearing completion. Data on cancer incidence in children and adolescents (ages 0–19 years) are being compiled in collaboration with more than 350 cancer registries. A European study undertaken within the EURO COURSE project has estimated population coverage of children in the European Union by PBCRs at 80%; the growing formation of paediatric cancer registries was noted, as well as a merging of existing registries (Steliarova-Foucher et al., 2015a).

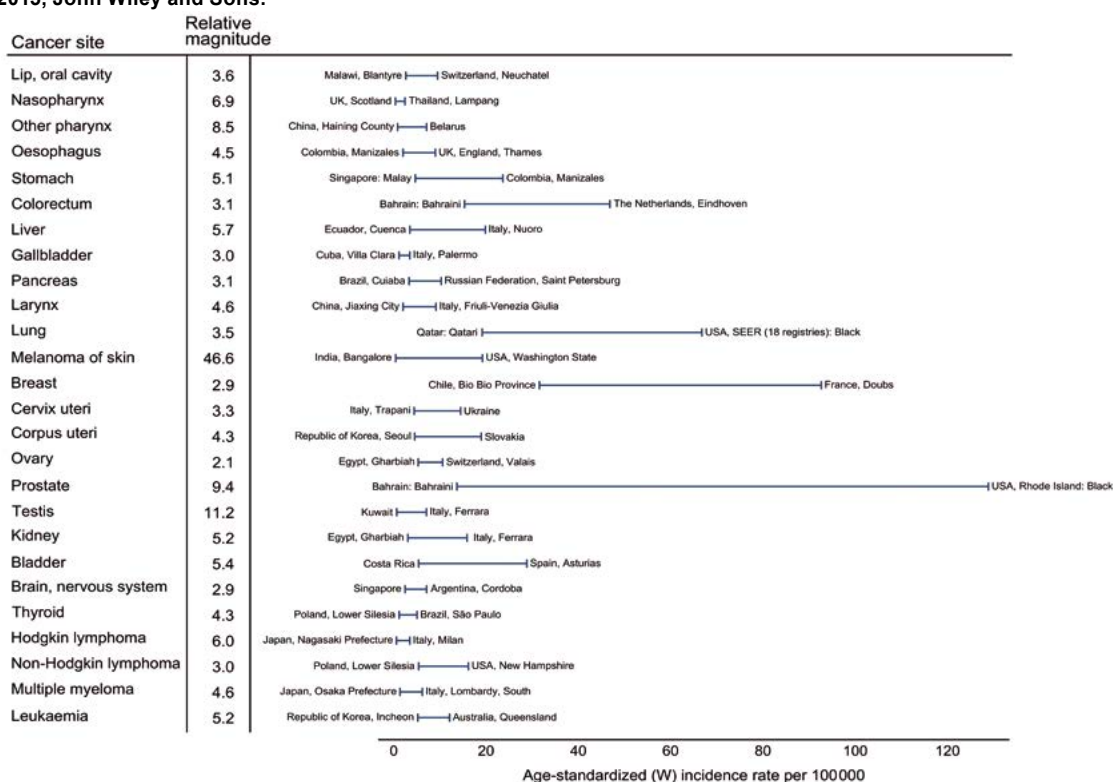
In supporting the development of cancer survival statistics in LMICs for benchmarking purposes, CSU is developing a third volume of the benchmark series *Cancer Survival in Africa, Asia, the Caribbean and Central America* (SURVCAN-3). Linked to local capacity-building, Module 1 of the IARC Summer School in 2015 focused on the training of registry staff in LMICs wishing to develop survival statistics at their registry (Figure 2). Finally, the Global Cancer Observatory (GCO) is under development by CSU following the

recruitment of a web programmer in 2015. The GCO will serve as an interactive, user-friendly, and data-driven online interface to examine and interpret global and regional cancer statistics based on the key databases held at CSU.

DESCRIPTIVE EPIDEMIOLOGY OF CANCER: CORE ACTIVITIES AND INNOVATION

A diverse set of research collaborations aim to interpret the changing magnitude and the transitional nature of cancer profiles. As well as the continued provision of global and regional cancer statistics with collaborators worldwide based on the GLOBOCAN estimates (Parkin et al., 2014; Torre et al., 2015), data from successive CI5 volumes continue to provide critical insights into changing trends and profiles of specific cancers, their determinants, and priorities for cancer control. Ad hoc collaborative studies have been published that describe the regional and global trends in, for example, female breast cancer (DeSantis et al., 2015),

Figure 1. Absolute and relative global variations in age-standardized incidence rates (world) of registry populations included in CI5 Volume X. The variability in the age-standardized rates for 27 cancer sites is according to the 10th and 90th percentiles for males, other than for female breast and three female-specific cancers (cervix uteri, corpus uteri, and ovary). Reprinted with permission from Bray et al. (2015a). Copyright © 2015, John Wiley and Sons.



testicular cancer (Le Cornet et al., 2014; Trabert et al., 2015; Znaor et al., 2014, 2015a), bladder cancer (Chavan et al., 2014), renal cell carcinoma (Znaor et al., 2015b, 2015c), and bone cancer (Valery et al., 2015).

More specific studies in collaboration with the Infections and Cancer Epidemiology Group (ICE) have looked at international

trends in thyroid cancer incidence and mortality in light of enhanced surveillance of the thyroid gland (Vaccarella et al., 2015), as well as the impact of screening on the burden of cervical cancer in the Nordic countries (Vaccarella et al., 2014). In the latter study, models predicted that up to 49% of the expected cervical cancer cases may have been prevented by the introduction of screening in the

late 1960s and early 1970s (Figure 3). In a study describing the major decrease in incidence rates of upper urinary tract cancer in Australia in 1983–2007, Antoni et al. hypothesized that the ban on phenacetin, an analgesic that was marketed widely for pain relief until the late 1970s, explained the observed decline (Antoni et al., 2014).

Approaches to global cancer surveillance research include the assessment of cancer in Indigenous peoples (Moore et al., 2014a, 2014b), who have disproportionately worse health and lower life expectancy than their non-Indigenous counterparts in high-income countries. As part of an IARC-Australia Fellowship, a recent study compared, for the first time, the cancer burden among Indigenous populations in Australia, New Zealand, Canada, and the USA, based on incidence data derived from PBCRs (Moore et al., 2015). Of note were the high rates of lung cancer among Indigenous men in all Australian regions, and in Alberta, Canada, and in the USA among Alaska Natives. Among women, lung cancer rates were considerably higher in Māori women in New Zealand and in

Figure 2. IARC Summer School 2015, Module 1: Cancer Survival Methods for Cancer Registries. © IARC/Roland Dray.

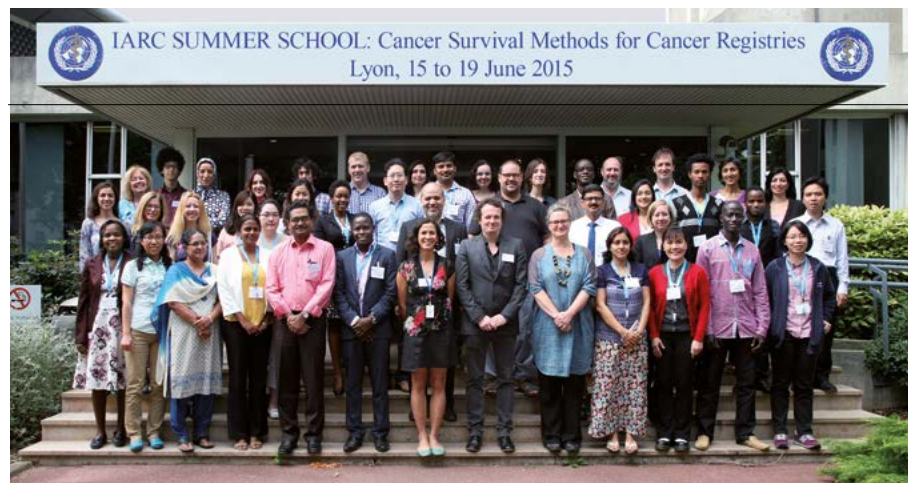
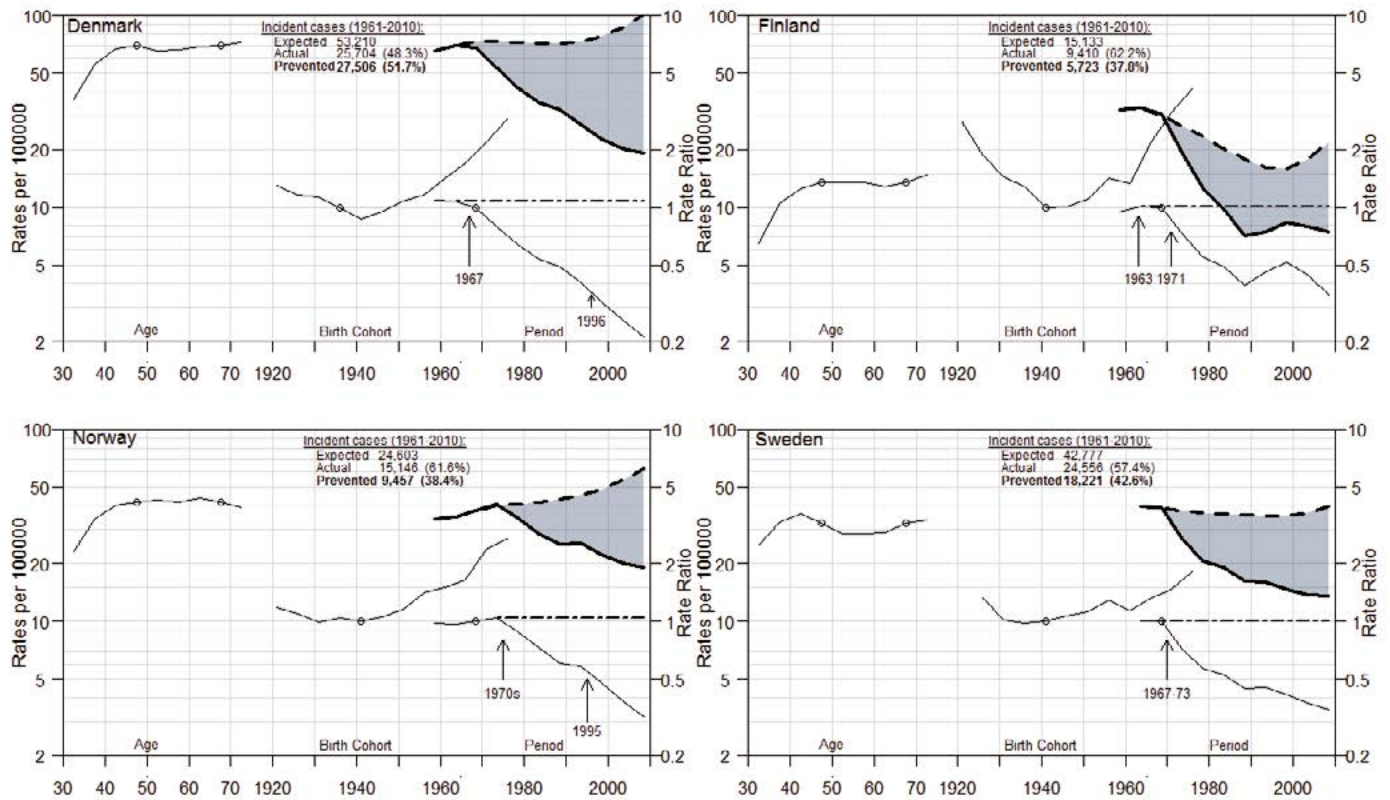


Figure 3. Effect of age, period, and cohort on observed and projected rates of incident cervical cancer in the Nordic countries. Reprinted with permission from Vaccarella et al. (2014).



Alaska Natives, whereas cervical cancer incidence was higher among Indigenous women in most areas.

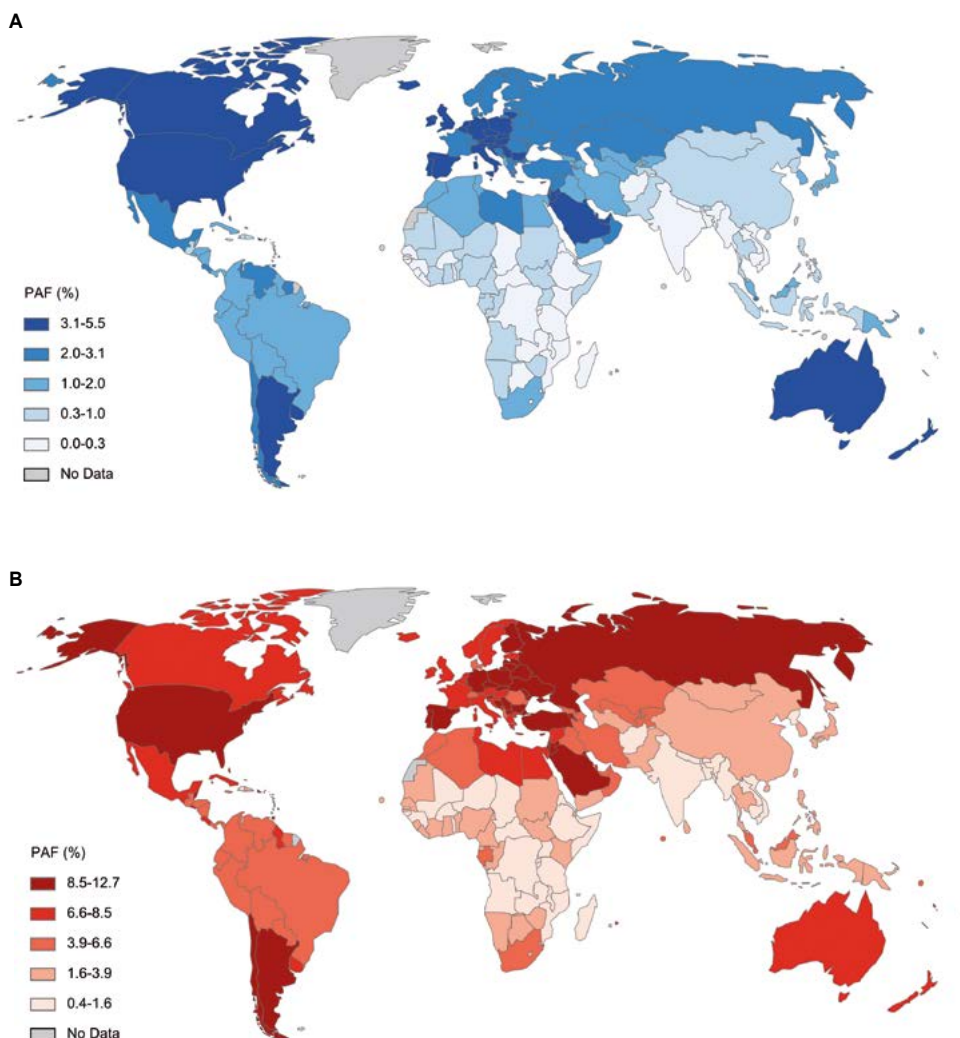
Studies also aim to increasingly capture the broader context of NCDs, as well as the continuum of cancer progression from a healthy state to end of life. Recent methodological research areas include the systematic development of population attributable fractions (PAFs) for various major risk determinants of cancer. An estimated half a million new cancer cases (or 3.6% of all new cancer cases) could be attributed to excess body weight (Figure 4) (Arnold et al., 2015a); further work will assess the time-specific risk of cancer after cumulative exposure to excess body weight over the life course. Worldwide PAF estimates for tobacco, alcohol, infection, and

other major risk factors are under development. CSU is also embarking on major PAF projects in France (partnering with Institut national du Cancer [INCa]) and the Eastern Mediterranean region (with the WHO Regional Office for the Eastern Mediterranean) that will estimate the proportion of cancers attributable to key lifestyle and environmental determinants. These projects rely heavily on collaboration and multidisciplinary groups of experts.

Several studies link the changing demographic, epidemiological, and cancer transitions to the evolving NCD agenda. For example, an average loss of life expectancy of 2.4 years in men and 1 year in women, associated with tobacco smoking, has recently been reported. With rates of cardiovascular

disease declining due to the success of preventing and treating the disease, cancer contributed to a larger portion of the total mortality in 1980–2010. Hanly et al. have examined the societal loss related to premature mortality from cancer among the workforce of Europe (Hanly et al., 2015). The average cost of productivity lost due to premature mortality was estimated at 0.58% of the 2008 European gross domestic product, highest in central and eastern Europe (0.81%) and lowest in northern Europe (0.51%). The analysis highlighted the potential advantages of implementing prevention strategies for stomach, pancreatic, and cervical cancer and melanoma of the skin, and of improving access to treatment for Hodgkin lymphoma and testicular cancer.

Figure 4. Population attributable fraction (PAF) of new cancer cases in 2012 due to excess body mass index in (A) men and (B) women, by country. Reprinted from Arnold et al. (2015a). Copyright 2015, with permission from Elsevier.



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THE FIRST STEP IN CANCER PREVENTION IS TO IDENTIFY THE CAUSES OF HUMAN CANCER. THE IARC MONOGRAPHS PROGRAMME ([HTTP://MONOGRAPHS.IARC.FR/](http://monographs.iarc.fr/)) IS AN INTERNATIONAL, INTERDISCIPLINARY APPROACH TO CARCINOGENIC HAZARD IDENTIFICATION. ITS PRINCIPAL PRODUCT IS THE SERIAL PUBLICATION OF THE IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS, WHICH BEGAN IN 1971 IN ACCORDANCE WITH ONE OF THE FUNDAMENTAL MISSIONS OF THE AGENCY: TO PREPARE AND DISTRIBUTE AUTHORITATIVE INFORMATION ON HUMAN CANCER AND ESPECIALLY ON ITS CAUSES AND PREVENTION.

Each Monograph consists of a comprehensive, critical summary and review of the published scientific literature and an evaluation of the overall evidence of carcinogenicity to humans. The IARC Monographs are a worldwide endeavour that has involved more than 1300 scientists from more than 50 countries. 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 expertise in the topic. 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. More than 100 of these agents have been identified as carcinogenic to humans (Group 1), and

more than 350 as probably carcinogenic or possibly carcinogenic to humans (Groups 2A and 2B).

The IARC Monographs have evolved into the World Health Organization's encyclopaedia on the roles of environmental agents in human cancer causation. National and international health agencies use the Monographs as a source of scientific information, and as scientific support for their actions to prevent exposure to these agents. A recent example was the reference to the Monographs in developing the fourth edition of the European Code Against Cancer. Individuals, too, use the conclusions from the Monographs to inform their choices to reduce their exposure to potential carcinogens. In this way, the IARC Monographs contribute to cancer prevention and the improvement of public health.

In 1995, the IARC Handbooks of Cancer Prevention were launched to complement the IARC Monographs by providing evaluations of approaches to cancer prevention. The same rigorous procedures of critical review and evaluation as for the IARC Monographs are used. Evaluations have included chemopreventive agents, preventive actions, effectiveness of screening, and effectiveness of tobacco control. The IARC Handbooks of Cancer Prevention programme has now been relaunched, with a focus on primary and secondary prevention.

ADVISORY GROUP TO RECOMMEND
PRIORITIES FOR THE IARC
MONOGRAPHS DURING 2015–2019
(7–9 APRIL 2014)

An Advisory Group of 21 scientists from 13 countries met at IARC in April 2014 to recommend evaluation topics for 2015–2019 and to discuss strategic matters for the IARC Monographs Programme. The Advisory Group considered responses to a call for nominations on the IARC website and recommended a broad range of agents and exposures with high or medium priority (Table 1); IARC will use this advice in making decisions on agents for future evaluations.

Table 1. Agents recommended for evaluation by the IARC Advisory Group with high priority

Acrylamide, Furan, 5-Hydroxymethyl-2-furfural
2-Amino-4-chlorophenol, 2-Chloronitrobenzene, 4-Chloronitrobenzene, 1,4-Dichloro-2-nitrobenzene, 2,4-Dichloro-1-nitrobenzene
Aspartame and sucralose
Bisphenol A
1-Bromopropane
Carbon nanotubes, multi-walled
Beta-carotene
3-Chloro-2-methylpropene
Coffee
Dietary iron and iron used as supplements or for medical purposes
Dimethylformamide
<i>N,N</i> -Dimethyl- <i>p</i> -toluidine
Disinfected water used for drinking, showering, bathing, or swimming
Electronic cigarettes and nicotine
Ethyl acrylate
Ethyl tertiary butyl ether (ETBE), Methyl tertiary butyl ether (MTBE), <i>tert</i> -Butyl alcohol (TBA)
Hot mate drinking
Human cytomegalovirus (HCMV)
Indium-tin oxide
Isobutyl nitrite
2-Mercaptobenzothiazole
Obesity and overweight
Opium
Pesticides (including Carbaryl, Diazinon, Lindane, Malathion, Pendimethalin, Permethrin)
Phenyl and octyl tin compounds
<i>ortho</i> -Phenylenediamine dihydrochloride
Physical inactivity and sedentary work
Red and processed meats
Shiftwork
Styrene
Tetrabromobisphenol A (TBBPA)
Tungsten
Welding and welding fumes

In addition, the Advisory Group endorsed the current system of expert reviews with strict management of conflict of interests; encouraged the Secretariat to explore the use of systematic review tools to further increase transparency and efficiency; supported recent recommendations of a separate Advisory Group on Quantitative Risk Characterization that the Monographs could progressively include exposure–response relationships, particularly from epidemiological studies, as a basis for estimates of global cancer burden by

IARC; recognized the need for systematic identification of mechanistic data, with transparent selection of publications and inclusion of high-throughput and high-content data streams, to focus on clear elucidation of mechanistic processes; and recommended exploration of additional opportunities to address cancer risk in low- and middle-income countries, including enhanced retrieval of relevant exposure data for Monographs and increased dissemination of pertinent evaluations (Straif et al., 2014).

VOLUME 110: PERFLUORO-OCTANOIC ACID, TETRAFLUOROETHYLENE, DICHLOROMETHANE, 1,2-DICHLOROPROPANE, AND 1,3-PROPANE SULTONE (3–10 JUNE 2014)

In June 2014, a Working Group assessed the carcinogenicity of perfluoro-octanoic acid (PFOA), tetrafluoroethylene (TFE), dichloromethane (DCM), 1,2-dichloropropane (1,2-DCP), and 1,3-propane sultone (1,3-PS). 1,2-DCP was classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* that exposure causes cancer of the biliary tract. The most important human evidence came from studies of workers in a small offset printing plant in Osaka, Japan, with a very high risk of cholangiocarcinoma. The Working Group classified DCM as *probably carcinogenic to humans* (Group 2A), based on *limited evidence* in humans for biliary tract cancer and non-Hodgkin lymphoma and *sufficient evidence* in experimental animals. TFE was upgraded from *possibly carcinogenic to humans* (Group 2B) to *probably carcinogenic to humans* (Group 2A), based on *inadequate evidence* in humans and *sufficient evidence* in experimental animals with unusual results (neoplasms at multiple sites and with very high incidence observed in exposed rodents of both sexes, including liver haemangiosarcoma, hepatocellular carcinoma, and histiocytic sarcoma in mice, and renal cell adenoma or carcinoma [combined], hepatocellular carcinoma, mononuclear cell leukaemia, and the rare liver haemangiosarcoma in female rats). 1,3-PS was classified as *probably carcinogenic to humans* (Group 2A), based on *inadequate evidence* in humans and *sufficient evidence* in experimental animals with a mechanistic upgrade supported by strong evidence for genotoxicity. PFOA was classified as *possibly carcinogenic to humans* (Group 2B), based on *limited evidence* in humans for testicular and kidney cancer and *limited evidence* in experimental animals (Benbrahim-Tallaa et al., 2014).

VOLUME 111: FLURO-EDENITE, SILICON CARBIDE FIBRES AND WHISKERS, AND CARBON NANOTUBES (30 SEPTEMBER–7 OCTOBER 2014)

In October 2014, a Working Group reviewed the carcinogenicity of fluoro-

edenite, silicon carbide (SiC) fibres and whiskers, and carbon nanotubes (CNTs), including single-walled and multi-walled types (SWCNTs and MWCNTs). Fluoro-edenite fibrous amphibole was classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* in humans that it causes mesothelioma and *sufficient evidence* in experimental animals. SiC fibres are by-products of the manufacture of SiC particles by the Acheson process; SiC whiskers are produced by other processes. Occupational exposures associated with the Acheson process were classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* in humans that they cause lung cancer. Fibrous SiC was classified as *possibly carcinogenic to humans* (Group 2B), based on *limited evidence* in humans that it causes lung cancer and *inadequate evidence* in experimental animals. SiC whiskers were upgraded from *possibly carcinogenic to humans* (Group 2B) to *probably carcinogenic to humans* (Group 2A), based on *inadequate evidence* in humans, *sufficient evidence* in experimental animals, and consideration of their physical properties.

There was no epidemiological study on CNTs. Regarding carcinogenicity in experimental animals, there was *sufficient evidence* for MWCNT-7, *limited evidence* for two types of MWCNTs with dimensions similar to MWCNT-7, and *inadequate evidence* for SWCNTs. MWCNT-7 was classified as *possibly carcinogenic to humans* (Group 2B), and SWCNTs and MWCNTs excluding MWCNT-7 were categorized as *not classifiable as to their carcinogenicity to humans* (Group 3) (Grosse et al., 2014).

HANDBOOK VOLUME 15: BREAST CANCER SCREENING (11–18 NOVEMBER 2014)

Breast cancer is the leading cancer in women worldwide, and the potential role of primary prevention is limited because most risk factors are directly linked with endogenous hormone levels and reproductive factors. Therefore, secondary prevention is a priority. In addition to breast cancer screening by mammography, clinical examination, and self-examination, which were already evaluated in 2002, the Working Group for this Handbook extended its review to

non-mammographic imaging techniques such as magnetic resonance imaging (MRI), digital breast tomosynthesis (or 3D mammography), breast-specific positron emission tomography, ultrasound as an adjunct to mammography for women with dense breasts, and computer-assisted diagnosis in combination with digital mammography; also, the effectiveness of screening high-risk women was evaluated.

Based on available data, there is sufficient evidence for the effectiveness of mammography screening in women aged 50–74 years. While the evidence for overdiagnosis is also sufficient, overall the Working Group concluded that there is a net benefit in screening women aged 50–69 years. Data on breast self-examination remain unconvincing. In contrast, clinical breast examination showed sufficient evidence for shifting the stage distribution of tumours detected towards a lower stage. Of all the new technologies considered, sufficient evidence was reached only for an increased detection rate, mostly of invasive tumours, with adjunct tomosynthesis compared with mammography alone. MRI as an adjunct to mammography in high-risk women with a *BRCA1* or *BRCA2* mutation provided an increased sensitivity but decreased specificity (Lauby-Secretan et al., 2015a).

VOLUME 112: TETRACHLORVINPHOS, PARATHION, MALATHION, DIAZINON, AND GLYPHOSATE (3–10 MARCH 2015)

In March 2015, a Working Group of 17 experts from 11 countries reviewed the carcinogenicity of five organophosphate pesticides. Four insecticides (tetrachlorvinphos, parathion, malathion, and diazinon) and glyphosate, the most widely used herbicide worldwide, were evaluated. The insecticides tetrachlorvinphos and parathion were classified as *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence* in experimental animals. The insecticides malathion and diazinon and the herbicide glyphosate were classified as *probably carcinogenic to humans* (Group 2A). For malathion and glyphosate, the evidence in experimental animals was *sufficient* and the evidence in humans was *limited*. For diazinon, *limited evidence* was found in both experimental animals and humans. The

limited evidence in humans supporting these three Group 2A classifications comprised reports of increased cancer risks from occupational cohort and case–control studies in Canada, Sweden, and the USA. The large Agricultural Health Study reported positive associations for malathion (prostate cancer) and diazinon (non-Hodgkin lymphoma subtypes, leukaemia, and lung cancer). An increased risk of non-Hodgkin lymphoma with glyphosate use was reported in multiple case–control studies but was not seen in the Agricultural Health Study. Strong mechanistic evidence, particularly for genotoxicity and oxidative stress, was found for malathion, diazinon, and glyphosate. Together with the *limited evidence* of human carcinogenicity for diazinon, this strong mechanistic evidence formed the basis for the Group 2A classification. The mechanistic evidence independently supported the Group 2A classifications of malathion and glyphosate (Guyton et al., 2015).

VOLUME 113: DDT, LINDANE, AND 2,4-D (2–9 JUNE 2015)

In June 2015, a Working Group of 26 experts from 13 countries evaluated the carcinogenicity of the insecticides dichlorodiphenyltrichloroethane (DDT) and lindane and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). DDT was heavily used for insect control in agriculture and public health, but current use is largely restricted to malaria control. DDT was classified as *probably carcinogenic to humans* (Group 2A), based on *limited evidence* in humans and *sufficient evidence* in experimental animals.

Epidemiological studies found positive associations between exposure to DDT and non-Hodgkin lymphoma, testicular cancer, and liver cancer. Lindane was formerly used for insect control, but its use is now largely banned. Lindane was classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* in both humans and experimental animals. Epidemiological studies of agricultural workers exposed to lindane showed a 60% increased risk of non-Hodgkin lymphoma. 2,4-D is a high production volume chemical that has been used since the 1940s to control weeds in agriculture, forestry, and urban settings. 2,4-D was classified as *possibly carcinogenic to humans* (Group 2B), based on *inadequate evidence* in humans and *limited evidence* in experimental animals. Experimental studies provided strong evidence that 2,4-D induces oxidative stress and moderate evidence that 2,4-D causes immunosuppression. However, epidemiological studies did not find strong or consistent increases in cancer risk in relation to 2,4-D exposure (Loomis et al., 2015).

VOLUME 114: CONSUMPTION OF RED MEAT AND PROCESSED MEAT (6–13 OCTOBER 2015)

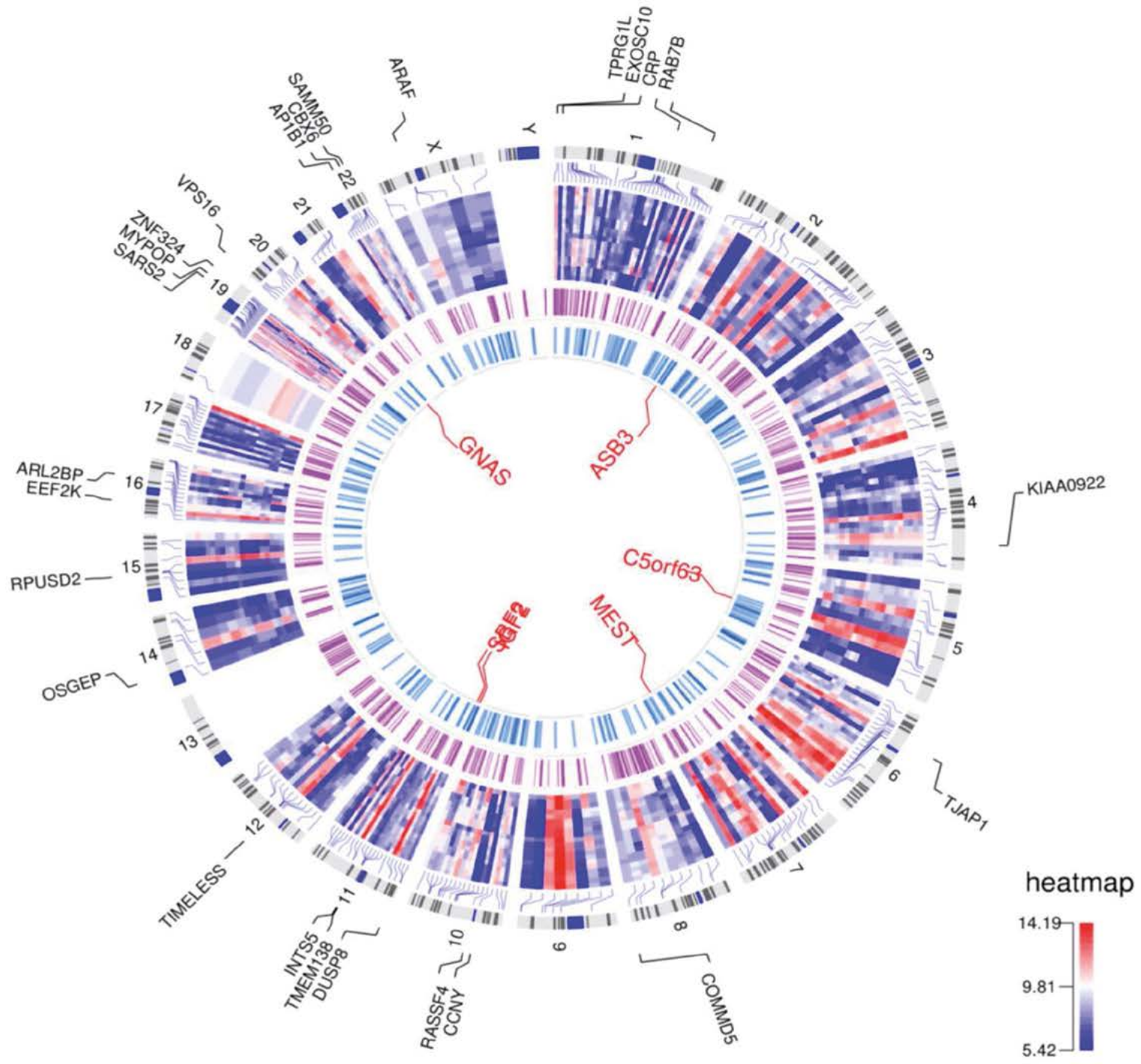
In October 2015, a Working Group assessed the carcinogenicity of the consumption of red meat and processed meat. Red meat refers to unprocessed mammalian muscle meat (e.g. beef, veal, pork, and lamb), including that which may be minced or frozen. Processed meat refers to meat that has been transformed through salting, curing, fermentation,

smoking, or other processes to enhance flavour or improve preservation. Meat curing and smoking can result in the formation of carcinogenic chemicals, including *N*-nitroso compounds (NOCs) and polycyclic aromatic hydrocarbons (PAHs). High-temperature cooking by pan-frying, grilling, or barbecuing produces high amounts of carcinogens, including heterocyclic aromatic amines (HAAs) and PAHs.

The Working Group assessed more than 800 epidemiological studies, including large cohorts in many countries on several continents and in populations with diverse ethnicities and diets. A meta-analysis of colorectal cancer in 10 cohort studies reported a statistically significant dose–response relationship with a 17% increased risk (95% confidence interval [CI], 1.05–1.31) per 100 g/day of red meat and an 18% increased risk (95% CI, 1.10–1.28) per 50 g/day of processed meat. The Working Group classified consumption of processed meat as *carcinogenic to humans* (Group 1), based on *sufficient evidence* for colorectal cancer. A positive association was found between consumption of processed meat and stomach cancer. Consumption of red meat was classified as *probably carcinogenic to humans* (Group 2A), based on substantial epidemiological data showing high *limited evidence* for colorectal cancer and on strong mechanistic evidence. Consumption of red meat was also positively associated with pancreatic cancer and with prostate cancer.

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National Institute of Environmental Health Sciences, National Institutes of Health, USA
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SECTION OF MECHANISMS OF CARCINOGENESIS (MCA)

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THE SECTION OF MECHANISMS OF CARCINOGENESIS (MCA) CONDUCTS STUDIES AIMED AT ELUCIDATING MOLECULAR MECHANISMS BY WHICH ENVIRONMENTAL EXPOSURES INDUCE GENETIC AND EPIGENETIC ALTERATIONS AND DEREGULATE MOLECULAR PATHWAYS CRITICAL FOR CANCER DEVELOPMENT AND PROGRESSION, THUS ENHANCING THE EVIDENCE BASE DIRECTLY RELEVANT TO STUDIES OF CANCER CAUSATION AND PREVENTION. EMPHASIS IS PLACED ON EVENTS THAT PRECEDE OR DRIVE TUMOUR INITIATION AND PROGRESSION. KEY MCA STRATEGIES INCLUDE INNOVATIVE RESEARCH AND THE DEVELOPMENT OF GENOMIC/EPIGENOMIC AND SCREENING METHODOLOGIES AND BIOINFORMATICS RESOURCES THAT ARE APPLICABLE TO EXPERIMENTAL MODELS AND BIOBANKS ASSOCIATED WITH POPULATION-BASED AND EPIDEMIOLOGICAL STUDIES. MCA ALSO CONTRIBUTES TO TRANSLATIONAL STUDIES, THROUGH THE DISCOVERY OF MECHANISM-BASED BIOMARKERS OF EXPOSURE, EARLY DETECTION, AND RISK STRATIFICATION. MCA STUDIES ARE INTERDISCIPLINARY IN NATURE, AND THE SYNERGISTIC COLLABORATIONS WITH OTHER IARC LABORATORY-BASED SCIENTISTS AND EPIDEMIOLOGISTS AS WELL AS EXTERNAL GROUPS ADVANCE MAJOR IARC PROGRAMMES. THE SECTION COMPRISES TWO GROUPS, THE EPIGENETICS GROUP (EGE) AND THE MOLECULAR MECHANISMS AND BIOMARKERS GROUP (MMB), WHICH WORK IN CLOSE COLLABORATION TO CREATE SYNERGIES AND BETTER EXPLOIT AND FURTHER EXPAND UNIQUE RESEARCH TOOLS AND EXPERTISE.

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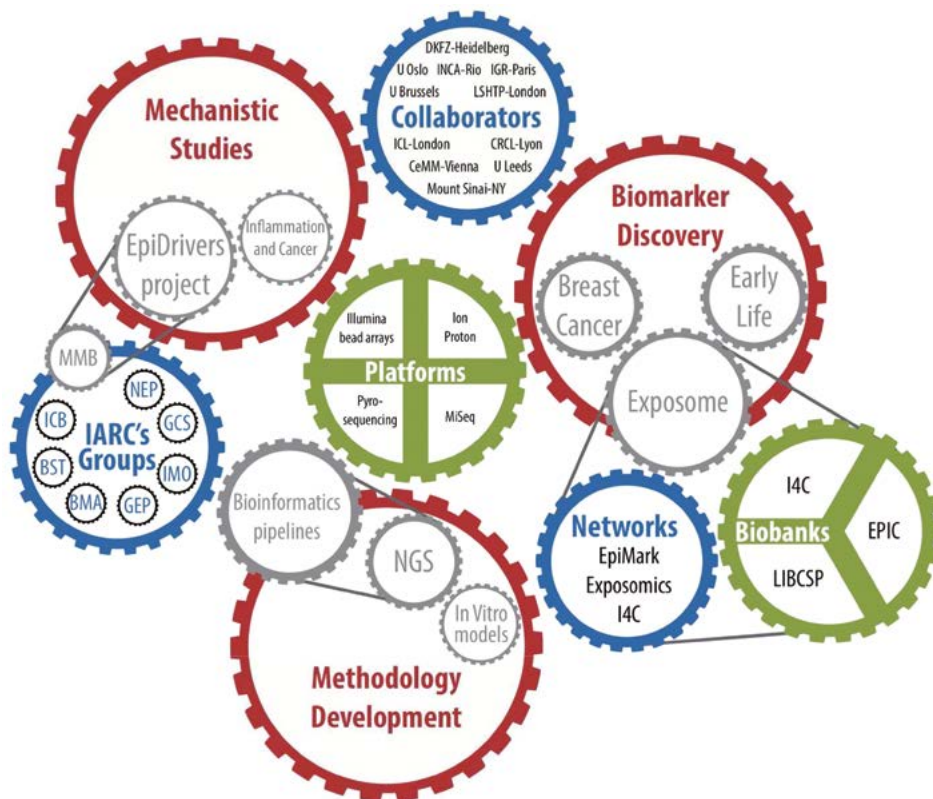
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The Epigenetics Group (EGE) conducts studies aimed at providing critical insights into epigenetic mechanisms of carcinogenesis through the identification of epigenome alterations and molecular pathways deregulated by environmental exposures. Another focus of EGE is identifying epigenetic biomarkers of exposure and cancer risk and contributing to the characterization of key components of the exposome. This is achieved through mechanistic studies of functionally important epigenetic “driver” genes and molecular pathways altered by specific cancer risk agents and by the application of cutting-edge epigenomics in conjunction with unique biospecimens from population-based cohorts (Figure 1). EGE also develops epigenomic methodologies, profiling strategies, and bioinformatics tools, applicable to population-based cohorts and molecular epidemiology studies coordinated by IARC researchers and external collaborators.

EXPOSURE TO AFLATOXIN B₁ IN UTERO IS ASSOCIATED WITH DNA METHYLATION CHANGES IN WHITE BLOOD CELLS OF INFANTS IN THE GAMBIA

Exposure to environmental toxins during embryonic development may lead to epigenetic changes that influence disease risk in childhood and later life. EGE investigated the consequences of early-life exposure to aflatoxin at the epigenome (DNA methylation [DNAm]) level. Aflatoxin exposure in women from a rural region in The Gambia was assessed in plasma taken at 1–16 weeks of pregnancy, and global DNAm of white blood cells from their infants was measured using the Illumina Infinium HumanMethylation450 BeadChip. Aflatoxin exposure in the mothers was found to be significantly correlated with DNAm in their infants for a subset of CpG sites. Aflatoxin-associated differential methylation was observed in growth factor genes, immune-related genes, and a gene involved in aflatoxin detoxification (Figure 2) (Hernandez-Vargas et al., 2015). In addition, EGE identified that the effect of maternal nutrition on DNAm at specific genomic loci exhibits the hallmarks of “metabolic imprinting”, including a critical window of sensitivity (in the pre-implantation embryo) and a dose–response relationship between

Figure 1. Research themes, collaborators, technological platforms, and resources of the Epigenetics Group (EGE). EGE conducts studies aiming to characterize epigenetic alterations and molecular pathways deregulated by specific cancer risk factors and to identify epigenetic biomarkers of exposure, early detection, and risk stratification. It also develops epigenomic and profiling strategies and bioinformatics tools applicable to in vitro models and population-based studies. EGE capitalizes on recent conceptual and technological advances that have resulted in exciting opportunities for cancer epigenetics in understanding the causes of common cancers. EGE’s programme is carried out in close collaboration with IARC scientists and epidemiologists as well as external collaborators, many of whom are part of international networks established to share technological platforms and biological resources. © IARC.



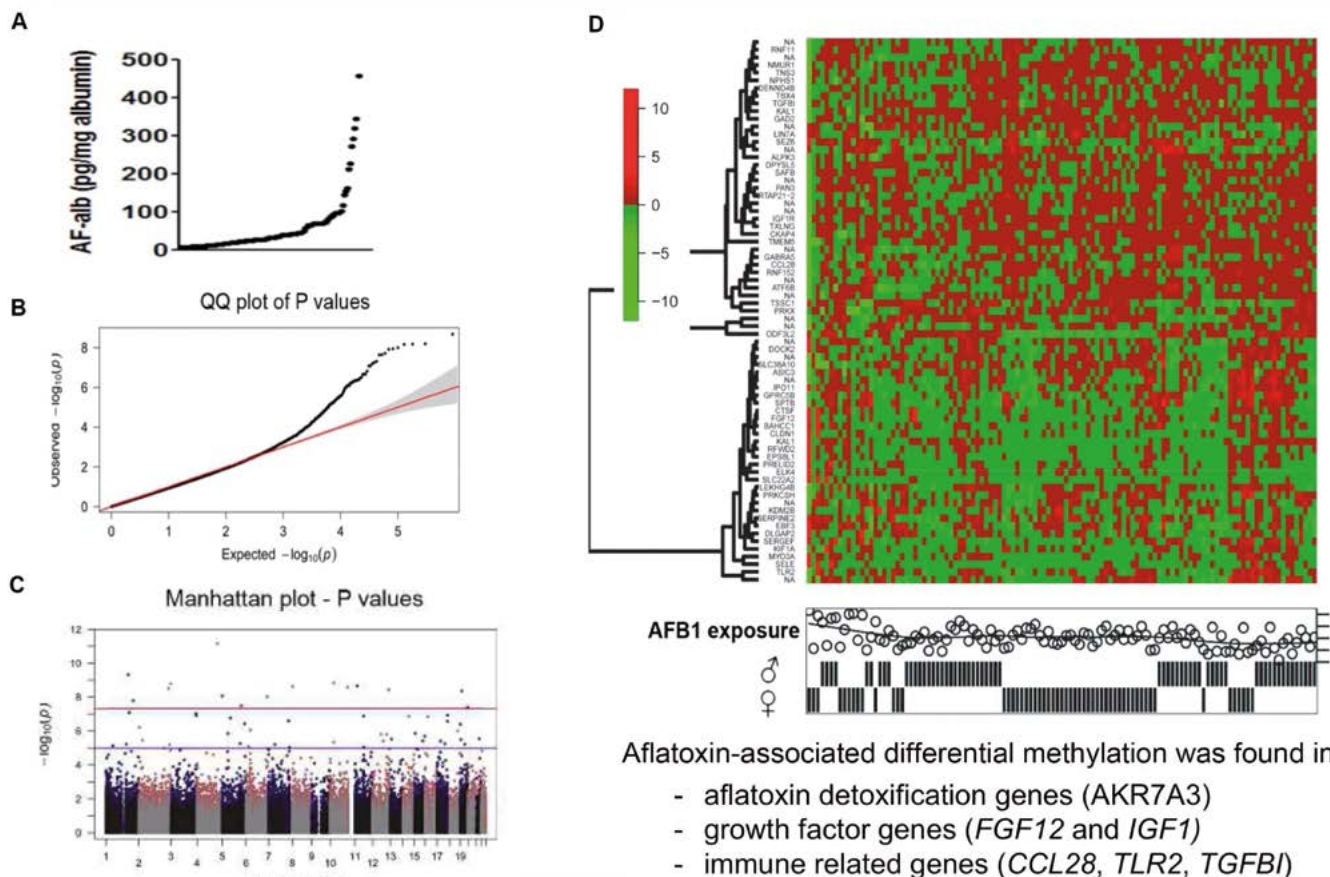
exposure and outcome (Silver et al., 2015). These studies show that maternal exposure and diet during the early stages of pregnancy is associated with changes in epigenome patterns of infants. This reinforces the need for interventions, especially during critical periods of fetal and infant development.

TARGETED DEEP DNA METHYLATION ANALYSIS OF CIRCULATING CELL-FREE DNA IN PLASMA USING MASSIVELY PARALLEL SEMICONDUCTOR SEQUENCING

Circulating cell-free DNA (cfDNA) isolated from the plasma of individuals with cancer has been shown to harbour cancer-associated changes in DNAm, and thus represents an attractive target for biomarker discovery. However, the reliable detection of DNAm changes in body fluids has proven to be technically

challenging. EGE has developed a novel method that enables sensitive and targeted deep DNAm analysis in minute amounts of DNA present in body fluids using massively parallel semiconductor sequencing (the Ion Torrent PGM sequencer). This approach was applied to assess in plasma cfDNA the methylation of a panel of genes, including *FBLN1*, *HINT2*, *LAMC1*, *LTBP1*, *LTBP2*, *PSMA2*, *PSMA7*, *PXDN*, *TGFB1*, *UBE2L3*, *VIM*, and *YWHAZ*, and to evaluate the potential of these genes as novel biomarkers for hepatocellular carcinoma in two different case–control studies, one in France and one in Thailand. Methylation in cfDNA was detected for specific genes (*FBLN1*, *PSMA7*, *PXDN*, and *VIM*), with substantial differences in methylation patterns between cases and controls (Figure 3) (Vaca-Paniagua et al., 2015a, and unpublished data from

Figure 2. Differential methylation associated with early-life exposure to aflatoxin. (A) Distribution of aflatoxin exposure during pregnancy in all mothers. (B) Quantile–quantile plot of the *P*-values after the association between DNA methylation and aflatoxin exposure (as a continuous variable). (C) Manhattan plot to illustrate the distribution of *P*-values across somatic chromosomes. (D) Heat map of the 71 CpGs associated with in utero aflatoxin B₁ (AFB₁) exposure. Annotations in the lower panel illustrate the corresponding aflatoxin exposure and sex. Reprinted with permission from Hernandez-Vargas et al. (2015), by permission of Oxford University Press.



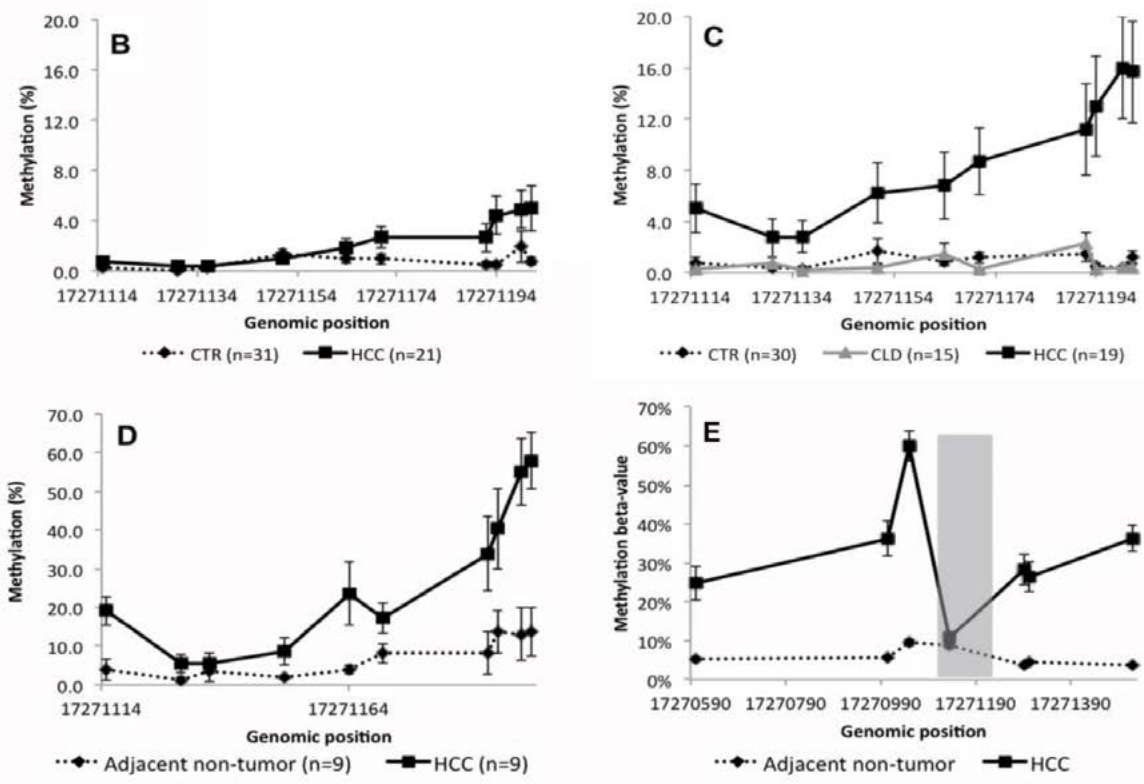
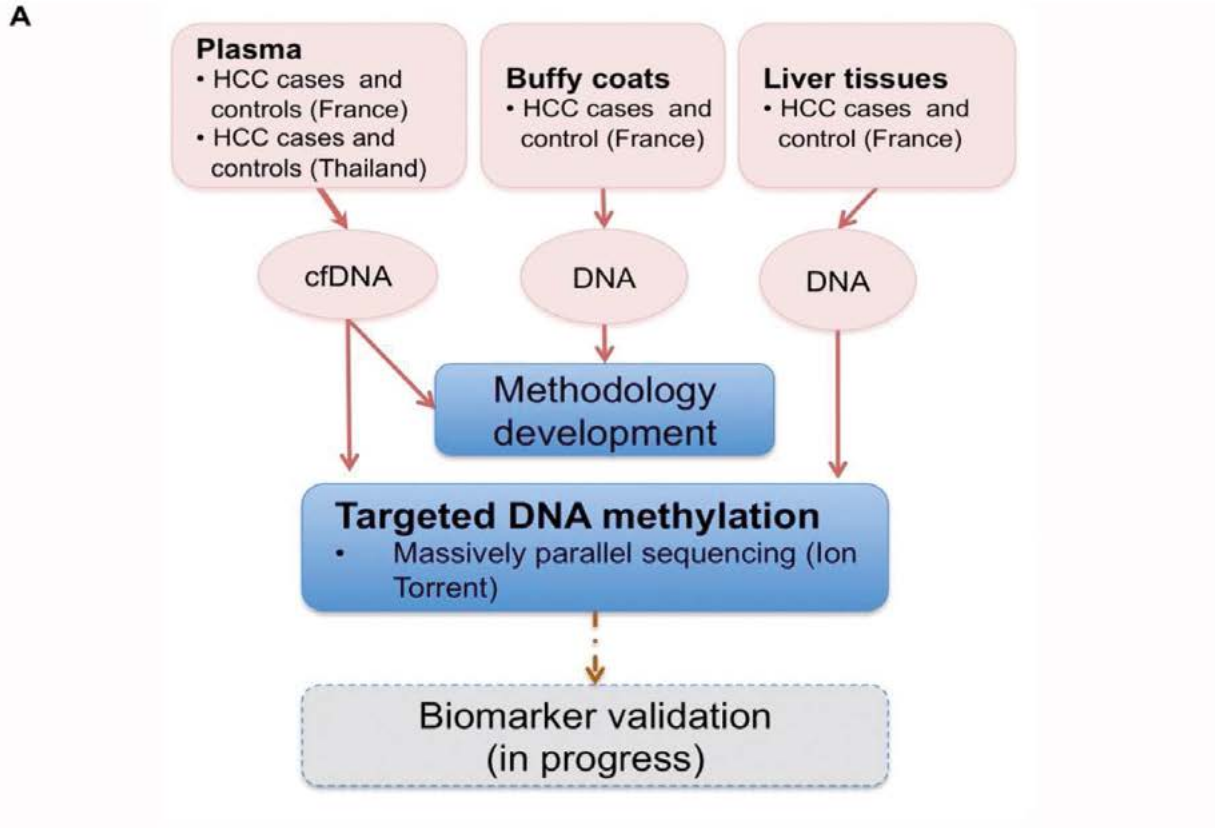
EGE). These results provide evidence that changes in methylation levels of *VIM* and *FBLN1* in cfDNA are associated with hepatocellular carcinoma and may represent useful plasma-based biomarkers for improved diagnostic accuracy and patient surveillance (Vaca-Paniagua et al., 2015a, and unpublished data from EGE). This study represents a proof of principle demonstrating the applicability of massively parallel semiconductor sequencing as a non-invasive, cost-effective, and time-efficient approach to identify, develop, and validate epigenetic biomarkers that are potentially translatable into epidemiological and clinical settings.

DEVELOPMENT OF EPIGENOMIC METHODOLOGIES AND BIOINFORMATIC TOOLS APPLICABLE TO POPULATION-BASED COHORTS AND MOLECULAR EPIDEMIOLOGY

EGE has exploited improvements in the throughput and cost of methylation, histone modifications, and microRNA sequencing brought about by the recent establishment of a new-generation array platform (Illumina Infinium) for methylome and transcriptome profiling, and next-generation sequencing (NGS)-based platforms (Illumina MiSeq, Illumina Genome Analyzer, and Ion Torrent) at IARC and external collaborators

(Figure 1). These methodologies have enabled EGE to move from focused approaches to comprehensive epigenome-wide approaches and to develop several new and original topics in cancer epigenetics (Ghantous et al., 2014; Hernandez-Vargas et al., 2015; Kuasne et al., 2015; Lambert et al., 2015; Martin et al., 2014; Silver et al., 2015; Vaca-Paniagua et al., 2015a). These developments have also motivated the building of bioinformatics capacity within EGE, with a first generation of data-mining tools specifically designed for epigenomic analyses.

Figure 3. DNA methylation analysis of plasma circulating cell-free DNA (cfDNA) by targeted deep sequencing to evaluate potential epigenetic biomarkers of cancer. (A) General outline of the study and methodology development. (B–E) The DNA isolated from plasma of cases and controls was subjected to targeted deep DNA methylation analysis using massively parallel semiconductor sequencing. *VIM* methylation in circulating DNA in cases from France (B) and from Thailand (C), in tissue (D), and in The Cancer Genome Atlas (TCGA) data (E); the grey area represents the area analysed by massively parallel sequencing in this study. CLD, chronic liver diseases; CTR, controls; HCC, hepatocellular carcinoma. The error bars represent the standard error of the mean. Compiled from Vaca-Paniagua et al. (2015a).



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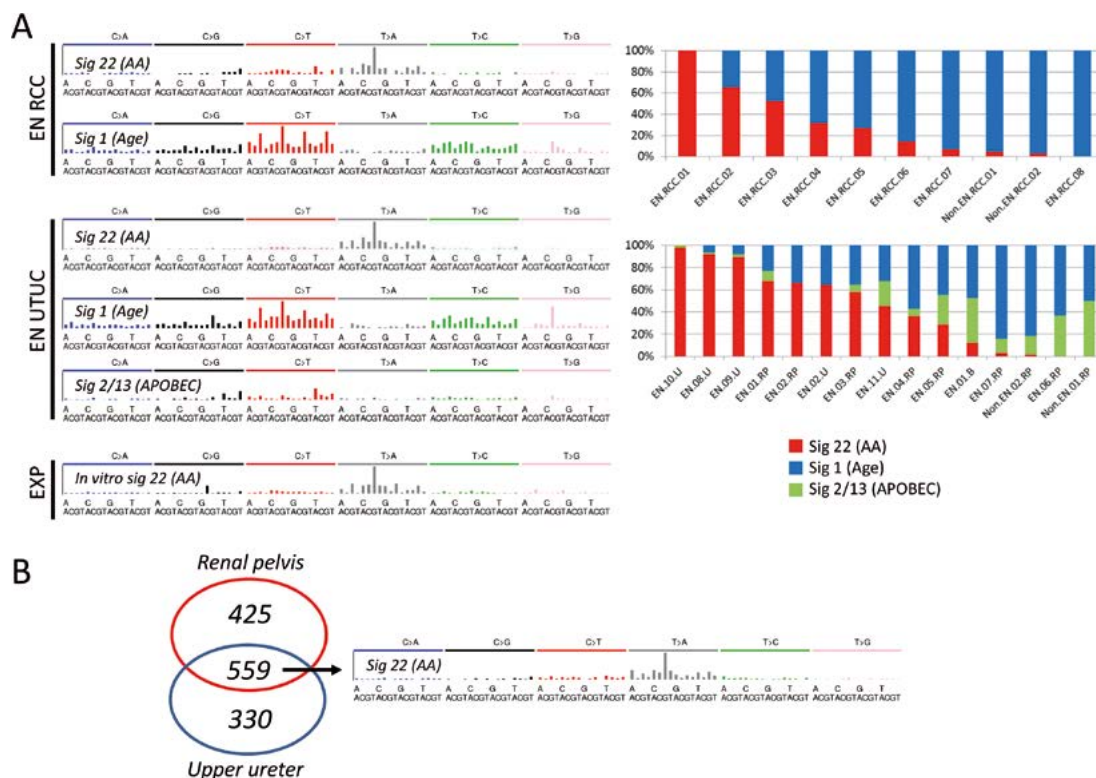
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Figure 2. Mutational signatures in urological tumours of endemic nephropathy (EN) patients. (A) Signature (Sig) 22 corresponding to the mutagenic effects of aristolochic acid (AA) was observed in renal cell carcinoma (RCC) and upper tract urothelial carcinoma (UTUC) tumours of Croatian and Bosnian patients with EN. The bar graphs on the left show the individual signatures found in the urological tumours studied and the AA single base substitutions (SBSs) are represented by colours and labelled on top of each graph, and the frequencies of each of the possible combinations of an SBS in a particular trinucleotide context (listed under each graph) are shown; the predominant T > A in the C_G context is the typical feature of the AA signature. The UTUC samples also harboured the signature for increased APOBEC enzyme activity. The bar graphs on the right show the relative percentage contribution of each signature to the mutation load in individual tumour samples. (B) Concurrent UTUC tumours found in distinct anatomical sites (the renal pelvis and upper ureter) of one EN patient harbour a high number of overlapping AA-specific mutations, suggesting a possible mechanism of tumour spread by tumour cell seeding along the urinary tract. © IARC.



the incidence and prevention of AA-associated cancers worldwide. The screen developed by MMB can address the role of AA in cancers observed in high-risk populations exposed to the compound through the widespread use of alternative herbal remedies.

ASSESSING THE PERFORMANCE OF DEEP SEQUENCING FOR THE IDENTIFICATION OF CLINICALLY RELEVANT SOMATIC TUMOUR MUTATIONS IN CIRCULATING cfDNA IN LUNG CANCER

Circulating cfDNA extracted from the plasma of cancer patients may contain a significant fraction of tumour DNA. Somatic mutation analysis is part of the standard management of metastatic lung cancer to select gene-targeted therapies. Biopsy samples are often the only material available to access the tumour DNA, but they provide

limited amounts of DNA and may not be representative of the entire tumour mass. To investigate whether cfDNA could be used as a surrogate tissue for detecting clinically relevant mutations in lung cancer from non-smokers, MMB used deep sequencing that enables highly sensitive mutation detection (Couraud et al., 2014). The results demonstrate that this method is suitable for the detection of tumour mutations in cfDNA with good sensitivity and specificity. Thus, cfDNA may be a promising resource for diagnosis and follow-up of lung cancer.

BIOINFORMATICS TOOLS FOR MOLECULAR CANCER RESEARCH

The recent interest in genome-wide mutational signatures observed in human cancers uncovered a need for user-friendly tools that would enable streamlined data analyses accessible

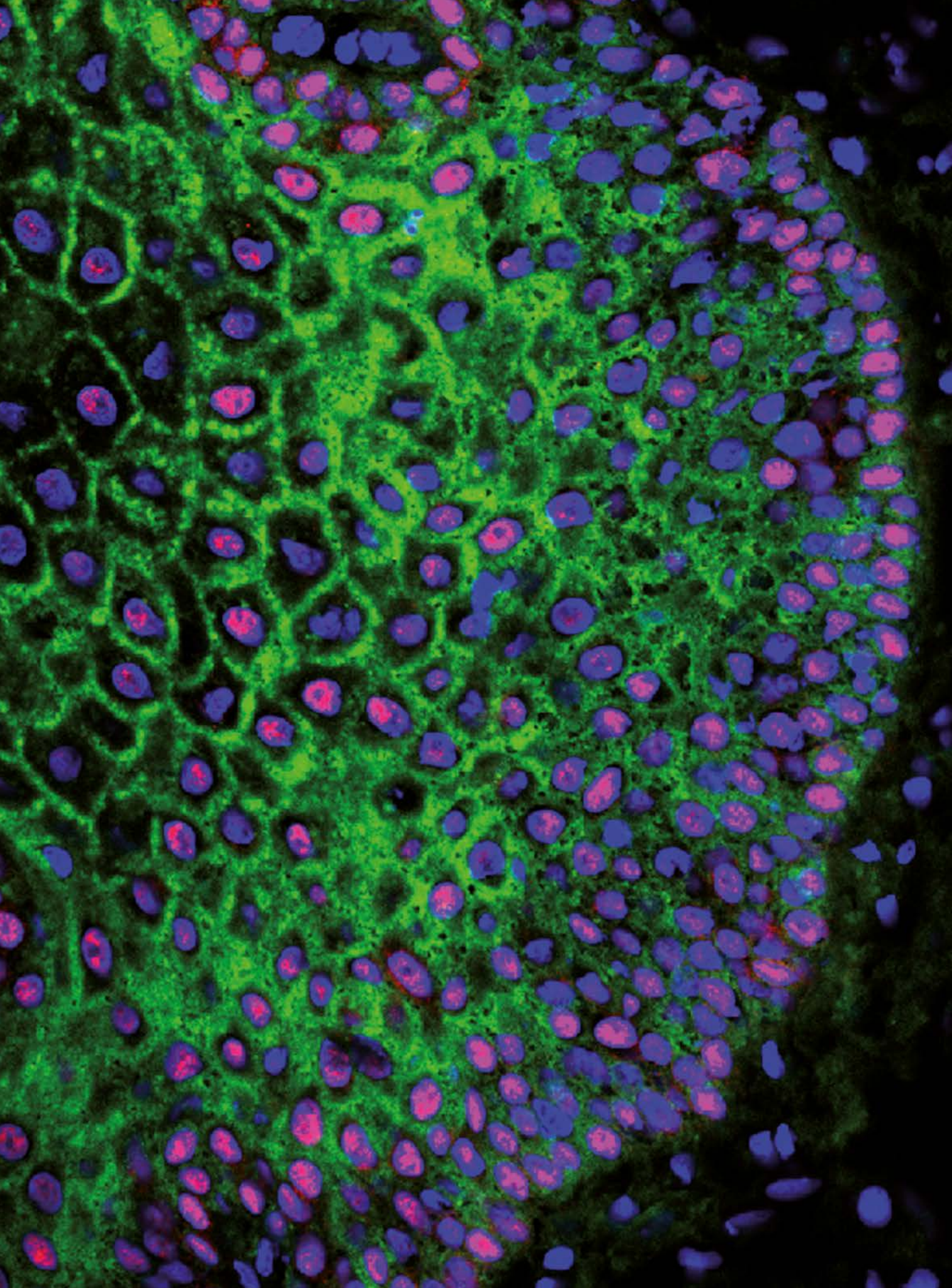
to scientists with limited expertise in bioinformatics. To fill this gap, MMB developed MutSpec, an open-source software package embedded in the popular, user-friendly bioinformatics platform Galaxy. MutSpec includes tools performing variant annotation and advanced statistics for identifying mutational signatures present in cancer genomes and comparing the signatures obtained with those in the COSMIC database and other sources. MutSpec can analyse data from whole-exome, whole-genome, or targeted sequencing performed in human or mouse samples. The results are organized in tabular and rich graphical summaries. MutSpec facilitates systematic analyses of mutation spectra by a wider range of scientists with basic bioinformatics skills, to promote new studies on cancer etiology.

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THE SECTION OF MOLECULAR PATHOLOGY (MPA) CONDUCTS ORIGINAL RESEARCH TO ELUCIDATE THE MOLECULAR BASIS AND GENETIC PATHWAYS OF HUMAN NEOPLASMS. MPA'S SPECIFIC AIMS ARE TO PROVIDE GENETIC INFORMATION THAT WILL BE USED AS THE BASIS FOR FUTURE MOLECULAR DIAGNOSIS AND CLASSIFICATION OF BRAIN TUMOURS, TO IDENTIFY GENETIC MARKERS FOR PROGNOSIS AND NOVEL TREATMENT STRATEGIES, AND TO USE GENETIC DATA TO IDENTIFY NEW CLUES TO UNDERSTAND THE ETIOLOGY OF HUMAN TUMOURS (KIM ET AL., 2014A; LOUIS ET AL., 2014; OHGAKI ET AL., 2014). GENETIC STUDIES ARE CARRIED OUT, USING TUMOUR SAMPLES FROM PATIENTS WITH EXCELLENT CLINICAL DATA THAT HAVE BEEN COLLECTED AT A POPULATION LEVEL OR INTERNATIONALLY, TO PROVIDE UNIQUE DATA COMBINING THE PATHOLOGY, GENETICS, CLINICAL FEATURES, AND EPIDEMIOLOGY OF TUMOURS. MPA'S RESEARCH PROGRAMME IS A KEY ELEMENT OF IARC'S GOALS OF ELUCIDATING THE MECHANISMS OF CARCINOGENESIS AND UNDERSTANDING THE ETIOLOGY OF CANCER.

MPA is also responsible for the World Health Organization (WHO) Classification of Tumours series (WHO Blue Books). MPA works with internationally recognized pathologists from around the world to reach consensus regarding tumour classification. Most human tumours have been diagnosed and classified based on histological features; more recently, molecular markers are increasingly being used to

define disease entities, taking advantage of rapid progress in the understanding of the genetics of human neoplasms.

Several of the main projects of MPA over the 2014–2015 biennium are detailed below.

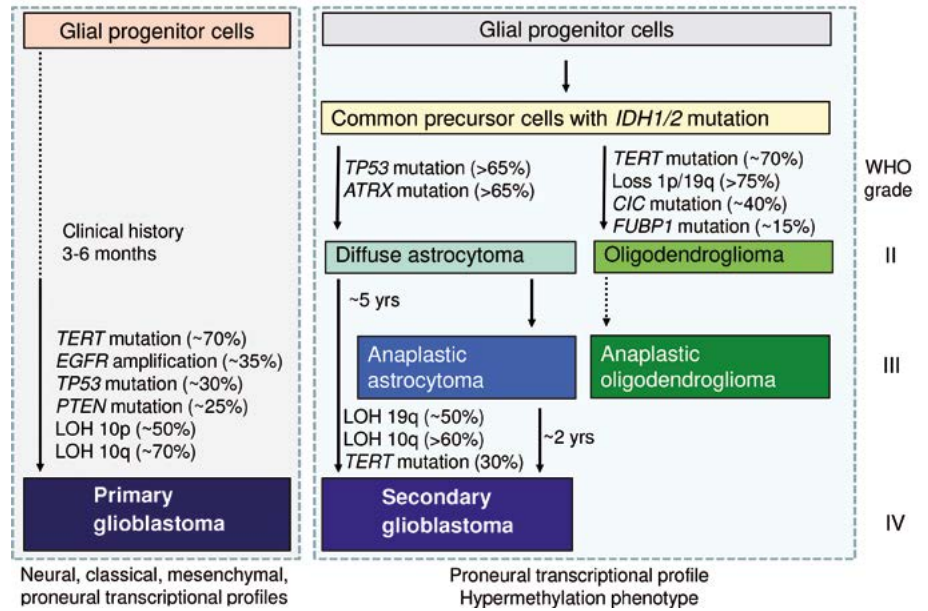
ALTERATIONS OF THE *RRAS* AND *ERCC1* GENES AT 19Q13 IN GEMISTOCYTIC ASTROCYTOMAS

Gemistocytic astrocytoma (WHO grade II) is a rare variant of diffuse astrocytoma, characterized by the presence of neoplastic gemistocytes and a consistent tendency to progress to secondary glioblastoma (WHO grade IV) and have a poor prognosis. Other than frequent *TP53* mutations (> 80%), little has been known about the molecular profile of gemistocytic astrocytomas. Exome sequencing was carried out in gemistocytic astrocytomas, and homozygous deletion of genes was identified at 19q13, i.e. *RRAS* and *ERCC1*. Further screening showed *RRAS* homozygous deletion in 7 of 42 (17%) gemistocytic astrocytomas and in 3 of 24 (13%) secondary glioblastomas. Patients with gemistocytic astrocytoma and secondary glioblastoma with *RRAS* deletion tended to have shorter survival times than those without deletion. Also, *ERCC1* homozygous deletion or promoter methylation was found in 10 of 42 (24%) gemistocytic astrocytomas and in 8 of 24 (33%) secondary glioblastomas. Homozygous deletions of *RRAS* and *ERCC1* were absent in other low-grade diffuse gliomas and in primary (de novo) glioblastomas (Ohta et al., 2014).

LOSS OF *FUBP1* EXPRESSION IN GLIOMAS PREDICTS *FUBP1* MUTATION AND IS ASSOCIATED WITH OLIGODENDROGLIAL DIFFERENTIATION, *IDH1* MUTATION, AND 1p/19q LOSS

Far upstream element-binding protein 1 (*FUBP1*) regulates several target genes, such as *MYC* and *p21*. *FUBP1* is upregulated in a variety of tumours and acts as an oncoprotein by stimulating proliferation and inhibiting apoptosis. *FUBP1* expression profiles in gliomas were examined by immunohistochemistry and immunofluorescence. *FUBP1* expression was higher in all glioma subtypes compared with normal

Figure 1. Genetic pathways to primary and secondary glioblastomas. Note that secondary glioblastomas share a common origin of cells with oligodendrogliomas. © IARC.



brain tissue, and was associated with increased cell proliferation. Loss of *FUBP1* expression predicted *FUBP1* mutation with a sensitivity of 100% and a specificity of 90%, and was associated with oligodendroglial differentiation, *IDH1* mutation, and 1p/19q loss, suggesting that *FUBP1* immunohistochemistry is useful for glioma diagnosis (Baumgarten et al., 2014).

THE *OLIG2* LABELLING INDEX IS CORRELATED WITH HISTOLOGICAL AND MOLECULAR CLASSIFICATIONS IN LOW-GRADE DIFFUSE GLIOMAS

Diagnosis of low-grade diffuse gliomas based on histology is highly subjective, with significant inter-observer variability. *Olig2* expression was assessed by immunohistochemistry in WHO grade II diffuse astrocytomas, oligoastrocytomas, and oligodendrogliomas. The mean *Olig2* labelling index was 44% in diffuse astrocytomas, 59% in oligoastrocytomas, and 76% in oligodendrogliomas. The *Olig2* labelling index was significantly higher in gliomas with 1p/19q loss with or without *IDH1/2* mutation than in those carrying *TP53* mutation with or without *IDH1/2* mutation or in those with *IDH1/2* mutation only (Suzuki et al., 2014).

TP53, *MSH4*, AND *LATS1* GERMLINE MUTATIONS IN A FAMILY WITH CLUSTERING OF NERVOUS SYSTEM TUMOURS

Exome DNA sequencing of blood samples from a Li–Fraumeni family with a *TP53* germline mutation and multiple nervous system tumours revealed additional germline mutations. Missense mutations in the *MSH4* DNA repair gene (c.2480T > A; p.1827N) were detected in three patients with gliomas. Two family members without a *TP53* germline mutation who developed peripheral schwannomas also carried the *MSH4* germline mutation and, in addition, a germline mutation of the *LATS1* gene (c.286C > T; p.R96W). *LATS1* is a downstream mediator of NF2 but has not previously been found to be related to schwannomas. Therefore, the entire coding sequence of the *LATS1* gene in sporadic schwannomas was screened, and a single base deletion at codon 827 was found in a spinal schwannoma. Mutational loss of *LATS1* function may thus play a role in some inherited schwannomas, but only exceptionally in sporadic schwannomas. This is the first study reporting a germline *MSH4* mutation. Since it was present in all patients, it may have contributed to the subsequent acquisition of *TP53* and *LATS1* germline mutations (Kim et al., 2014a).

ALTERATIONS IN THE NF2/LATS1/LATS2/YAP PATHWAY IN SCHWANNOMAS

Schwannoma is a benign nerve sheath tumour composed of well-differentiated Schwann cells. Other than frequent *NF2* mutations (50–60%), the molecular basis of schwannomas is not fully understood. *LATS1* and *LATS2* are downstream molecules of *NF2* and negative regulators of the *YAP* oncogene in the Hippo signalling pathway. MPA assessed mutations of the *NF2*, *LATS1*, and *LATS2* genes, promoter methylation of *LATS1* and *LATS2*, and expression of *YAP* and phosphorylated *YAP* (p*YAP*) in 82 sporadic schwannomas. Targeted sequencing using the Ion Torrent Proton instrument revealed *NF2* mutations in 45 (55%) schwannomas, *LATS1* mutations in 2 (2%) schwannomas, and *LATS2* mutations in 1 (1%) schwannoma. Methylation-specific polymerase chain reaction (PCR) showed promoter methylation of *LATS1* and *LATS2* in 14 (17%) and 25 (30%) cases, respectively. Overall, 62 (76%) cases had at least one alteration in the *NF2*, *LATS1*, and/or *LATS2* genes. Immunohistochemistry revealed nuclear *YAP* expression in 18 of 42 (43%) and reduced cytoplasmic p*YAP* expression in 15 of 49 (31%) schwannomas analysed, all of which had at least one alteration in the *NF2*, *LATS1*, and/or *LATS2* genes. These results suggest that an abnormal Hippo signalling pathway is involved in the pathogenesis of the majority of sporadic schwannomas (Oh et al., 2015).

ROLE OF MICRORNAS IN THE PATHOGENESIS AND PROGRESSION OF MEDULLOBLASTOMAS

Medulloblastoma is the most frequent malignant central nervous system tumour in children. MicroRNAs (miRs) are small, non-coding RNAs that target protein-coding and non-coding RNAs and play roles in a variety of cellular processes through regulation of multiple targets.

MPA assessed miR-22 expression and its effect on cell proliferation and apoptosis in medulloblastomas. Quantitative reverse transcription PCR (RT-PCR) revealed significantly lower expression of miR-22 in 19 of 27 (70%) medulloblastomas and three

medulloblastoma cell lines, compared with normal cerebellum. Forced expression of miR-22 by lentiviral vector transfection reduced cell proliferation and induced apoptosis, while knockdown of miR-22 increased proliferative activity in DAOY and ONS-76 medulloblastoma cells. Microarray analysis in DAOY cells with forced miR-22 expression showed significant changes in expression profiles; *PAPST1* was the most significantly (10-fold) downregulated gene. Quantitative RT-PCR revealed *PAPST1* mRNA upregulation in 18 of 27 (67%) medulloblastomas. In addition, a luciferase reporter assay suggested that miR-22 directly targets the *PAPST1* gene, and lentivirus-mediated knockdown of *PAPST1* suppressed proliferation of medulloblastoma cells. These results suggest that frequently downregulated miR-22 expression is associated with cell proliferation in medulloblastomas, and this may be at least in part via *PAPST1*, which is a novel target of miR-22 (Xu et al., 2014).

miR-9, a key regulator of neuronal development, is aberrantly expressed in brain malignancies. MPA showed that miR-9 expression is frequently downregulated in medulloblastomas, and that this is at least in part due to promoter methylation. Low miR-9 expression correlated significantly with the diagnosis of unfavourable histopathological variants and with poor clinical outcome. Furthermore, *HES1* was identified as a direct target of miR-9 in medulloblastoma. Restoration of miR-9 was shown to trigger cell cycle arrest, inhibit clonal growth, and promote cell differentiation. Re-expression of miR-9 may constitute a novel epigenetic regulation strategy against medulloblastomas (Fiaschetti et al., 2014).

WHO CLASSIFICATION OF TUMOURS SERIES (WHO BLUE BOOKS)

The objective of this project is to establish a histopathological and molecular 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 for pathology communities but also for cancer registration, epidemiological studies, clinical trials, and cancer research in general.

IARC has been responsible for this project since the third edition (2000–2005; 10 volumes). The current (fourth) edition 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). So far, seven volumes have been published, and for each volume, 20 000–50 000 copies were printed and distributed worldwide.

In 2014–2015, the sixth volume (Tumours of Female Reproductive Organs) and seventh volume (Tumours of the Lung, Pleura, Thymus and Heart) have been published, and preparation of the eighth volume (Tumours of the Urinary System and Male Genital Organs), the ninth volume (Head and Neck Tumours), and the tenth volume (Tumours of Endocrine Organs) is under way. In addition, updates to the first and second volumes of the fourth edition, Tumours of the Central Nervous System and Tumours of Haematopoietic and Lymphoid Tissues, are in progress.

Figure 2. Cover of *WHO Classification of Tumours of Female Reproductive Organs*, fourth edition.



Figure 3. Working Group members at the consensus and editorial meeting of *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*. The meeting was held at IARC on 24–26 April 2014. © IARC/Roland Dray.



The sixth volume, *Tumours of Female Reproductive Organs*, was published in April 2014. It was edited by four volume editors (Dr Robert J. Kurman, Johns Hopkins University, Baltimore, USA; Dr Maria Luisa Carcangiu, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy; Dr C. 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) and prepared by 92 authors from 18 countries.

The seventh volume, *Tumours of the Lung, Pleura, Thymus and Heart*, was published in March 2015. It was edited by five volume editors (Dr William D. Travis, Memorial Sloan Kettering Cancer Center, New York, USA; Dr Elisabeth Brambilla, Centre Hospitalier Universitaire de Grenoble, France; Dr

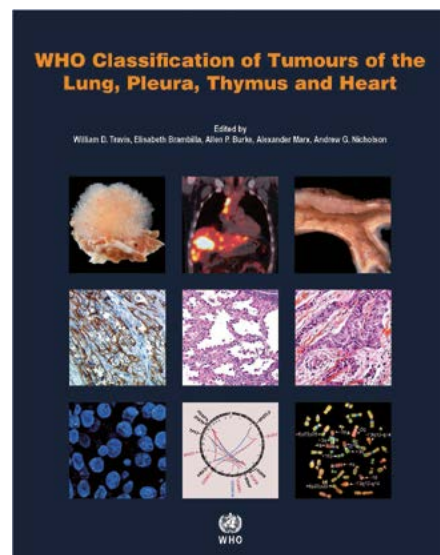
Allen P. Burke, University of Maryland, Baltimore, USA; Dr Alexander Marx, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany; and Dr Andrew G. Nicholson, Royal Brompton Hospital, London, United Kingdom) and prepared by 157 authors from 29 countries.

The eighth volume, *Tumours of the Urinary System and Male Genital Organs*, is being edited by four volume editors (Dr Holger Moch, University Hospital Zurich, Zurich, Switzerland; Dr Peter A. Humphrey, Yale University School of Medicine, New Haven, USA; Dr Thomas M. Ulbright, IU Health Pathology Laboratory, Indiana University School of Medicine, Indianapolis, USA; and Dr Victor E. Reuter, Memorial Sloan Kettering Cancer Center, New York, USA) and prepared by 103 authors from 19 countries. The consensus and editorial meeting was held in collaboration with

the University of Zurich on 11–13 March 2015, and the book is scheduled to be published in early 2016.

The ninth volume, *Head and Neck Tumours*, is being prepared by five volume editors (Dr Adel K. El-Naggar, MD Anderson Cancer Center, Houston, USA; Dr John K.C. Chan, Queen Elizabeth Hospital, Hong Kong Special Administrative Region, China; Dr Jennifer R. Grandis, Clinical and Translational Science Institute, UCSF School of Medicine, San Francisco, USA; Dr Takashi Takata, Hiroshima University, Hiroshima, Japan; and Dr Pieter J. Slootweg, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands). The consensus and editorial meeting is scheduled for January 2016.

Figure 4. Cover of *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*, fourth edition.

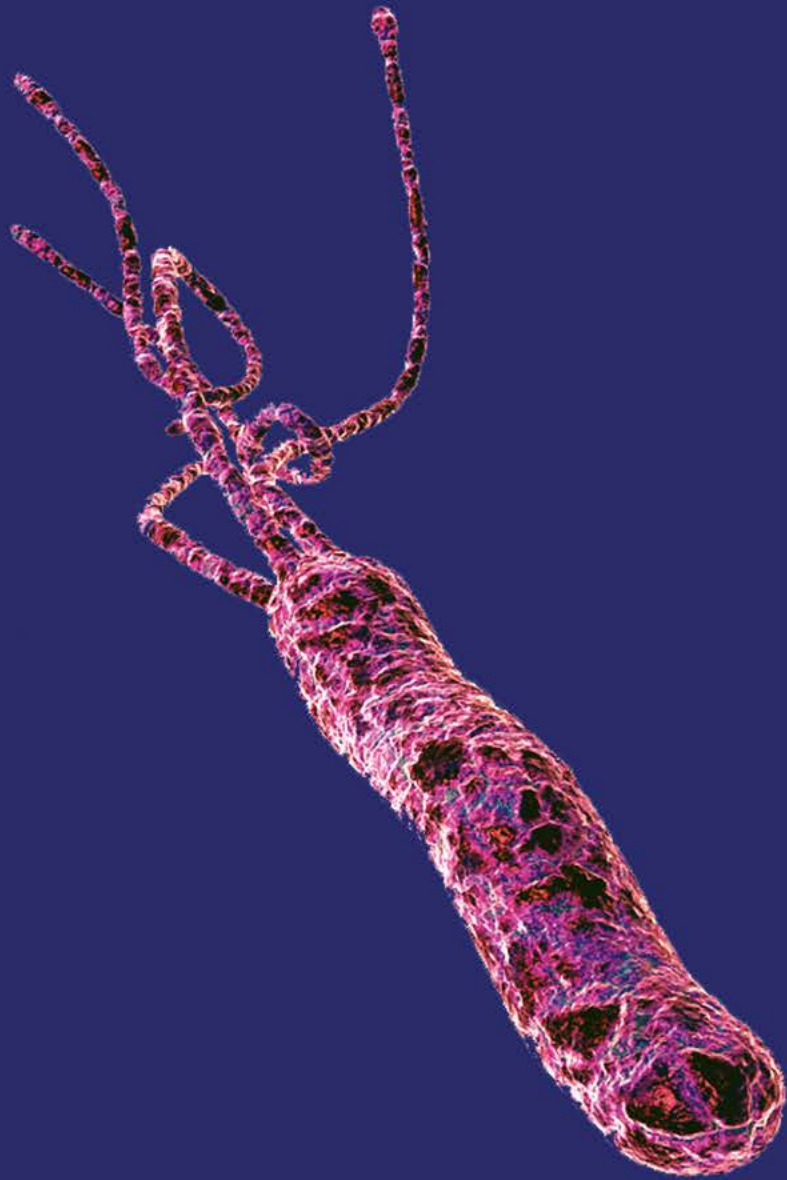


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THE SECTION OF INFECTIONS (INF) CONSISTS OF TWO GROUPS: THE INFECTIONS AND CANCER BIOLOGY GROUP (ICB) AND THE INFECTIONS AND CANCER EPIDEMIOLOGY GROUP (ICE). THE GROUPS HAVE SIMILAR GOALS IN EVALUATING THE ROLE OF INFECTIOUS AGENTS IN HUMAN CARCINOGENESIS USING COMPLEMENTARY STRATEGIES. ICB IS MAINLY FOCUSED ON THE CHARACTERIZATION OF THE BIOLOGICAL PROPERTIES OF WELL-ESTABLISHED AND NOVEL POTENTIAL ONCOGENIC VIRUSES. IN ADDITION, ICB OFFERS MANY LABORATORY ASSAYS THAT ARE WIDELY USED IN EPIDEMIOLOGICAL RESEARCH. THE WORK IN ICE FOCUSES ON THE ELUCIDATION OF THE SPECTRUM OF CANCERS ASSOCIATED WITH INFECTIONS AND THE IMPACT OF PREVENTION STRATEGIES.

In the 2014–2015 biennium, ICB has performed several functional studies on well-known and potential oncogenic viruses, such as Epstein–Barr virus (EBV) and members of the human papillomavirus (HPV) family. In particular, research by ICB highlighted the fact that oncogenic viruses share the ability to deregulate the same cellular pathways, although via different mechanisms. Thus, functional studies can be used as a tool to predict the role of novel viruses in human carcinogenesis.

Recent research efforts in ICE include the estimation of the global burden of cancer attributable to hepatitis B virus and hepatitis C virus infection, and that due to HIV after the introduction of antiretroviral treatment. Special efforts have been made to establish multiyear studies on the effectiveness of HPV

vaccination and HPV-based screening in Bhutan and Rwanda, the first two low-income countries to successfully adopt HPV vaccination practices. Much energy has also gone into the improvement of statistical and other quantitative methods to estimate infection-associated cancers.

In addition, ICB and ICE have performed several collaborative studies that led to the characterization of the relationship between natural variations of mucosal high-risk HPV types, geographical distribution, and the severity of cervical disease. The two Groups have also intensively collaborated to better understand the natural history of HPV infection in the oral cavity and to further define the role of the viral infection in the etiology of cancer of the head and neck in Europe and Asia.

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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 deregulating pathways related to cellular proliferation and transformation as well as to the immune response. ICB's findings showed that several oncogenic viruses have the ability to induce epigenetic changes and deregulate cellular gene expression. As a consequence, these viruses promote cellular transformation and inactivate pathways involved in the innate immune response (Figure 1). In the 2014–2015 biennium, ICB has characterized new biological properties of some of these viruses (Bazot et al., 2014; Leitz et al.,

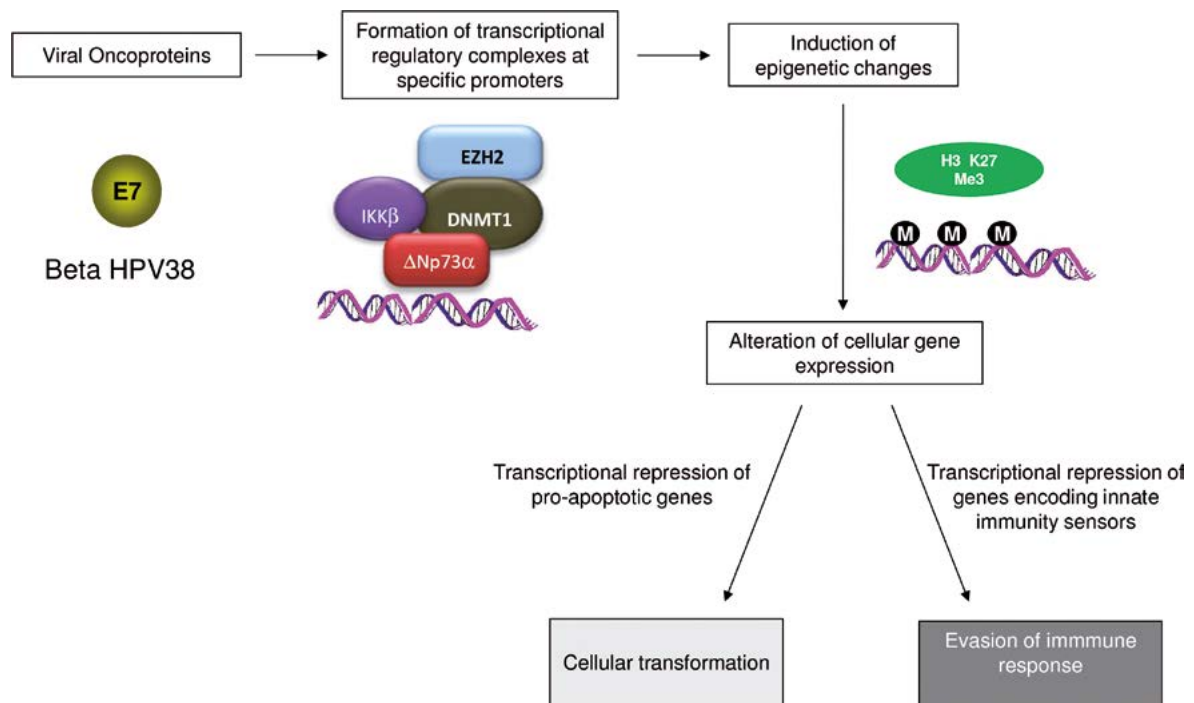
2014; Shterzer et al., 2014; Siouda et al., 2014; Frecha et al., 2015; Pacini et al., 2015).

In addition to functional studies, ICB has performed several collaborative epidemiological studies using laboratory assays established by the Group, aiming to characterize the natural history of several viruses at different anatomical regions (Hampras et al., 2014; Donà et al., 2015; Franceschi et al., 2015; Hampras et al., 2015; Torres et al., 2015) and their contribution to cancer development (Anantharaman et al., 2014a; Bussu et al., 2014; Corbex et al., 2014; Gheit et al., 2014; Iannacone et al., 2014; Joshi et al., 2014; Toll et al., 2014).

ROLE OF HUMAN PAPILLOMAVIRUS INFECTION AND OTHER CO-FACTORS IN THE ETIOLOGY OF HEAD AND NECK CANCER IN EUROPE AND INDIA (HPV-AHEAD)

For four years (2010–2015), ICB has coordinated the HPV-AHEAD consortium, which included a multi-disciplinary team in Europe and India, to evaluate the role of human papillomavirus (HPV) infection and other cofactors in the development of head and neck cancer (HNC) in Europe and India. The consortium collected and analysed plasma/serum samples ($n = 4000$) from many European centres and HNC tissues ($n = 8000$) from 42 centres in

Figure 1. Viral oncoproteins alter cellular gene expression, deregulating key pathways involved in cellular transformation and immune response. Many viral oncoproteins, such as LMP1 from Epstein–Barr virus (EBV) or E7 from several human papillomavirus (HPV) types, have the ability to induce the formation or alter the composition of transcriptional regulatory complexes, resulting in the deregulation of cellular gene expression. The figure shows, as an example, a mechanism characterized in ICB studies of E7 oncoprotein from beta HPV type 38 (reviewed in Tommasino, 2014). This virus belongs to genus beta of the HPV phylogenetic tree, which is suspected to be involved, together with ultraviolet (UV) radiation, in the development of non-melanoma skin cancer. Beta HPV 38 E7 oncoprotein has the ability to increase the level of a p53 antagonist, $\Delta Np73\alpha$, leading to the formation of a transcriptional regulatory complex containing $\Delta Np73\alpha$, IKK β , and two epigenetic enzymes, DNA methyltransferase 1 (DNMT1) and enhancer of zeste homologue 2 (EZH2). This complex binds many promoters, inducing epigenetic changes (e.g. histone 3 K27 trimethylation and/or DNA methylation) and repressing the expression of genes encoding innate immunity sensors (e.g. Toll-like receptor 9) and pro-apoptotic genes (e.g. *Pig3*). © IARC.



16 European countries as well as from 6 centres in India. HNC tissues were analysed by several laboratory assays, including detection of viral DNA and RNA, to precisely determine the fraction of HNCs attributable to mucosal high-risk HPV types in many geographical regions in Europe and India. Analyses of the results are under way.

EPIDERMODYSPLASIA VERRUCIFORMIS-ASSOCIATED GENES *EVER1* AND *EVER2* AS POTENTIAL NOVEL DNA SENSORS OF THE INNATE IMMUNITY TARGETED BY EBV

A recent study has shown that the products of two human genes, *EVER1* and *EVER2*, which appear to be associated with virus-induced carcinogenesis, may act as exogenous DNA sensors of the innate immunity (Frecha et al., 2015). Both genes were initially identified because they are mutated in patients with the rare genetic disorder epidermodysplasia verruciformis (EV). Patients with EV have an increased susceptibility to infection with cutaneous HPV types and development of squamous cell carcinoma. It has also been shown that specific single-nucleotide polymorphisms in *EVER1* and *EVER2* are associated with an increased risk of persistent infection with mucosal high-risk HPV types and consequent development of premalignant and malignant cervical lesions. ICB's recent findings showed

that the expression of both genes was strongly upregulated immediately after infection with EBV or herpes simplex virus 1 in primary or immortalized human cells, suggesting that the activation of *EVER* expression could be part of the innate immune response to exogenous DNA. Importantly, *EVER1* and *EVER2* transcription were strongly repressed at a later stage of EBV infection. Finally, EBV infection was hampered in cells expressing ectopic levels of *EVER1* or *EVER2*. Together, these findings indicate a link between *EVER* proteins and oncogenic virus infections; the proteins most likely serve as DNA sensors as part of the innate immune response.

NATURAL HISTORY OF BETA HPV TYPES AND THEIR ROLE IN HUMAN CARCINOGENESIS

Due to the development by ICB of a Luminex-based diagnostic platform that enables the detection of more than 140 double-stranded DNA viruses, ICB has established a large number of collaborative epidemiological studies. One of the focuses of the Group's research is to evaluate the role of cutaneous HPV types in the development of non-melanoma skin cancer. The best candidates are the cutaneous HPV types that belong to the genus beta of the viral phylogenetic tree, which is subdivided into five species (beta 1–5). They were initially isolated in skin cancer of cancer-

prone patients with the rare autosomal recessive genetic disorder EV (reviewed in Tommasino, 2014). Patients with EV are highly susceptible to infection with beta HPV types and ultraviolet (UV) radiation-induced skin cancers. It is now clear that beta HPV types are also abundantly present in the skin of healthy individuals. In a recent study, using anti-HPV antibodies and viral DNA as a marker of infection, ICB provided evidence that non-EV individuals with a history of skin cancer show a higher positivity for beta HPV infections compared with control subjects (Iannacone et al., 2014).

In agreement with other independent studies, ICB showed that the beta HPV types, in addition to the skin, can colonize different sites of the anogenital tract (Hampras et al., 2014; Donà et al., 2015; Torres et al., 2015), suggesting that their tropism is not strictly limited to the skin. Determination of the prevalence of beta HPV types in the anal canal of HIV-positive and HIV-negative men who have sex with men showed that HPV types belonging to the beta 1 and beta 3 species are increased in immunocompromised individuals. In contrast, the beta 2 species was equally distributed in the two groups (Torres et al., 2015). The fact that impairment of the host's immune surveillance affects beta HPV infections differently indicates that beta species have different biological properties.

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In 2014–2015, the Infections and Cancer Epidemiology Group (ICE) has contributed to progress in the understanding and prevention of cancer associated with infections by means of three main types of studies.

IMPLEMENTATION AND MONITORING OF HPV VACCINATION AND HPV-BASED SCREENING IN LOW-INCOME COUNTRIES

Bhutan and Rwanda, in which human papillomavirus (HPV) vaccination started in 2010 and 2011, respectively, are two model countries chosen by ICE to provide the first evaluations of the effectiveness and sustainability of an entirely HPV-based cervical cancer prevention strategy in low-income countries. Figure 1 shows the fairly high pre-vaccination prevalence of HPV in Bhutan (Baussano et al., 2014b; Tshomo et al., 2014).

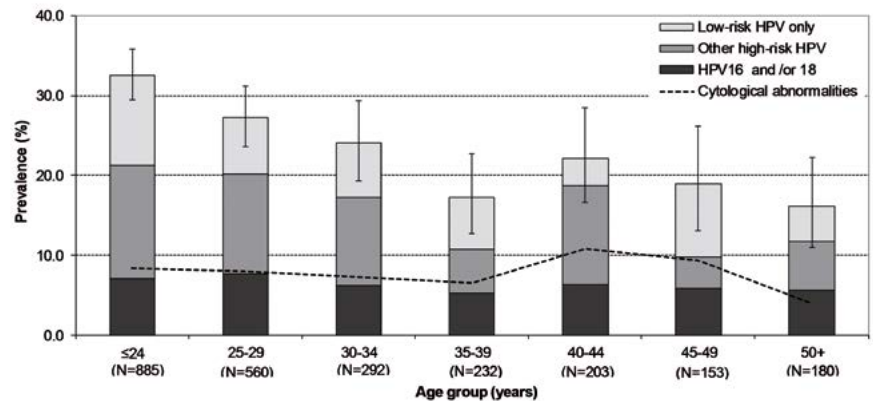
Screening of HIV-positive women is a special challenge. In Kenya, ICE showed a relatively high efficacy of cryotherapy in treating cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) (77%; 95% CI, 66–86%) but very frequent persistence of HPV infection (78%) (de Vuyst et al., 2014). ICE also reported for the first time that in women co-infected with HIV and HPV, triage with a tri-marker methylation test was not inferior to cytology in predicting CIN2 or worse and was superior to visual inspection with acetic acid (VIA) (de Vuyst et al., 2015).

ICE also took advantage of the historical IARC cell repository (from 27 different countries) to study variants that may affect the transformation potential of high-risk HPV types. The distribution of HPV 33 variants, for instance, varies by region, and the A1 sublineage was strongly over-represented in cervical cancer cases compared with controls in Africa and Europe (Chen et al., 2014a, 2014b).

SPECTRUM, NATURAL HISTORY, AND PREVENTION OF INFECTION-ASSOCIATED CANCERS OTHER THAN CERVICAL CANCER

The contribution of HPV infection to head and neck cancer (HNC) is still ill defined and varies substantially by cancer site and world region. ICE carried out a meta-analysis of studies in which the

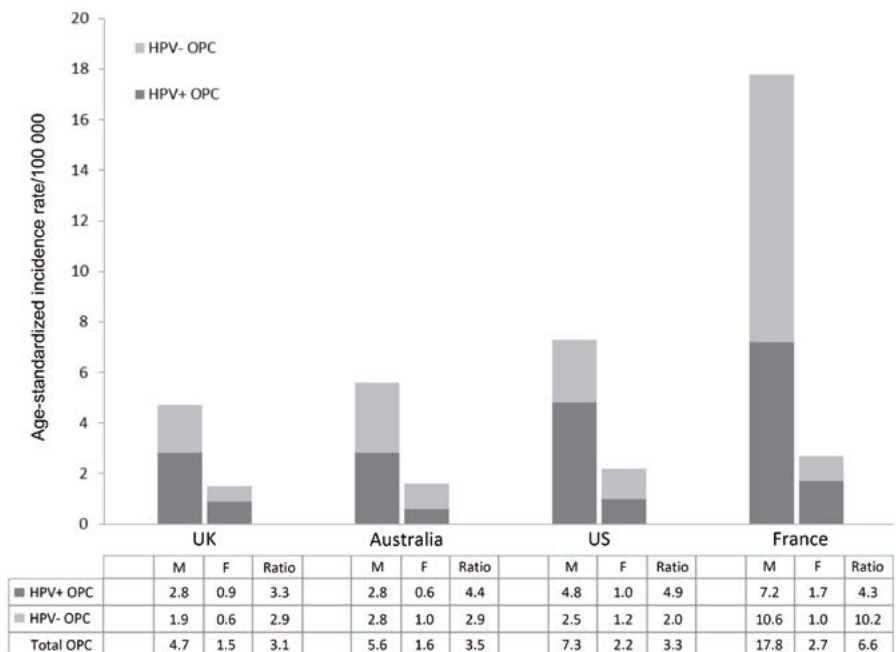
Figure 1. Age-specific prevalence of human papillomavirus (HPV) DNA and of cytological abnormalities among 2505 women in Bhutan in 2011–2012. Reprinted with permission from Tshomo et al. (2014). © 2014 Tshomo et al.; licensee BioMed Central Ltd.



prevalence of molecular and serological HPV markers was compared across different HNC and cancer-free controls (Combes and Franceschi, 2014). Data on markers of HPV-driven carcinogenesis, i.e. in situ hybridization or HPV E6/E7 mRNA, showed that HPV-attributable HNC is frequent in oropharyngeal cancer (OPC) (~50%) but rare in cancers of the oral cavity (~3%), larynx (~7%), and hypopharynx (~0%). ICE also showed

that HPV prevalence differs by sex and country, possibly as a consequence of the vast international variation in smoking habits in men and women (Combes et al., 2014a). Nevertheless, HPV-positive OPC may systematically cause more OPC in men than in women, for reasons that are unclear but may include higher prevalence of HPV or lifestyle risk factors in men (Figure 2).

Figure 2. Age-standardized (world) incidence rates of oropharyngeal cancer (OPC) per 100 000 people stratified by country, sex, and estimates of human papillomavirus (HPV) status. Corresponding male (M) to female (F) ratios are also shown in the table. Reprinted from Combes et al. (2014a), by permission from the American Association for Cancer Research.



ICE regularly updates the fraction of cancer attributable to infections worldwide by region and individual carcinogenic infectious agent; see Plummer et al. (2015) for *Helicobacter pylori*. Recently, such a fraction was quantified in a particularly vulnerable population: HIV-positive people in the USA (Figure 3). The infection-attributable

fraction was 40%, i.e. 10 times that seen in the general population (de Martel et al., 2015). The attributable fraction in HIV-positive people was also higher than that in the general population of any other world region, including sub-Saharan Africa, where 33% of cancers are attributable to infection.

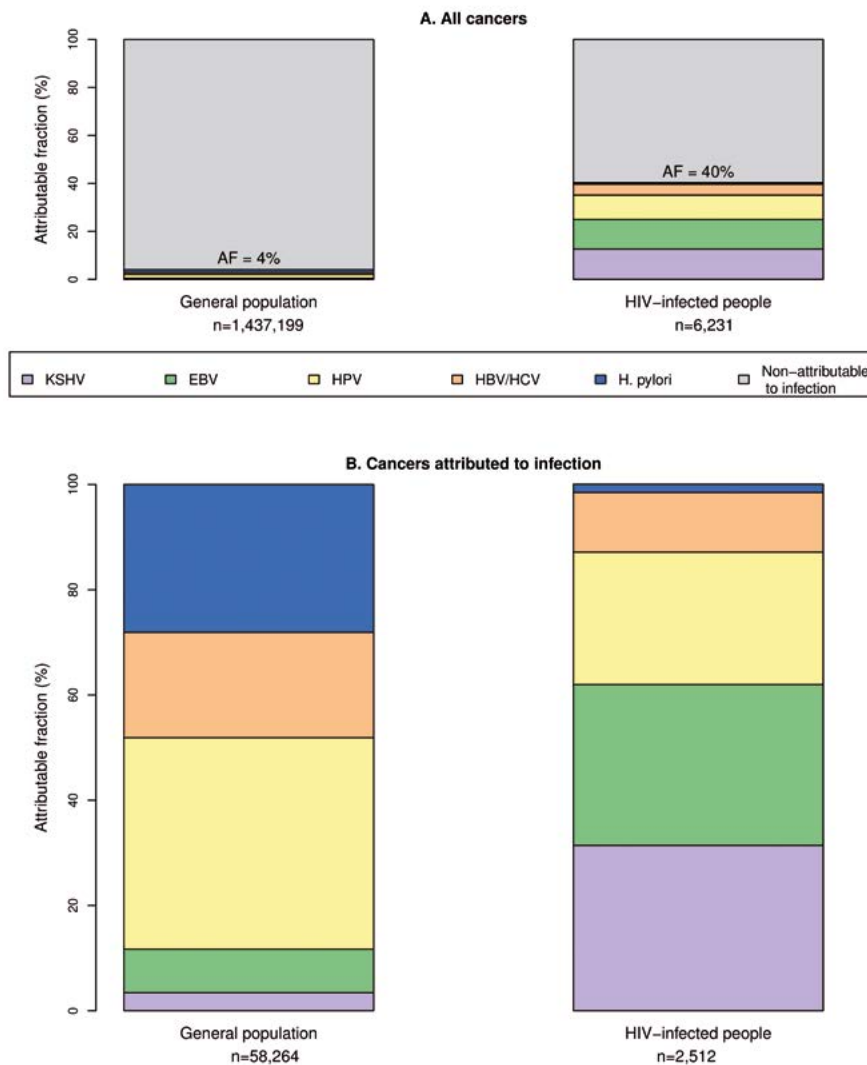
ICE published several model-based reports on the natural history of HPV infections and on the performance and costs of different strategies of

vaccination and screening, using high-quality data sets for IARC and European consortia (Franceschi and Baussano, 2014). ICE also reviewed the main principles of transmission dynamics, the basic structure of infection transmission models, and their use in combination with empirical data. The review also summarized models of carcinogenesis and their possible integration with models of the natural history of infections (Baussano et al., 2014a).

To disentangle the impacts of temporal changes in lifestyle, screening, and diagnostic practices on cancer trends, ICE produced ad hoc modifications of the age-period-cohort (APC) model in which non-identifiability was partly circumvented by making assumptions based on a consistent relationship between age and individual cancer incidence. For instance, it was shown that in the absence of cervical screening, incidence rates of cervical cancer for 2006–2010 in the Nordic countries would have been 3–5 times those observed (Vaccarella et al., 2014). Diagnostic changes (mainly the spread of neck ultrasonography and other imaging techniques) may account for more than 50% of differentiated thyroid carcinomas currently diagnosed in women younger than 80 years in many high-income countries, notably the Republic of Korea (> 80%), France, Italy, the USA, and Australia (Franceschi and Vaccarella, 2015; Vaccarella et al., 2015).

Finally, ICE staff participated in the development and dissemination of the R package for statistical computing.

Figure 3. Cancer attributable to infection in the general population and HIV-positive people in the USA in 2008. AF, attributable fraction; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; *H. pylori*, *Helicobacter pylori*; KSHV, Kaposi sarcoma-associated herpesvirus. Reprinted with permission from de Martel et al. (2015).

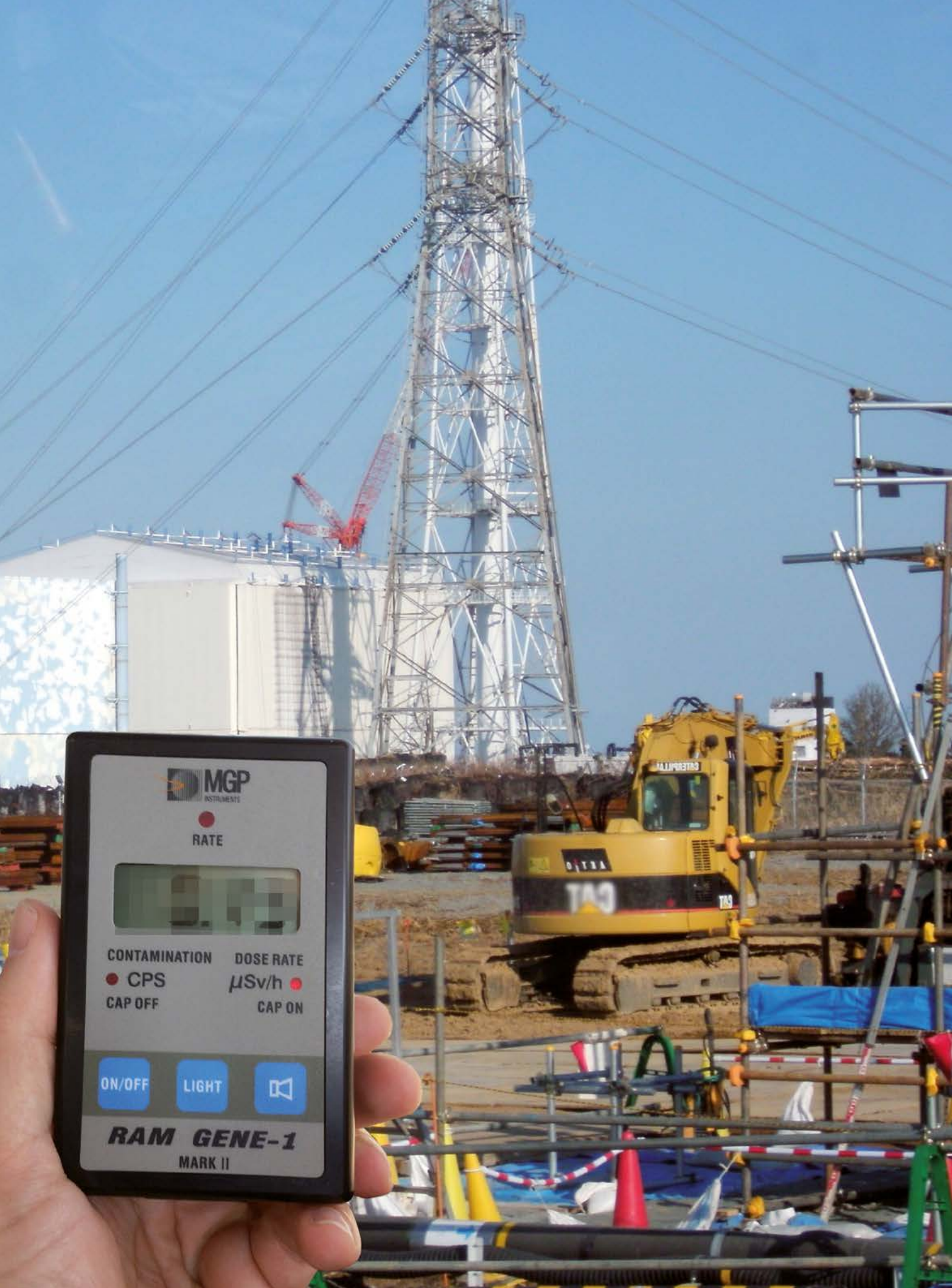


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MARK II

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THE SECTION OF ENVIRONMENT AND RADIATION (ENV) IS CHARGED WITH INVESTIGATING 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 THE 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 the investigation of external environmental exposures, such as pollutants and occupational exposures, and lifestyle factors. Major areas of interest are pesticides, asbestos, other occupational risk factors for lung cancer, and uranium. Potential interactions between environmental and other factors for the risk of and survival from cancer are investigated in studies in sub-Saharan African countries, with a focus on breast and oesophageal cancers. ENV is also involved in many projects related to ionizing radiation from medical diagnostic examinations, occupational activities, and environmental exposures from fallout from nuclear accidents, nuclear weapons testing, and nuclear waste disposal. 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 played a large role in IARC's update of the European Code Against Cancer, which makes recommendations about what actions to take to improve general health and reduce the risk of cancer.

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

PESTICIDES

Parental exposure to pesticides has been suggested to increase the risk of cancer in their offspring. Data from case-control studies participating in the Childhood Leukemia International Consortium were pooled, totalling more than 8000 cases of acute lymphoblastic leukaemia (ALL), more than 1300 cases of acute myeloid leukaemia (AML), and more than 14 000 controls. A 20% increased risk of ALL was observed for paternal occupational exposure before conception and a 90% increased risk of AML for maternal occupational exposure during pregnancy (Bailey et al., 2014a). Home pesticide use before conception, during pregnancy, and after birth also showed positive associations with the risk of ALL (a 30–50% increased risk) as well as AML (a similarly increased risk, except for after birth, where there was no association) (Bailey et al., 2015a). In contrast, a register-based nested case-control approach in the Nordic populations, totalling almost 10 000 cases and more than 30 000 controls, showed no association between paternal or maternal exposure to pesticides and the risk of testicular cancer in their sons (Le Cornet et al., 2015). Risks of haematological malignancies in agricultural workers are currently being investigated by pooling large cohort studies from France, Norway, and the USA; a systematic review suggested a positive association between exposures to some pesticides and the risk of non-Hodgkin lymphoma (Schinasi and Leon, 2014).

OCCUPATIONAL RISK FACTORS FOR LUNG CANCER

A study pooling data from 16 case-control studies on lung cancer from Europe and Canada with information on occupational history and lifetime smoking history (the SYNERGY project), comprising almost 20 000 cases and more than 23 000 controls, showed some positive associations between occupations and lung cancer after adjustment for smoking. Risk increases were about 30–50% for bricklayers (Consonni et al., 2015), painters, miners (Taeger et al., 2015), and welders. Increased risks of lung cancer seen in cooks (Bigert et al., 2015) and hairdressers are most likely attributable to their smoking behaviour. No increased risk was seen in bakers. The results are summarized in Figure 1. Further findings indicate that after accounting for co-occurring respiratory diseases, chronic bronchitis and emphysema have a positive association with lung cancer risk (Denholm et al., 2014). Using a modelling approach, analyses are under way to investigate the effect of known lung carcinogens such as respirable crystalline silica, nickel, chromium, polycyclic aromatic hydrocarbons, and asbestos, including the effects accounting for smoking and simultaneous exposures to several of these carcinogens. Cancer risks in workers exposed to asbestos in a large open-pit mine in the Southern Urals,

Russian Federation, are also being explored, including the quantification of known associations such as with mesothelioma or lung cancer, but asbestos may also be related to other cancers for which the scientific evidence has not been established so far, for instance stomach or colorectal cancer. Although the use of asbestos has been banned in many countries, the peak burden of mesothelioma is still to occur, as illustrated using mortality data for Germany (Schonfeld et al., 2014a).

RADIATION

IONIZING RADIATION AND RISK OF DEATH FROM CANCER IN NUCLEAR WORKERS

Quantification of the risks associated with very low doses of ionizing radiation is a challenging task because the expected effects are small and difficult to detect. Nevertheless, even small effects become non-negligible when considering millions of people exposed occupationally or millions of patients undergoing diagnostic procedures involving ionizing radiation. A landmark international study coordinated by IARC, the International Nuclear Workers Study (INWORKS) of more than 300 000 nuclear workers in France, the United Kingdom, and the USA, examined causes of death in the workers and has provided the strongest evidence yet that long-term exposure to low-dose radiation increases the risk of subsequent death

Figure 1. Occupations showing (left) increased lung cancer risk after adjustment for smoking, (centre) no increased risk after adjustment for smoking, and (right) no increased risk; data from the SYNERGY project (pool of 16 case-control studies from Europe and Canada). © IARC/ Joachim Schüz.



Table 1. Comparison between risks derived from analyses of the Life Span Study population exposed to higher radiation doses and dose rates, and risks observed in the INWORKS study

Cause of death	INWORKS		Life Span Study	
	Number of deaths	Excess relative risk	Number of deaths	Excess relative risk
Leukaemia, excluding chronic lymphocytic leukaemia	531	2.96 (90% CI, 1.17–5.21) ^a	94	2.63 (90% CI, 1.50–4.27) ^b
Solid cancer	17 957	0.47 (90% CI, 0.18–0.79) ^c	3475	0.32 (95% CI, 0.01–0.50) ^d

CI, confidence interval.

^a Leuraud et al. (2015).

^b Metz-Flamant C, Laurent O, Samson E, Caër-Lorho S, Acker A, Hubert D, et al. (2013). Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med.* 70(9):630–8. <http://dx.doi.org/10.1136/oemed-2012-101149> PMID:23716722

^c Richardson et al. (2015).

^d Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. (2005). Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *BMJ.* 331(7508):77. <http://dx.doi.org/10.1136/bmj.38499.599861.E0> PMID:15987704

caused by leukaemia (excluding chronic lymphocytic leukaemia) (Leuraud et al., 2015) and solid cancer (Richardson et al., 2015). The workers received average doses of just 1.1 mSv per year above background radiation, which is about 2–3 mSv per year from sources such as cosmic rays and radon (Thierry-Chef et al., 2015). Although based on a substantially lower dose distribution, the estimated excess relative risk of leukaemia mortality excluding chronic lymphocytic leukaemia (2.96 per Gy; 90% CI, 1.17–5.21) was consistent with risks derived from analyses of other populations exposed to higher radiation doses and dose rates (Table 1). The rate of mortality from all cancers was estimated to increase with cumulative dose by 51% per Gy (90% CI, 23–82%), lagged 10 years (Richardson et al., 2015). A similar association was estimated for all solid cancers (an increase of 47% per Gy; 90% CI, 18–79%), and further excluding lung cancer deaths from the analysis led to a minimal change in the magnitude of the estimated association, suggesting that positive bias due to confounding by smoking was unlikely. These findings show the importance of adherence to the basic principles of radiation protection: to optimize protection to reduce exposures as much as is reasonably achievable and – in the case of patient exposure – to justify that the exposure does more good than harm.

CANCER RISK RELATED TO COMPUTED TOMOGRAPHY EXAMINATIONS DURING CHILDHOOD

The growing use of computed tomography (CT) technology raises concerns about radiological protection, especially for children and adolescents. The EPI-CT multinational collaborative study, which aims to estimate individual radiation organ doses (and associated uncertainties) from CTs in young people and assess subsequent cancer risk, was specifically designed to address factors that can affect the interpretation of results from CT studies, including reverse causation, confounding by predisposing factors and other causes, and possible effect modification (Bosch

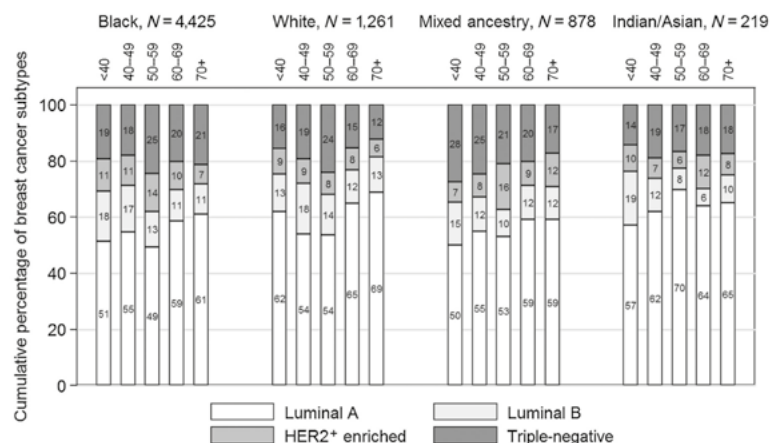
de Basea et al., 2015). To date, the study includes 1 163 571 patients from nine European countries (Belgium, Denmark, France, Germany, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). Data on 2 166 479 CT examinations (53.33% of them head CT scans) have been retrieved from participating radiology departments. An in vitro assessment of the γ -H2AX-foci assay as a cellular biomarker of age-dependent radiosensitivity demonstrated that it is feasible to apply the assay in a multicentre prospective study in paediatric CT imaging (Vandevorde et al., 2015). EPI-CT, the first large-scale international collaborative study, will contribute to estimating effects of low-level radiation in children and providing a basis for the optimization of paediatric CT protocols and patient protection, and also has the potential to consolidate a European paediatric cohort for long-term follow-up.

LIFESTYLE AND BEHAVIOUR

BREAST CANCER

In a study of more than 12 000 women with histologically confirmed breast cancer in South Africa and Namibia, it was found that estrogen receptor-positive cancer dominated in all races but that Black women had a modest excess of aggressive subtypes (Figure 2; Dickens et al., 2014a). In more than 1000 breast cancer patients from the largest hospital in Southern Africa,

Figure 2. Cumulative age-specific percentages of breast cancer subtypes in patients from South Africa and Namibia, by race. Numbers within bars indicate subtype percentages. Reprinted from Dickens et al. (2014a) by permission from the American Association for Cancer Research.



the risk of late-stage breast cancer increased with increasing distance from a patient's residence to the hospital, highlighting the prevention potential in this population (Dickens et al., 2014b). To study factors influencing breast cancer survival in sub-Saharan Africa, ENV has recently launched a large-scale survival study including South Africa, Namibia, Uganda, and Nigeria, the African Breast Cancer - Disparities in Outcomes (ABC-DO) study.

ESOPHAGEAL CANCER

Oesophageal cancer has a peculiar spatial distribution worldwide, including a high-incidence easterly corridor in Africa, which stretches north-south from Ethiopia and Kenya to South Africa (Figure 3). ENV has established a consortium (the ESCCAPE project) with ongoing case-control studies in Kenya and the United Republic of Tanzania and pilot work in Ethiopia, Malawi, and South Africa. Consumption of hot

beverages and food is a candidate risk factor, and a tea temperature survey in the United Republic of Tanzania showed that participants started drinking tea at a mean temperature of 70.6 °C (Munishi et al., 2015). In Ethiopia, another candidate risk factor is khat chewing, which is also a suspected risk factor for malignant oral disorders (El-Zaemey et al., 2015).

CHILDHOOD CANCERS

Childhood cancer, especially ALL, shows great international variation, although the disease may be underdiagnosed in low- and middle-income countries (Erdmann et al., 2015a). ENV therefore aims to involve more such countries in the research and has established the Global Acute Leukaemia network (GALnet). Recent research from high-income countries suggests roles, although modest, of parental pesticide exposure (see above) and parental home paint exposure (Bailey et al., 2015b), and a protective effect of maternal

supplementation with folic acid (Metayer et al., 2014).

CANCER PREVENTION

The European Code Against Cancer is a preventive tool aimed at reducing the cancer burden by informing people about how to avoid or reduce carcinogenic exposures, adopt behaviours to reduce their cancer risk, or participate in organized intervention programmes. The fourth edition of the Code was launched in October 2014. This update, led by ENV together with the Quality Assurance Group, also includes recommendations on occupational and environmental exposures as well as ionizing radiation and ultraviolet radiation; the Code is shown in Figure 4. It is estimated that the cancer burden could be reduced by up to one half if scientific knowledge on the causes of cancer could be translated into successful prevention.

Figure 3. Incidence of oesophageal cancer (EC) in men and women in African countries, showing high rates in countries along the Great Rift Valley. Reprinted from Schaafsma et al. (2015). © 2015 Schaafsma et al.

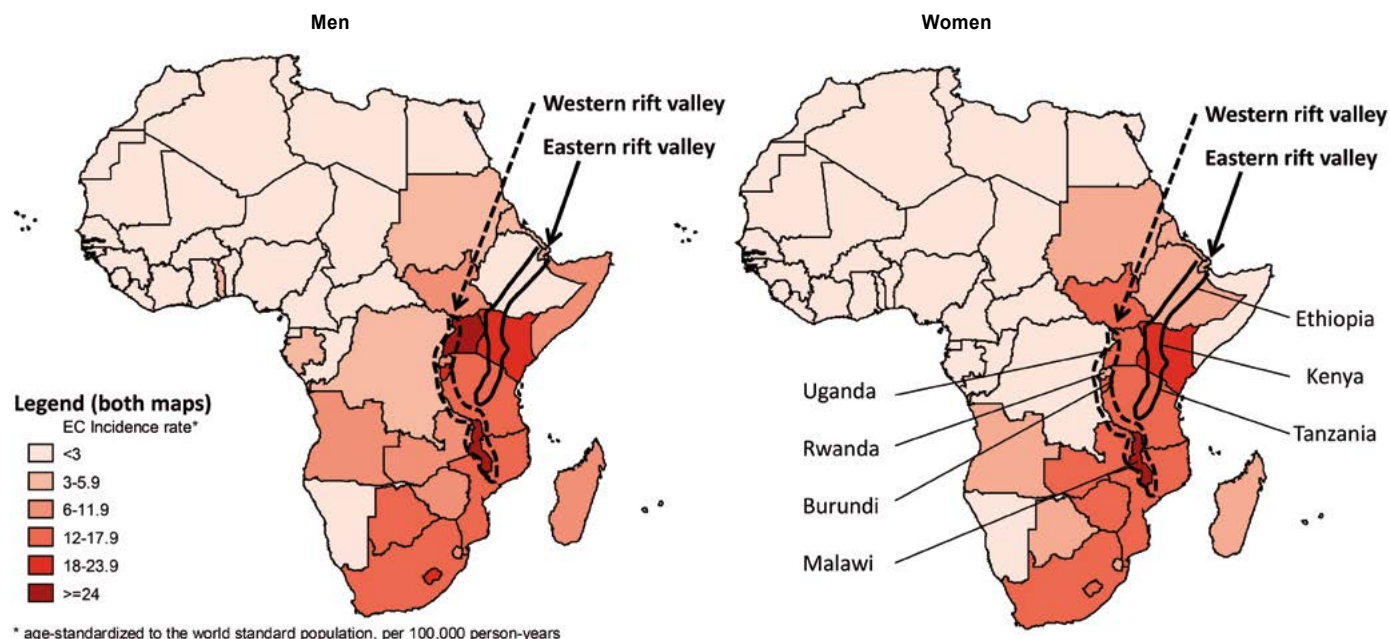


Figure 4. The fourth edition of the European Code Against Cancer, launched in October 2014: 12 recommendations to reduce your cancer risk (<http://cancer-code-europe.iarc.fr>). © IARC.

European Code Against Cancer

12 ways to reduce your cancer risk

- 1 Do not smoke. Do not use any form of tobacco.
- 2 Make your home smoke free. Support smoke-free policies in your workplace.
- 3 Take action to be a healthy body weight.
- 4 Be physically active in everyday life. Limit the time you spend sitting.
- 5 Have a healthy diet:
 - Eat plenty of whole grains, pulses, vegetables and fruits.
 - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
 - Avoid processed meat; limit red meat and foods high in salt.
- 6 If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.
- 7 Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.
- 8 In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.
- 9 Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.
- 10 For women:
 - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
 - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.
- 11 Ensure your children take part in vaccination programmes for:
 - Hepatitis B (for newborns)
 - Human papillomavirus (HPV) (for girls).
- 12 Take part in organized cancer screening programmes for:
 - Bowel cancer (men and women)
 - Breast cancer (women)
 - Cervical cancer (women).

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

Find out more about the European Code Against Cancer at: <http://cancer-code-europe.iarc.fr>

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SECTION OF NUTRITION AND METABOLISM (NME)

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DIET, NUTRITION, METABOLIC/HORMONAL IMBALANCES, EXCESS ENERGY CONSUMPTION, OBESITY, AND PHYSICAL INACTIVITY ARE THOUGHT TO BE IMPORTANT CONTRIBUTORS TO INCREASING CANCER INCIDENCE RATES WORLDWIDE. HOWEVER, THE MECHANISMS OF ACTION OF THESE FACTORS REMAIN POORLY UNDERSTOOD. IN ADDITION, THE CONTRIBUTING INFLUENCES OF DIETARY TRANSITIONS FROM TRADITIONAL DIETS TO DIETS TYPICAL OF INDUSTRIALIZED COUNTRIES, WHICH IS TAKING PLACE IN LOW- AND MIDDLE-INCOME COUNTRIES (E.G. IN LATIN AMERICA), AND OF EXPOSURES IN FETAL LIFE OR EARLY INFANCY ARE NOT WELL STUDIED. THUS, THE MAIN OBJECTIVE OF THE SECTION OF NUTRITION AND METABOLISM (NME) IS TO ADDRESS THESE ISSUES BY EVALUATING THE ASSOCIATION OF DIET, DIETARY PATTERNS, NUTRITION, PHYSICAL ACTIVITY, AND ENERGY IMBALANCE WITH CANCER RISK IN HIGH-INCOME AND MEDIUM-TO-LOW-INCOME COUNTRIES USING COHORT AND CASE–CONTROL DESIGNS OR HUMAN INTERVENTION STUDIES. THE EMPHASIS IS ON IMPROVING THE ASSESSMENT OF DIETARY EXPOSURES THROUGH STANDARDIZED DIETARY METHODOLOGIES RELEVANT TO INTERNATIONAL STUDY SETTINGS; APPLYING BIOMARKERS AND METABOLOMICS TO STUDY CELLULAR, BIOCHEMICAL, AND PHYSIOLOGICAL CHANGES; AND CONSIDERATION OF GENE–ENVIRONMENT INTERACTIONS. THE TRANSLATION OF FINDINGS INTO PUBLIC HEALTH RECOMMENDATIONS FOR CANCER PREVENTION IS OF MAJOR IMPORTANCE TO THE SECTION.

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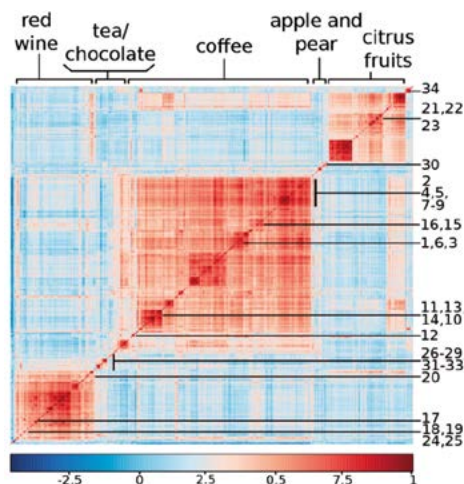
The activities of the Biomarkers Group (BMA) have shown a significant development over the 2014–2015 biennium, with the recruitment of three new technicians and three postdoctoral researchers, the relocation of the BMA laboratory and offices to the tower building with a larger space, and the acquisition of two new mass spectrometers and a robot for sample handling.

Several methods based on mass spectrometry have been developed to analyse the metabolome in blood and urine samples (polyphenols, sex steroids, and intermediate metabolism). Methodological studies on the application of these methods to epidemiological studies have been performed (Carayol et al., 2015). The methods were applied to a prospective study on the etiology of hepatocellular carcinoma, in collaboration with the Nutritional Epidemiology Group (NEP), and studies on breast cancer are in progress.

Standard operating procedures were developed to analyse the metabolome on a broader scale (> 3000 metabolites detected) in urine and plasma samples by high-resolution mass spectrometry (Edmands et al., 2014, 2015). These methods were used to characterize the food metabolome (Scalbert et al., 2014) and to identify novel dietary biomarkers (coffee, tea, red wine, citrus fruits, and apples) in a cross-sectional study in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (Figure 1) (Edmands et al., 2015). A new database is being developed called Exposome-Explorer, which includes detailed information on all known dietary biomarkers.

A new food composition table for all known polyphenols was built within the EPIC study, in collaboration with the Dietary Exposure Assessment Group (DEX), and was used to calculate the intake of more than 400 polyphenols in the EPIC cohort (Figure 2). In parallel, a new analytical method was developed to measure the levels of 34 polyphenol biomarkers in urine. The method was applied to 24-hour urine samples collected from 475 subjects in the EPIC cohort. High correlations were observed between polyphenol biomarkers and

Figure 1. Heat map showing clusters of signals detected by high-resolution mass spectrometry and associated with the consumption of six specific foods, in 475 urine samples collected in the European Prospective Investigation into Cancer and Nutrition (EPIC) cross-sectional study. Numbers indicate metabolites identified as best predictors of intake. Reprinted with permission from Edmands et al. (2015).

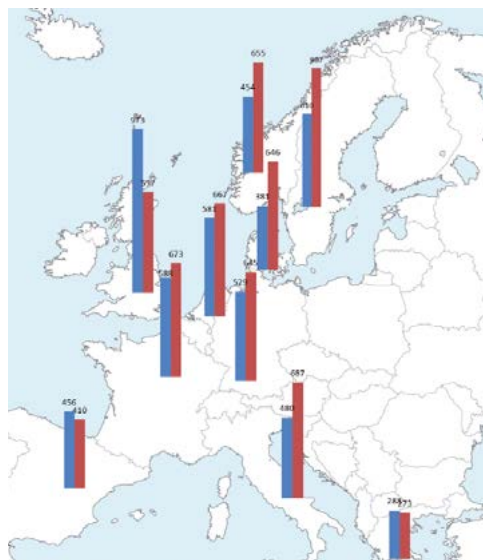


intake measurements, showing the high quality of the new food composition table. Studies on reproductive and menstrual factors, as well as on energy and macronutrient intake and the risk of differentiated thyroid cancer, have been undertaken within the EPIC cohort (Zamora-Ros et al., 2015a), and circulating inflammatory factors and sex steroids are currently being analysed in the same studies. Associations between growth factors, adipokines, and body size in young Mexican women have been inves-

tigated in the Mexican Teachers' Cohort, in collaboration with NEP (Rinaldi et al., 2014a, 2015) to assess whether different adipose tissues are associated with different metabolic alterations.

A method based on gas chromatography has been validated to determine in plasma/serum 60 fatty acids from dietary sources and endogenous metabolism. It is currently being applied to large epidemiological studies, in collaboration with NEP.

Figure 2. Polyphenol intake in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Intake (in mg/day) is shown for the two main classes of polyphenols (flavonoids, blue bars; phenolic acids, red bars) in the 10 countries of the cohort. Compiled from Zamora-Ros R, Knaze V, Rothwell JA, Hémon B, Moskal A, Overvad K, et al. (2015). Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Nutr. <http://dx.doi.org/10.1007/s00394-015-0950-x> PMID:26081647.



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International nutrition surveillance systems to monitor trends and better understand the nutrition transition and its association with the global burden of noncommunicable diseases (NCDs) are currently lacking. To address this gap, the Dietary Exposure Assessment Group (DEX) launched the IARC-WHO Global Nutrition Surveillance initiative in 2014–2015, with the aim of collecting standardized dietary data worldwide, using DEX methodologies, to support dietary surveillance, research, and prevention of cancer and other NCDs, and ultimately to promote more concerted prevention and research action plans. The GloboDiet-Europe consortium, involving seven countries using the DEX methodology in their national surveys (Austria, Belgium, France, Germany, Malta, the Netherlands, and Switzerland), has been developed as a proof of concept of the global initiative, and the legal consortium framework to support it is being explored. In parallel, pilot initiatives have been pursued in other regions worldwide (Latin America,

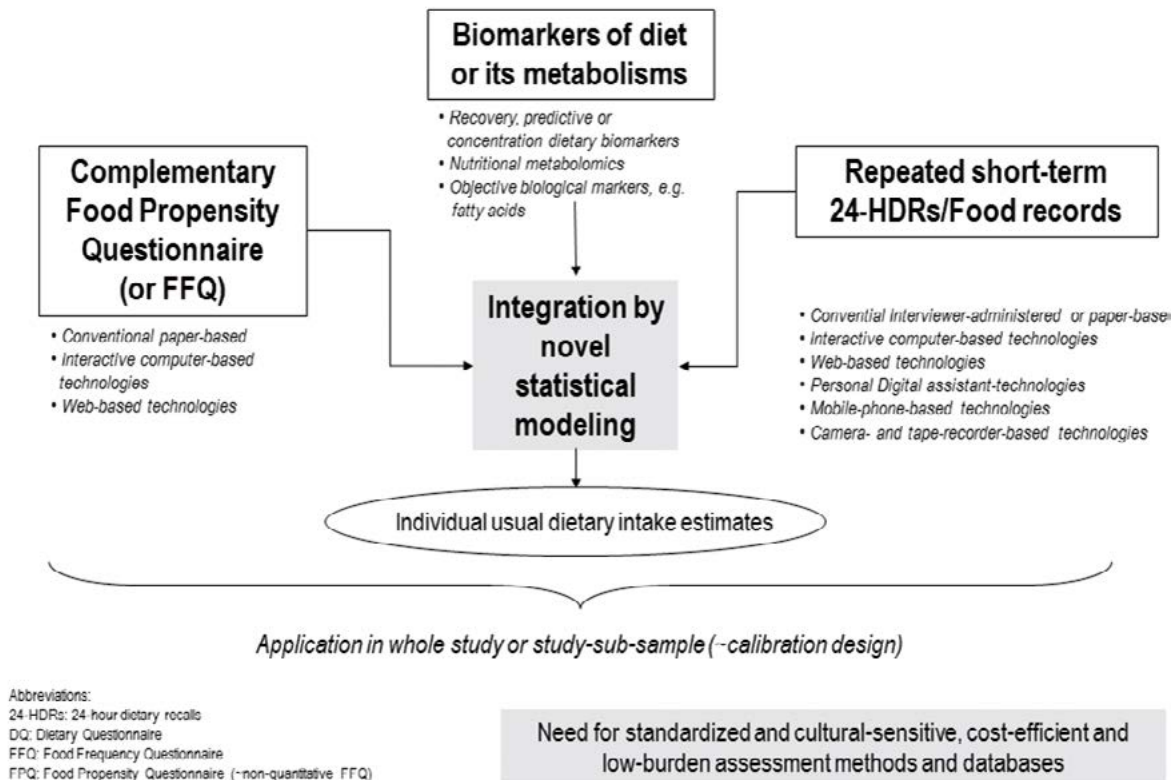
Asia, and Africa). Korean (Park et al., 2015), Mexican, and Brazilian versions of GloboDiet have been completed, and road maps for their local validation and implementation are advanced. In Africa, an inventory, conducted as a prerequisite of any implementation, highlighted a lack of comparable dietary assessment methods and support infrastructure for research across the 18 countries represented, and elucidated specific needs and obstacles for implementation.

DEX, as part of its advanced methodological research on improving dietary assessment (Freisling and Slimani, 2015; Leclercq et al., 2015; Julián-Almárcegui et al., 2015; Slimani et al., 2015) and its contribution to the transfer of knowledge and training (Figure 1), and through partnerships and grant projects (e.g. Determinants, Intake, Status, Health [EuroDISH]; Biobanking and Biomolecular Resources Research Infrastructure – Large Prospective Cohorts [BBMRI-LPC]; Determinants of Diet and Physical Activity [DEDIPAC]; and Pilot Study for the Assessment of Nutrient Intake and Food Consumption Among Kids in Europe [PANCAKE]),

has led the development of a strong virtual research environment/research infrastructure (GloboDiet-VRE/RI) concept. GloboDiet-VRE/RI aims to support the GloboDiet initiative, as well as new international targeted tools (e.g. tools targeted to children validated in the PANCAKE project) (Freisling et al., 2015; Ocké et al., 2015) and validation against biomarkers of WHO health indicators obtained with GloboDiet (e.g. sodium intakes) (De Keyzer et al., 2015a). This GloboDiet-VRE will feed into the European Strategy Forum on Research Infrastructures (ESFRI) road map of implementation of a pan-European Union interfaced food and nutrient intake RI.

New approaches to analyse nutrient patterns in international study settings have been initiated by DEX in collaboration with the Nutritional Epidemiology Group (NEP), starting with a first European-wide nutrient patterns analysis (Moskal et al., 2014). These patterns were shown to be associated with moderate but significant long-term differences in weight gain in adults.

Figure 1. Towards an integrated approach to measure diet in international epidemiological studies. Reprinted from Illner AK, Freisling H, Boeing H, Huybrechts I, Crispim SP, Slimani N (2012). Review and evaluation of innovative technologies for measuring diet in nutritional epidemiology. *Int J Epidemiol.* 41(4):1187–203. <http://dx.doi.org/10.1093/ije/dys105> PMID:22933652, by permission of Oxford University Press.



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EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION (EPIC)

The Nutritional Epidemiology Group (NEP) ensures the coordination of the European Prospective Investigation into Cancer and Nutrition (EPIC) by centralizing up-to-date cancer end-point/vital status data (Table 1), centralizing multiple end-points and updated exposure information, delivering project-specific databases to the EPIC network, and tracking biological sample retrieval/use.

NUTRITIONAL AND LIFESTYLE CANCER PREDICTORS

OBESITY

Maintaining a healthy weight is important for cancer prevention. NEP's analysis, in collaboration with the Dietary Exposure Assessment Group (DEX) and the Biomarkers Group (BMA), of circulating industrial trans fatty acids (biomarkers of highly processed foods) shows a positive association with weight gain over time (Chajès et al., 2015) and has been extended to countries in Latin America, the Middle East, and Africa.

ALCOHOL CONSUMPTION AND CANCER

Higher lifetime alcohol consumption was identified as a major determinant of mortality (Ferrari et al., 2014). However, an inverse association was noted for papillary and follicular thyroid carcinomas (Sen et al., 2015). A consortium of worldwide cohorts was created to evaluate alcohol–cancer associations at less-studied anatomical sites.

EARLY ENVIRONMENTAL EXPOSURE, METABOLIC DISORDERS, AND CANCER

NEP's study of fetal and childhood exposures and the incidence of intermediate cancer outcomes shows an influence of supplementation with docosahexaenoic acid (DHA) on methylation at *IGF2/H19* imprinted genes (Lee et al., 2014a) and an important role of breastfeeding on lowered adiposity and total cholesterol levels in childhood (Ramirez-Silva et al., 2015).

BREAST CANCER

NEP's work on dietary and lifestyle patterns has shown reduced breast

cancer risk in women with nutrient patterns high in micronutrients originating from vegetables, fruits, and cereals, or women who score highly on a healthy lifestyle index (McKenzie et al., 2015). Further analysis showed a link between higher alcohol consumption and breast cancer of all receptor-based phenotypes, particularly among women consuming alcohol before their first full-term pregnancy (Figure 1) (Romieu et al., 2015).

Two nutrients of interest are dietary folate and fatty acids. Higher intake of dietary folate was associated with lower risk of estrogen receptor (ER)-negative breast cancers in premenopausal women (de Batlle et al., 2015). Preliminary biomarker-based results suggest different breast cancer risks for specific fatty acid subgroups (Pouchieu et al., 2014).

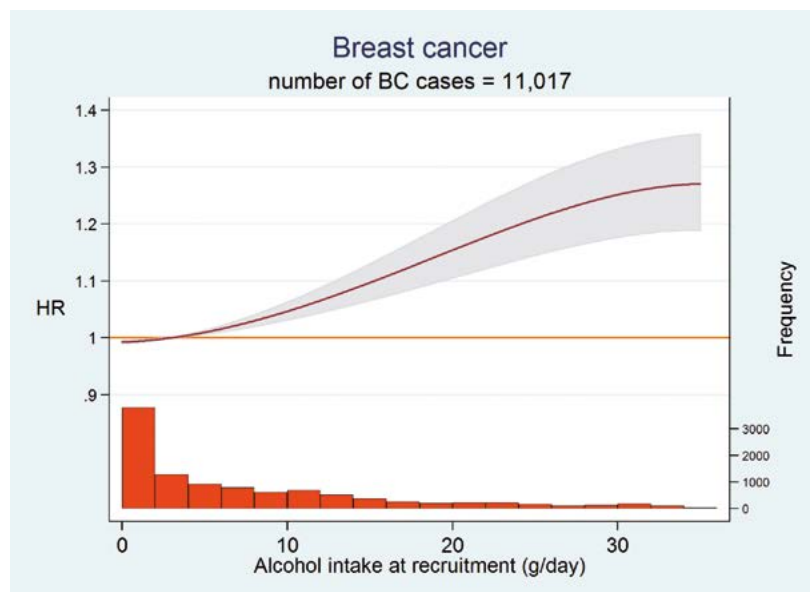
STUDIES ON BREAST CANCER IN LOW- AND MIDDLE-INCOME COUNTRIES

NEP collaborated with national institutions in Mexico in the large prospective Mexican Teachers' Cohort to explore

Table 1. Description of the European Prospective Investigation into Cancer and Nutrition (EPIC) study

Sex	Country	Number of participants	Person-years	Number of incident cancers	Number of incident deaths
Women	France	74 523	1 420 115	9015	5723
	Italy	32 577	498 612	3561	1551
	Spain	25 808	479 249	2288	1528
	United Kingdom	60 967	1 007 559	7325	7669
	Netherlands	29 751	484 984	3579	3042
	Greece	16 614	181 903	770	1213
	Germany	30 255	411 560	2354	1453
	Sweden	30 328	552 306	4620	4668
	Denmark	29 875	490 930	5778	4110
	Norway	37 200	514 326	3802	1452
	Total		367 898	6 041 544	43 092
Men	France	—	—	—	—
	Italy	15 168	237 627	1829	1133
	Spain	15 629	284 030	2466	2155
	United Kingdom	26 917	424 843	4445	6396
	Netherlands	10 260	166 222	869	885
	Greece	11 947	121 475	740	1537
	Germany	22 833	311 217	2597	2590
	Sweden	23 494	413 112	4764	5455
	Denmark	27 178	428 296	6206	5886
	Norway	—	—	—	—
	Total		153 426	2 386 821	23 916

Figure 1. Dose–response curve of breast cancer (BC) risk with alcohol intake at recruitment. The dose–response curve is displayed up to 35 g/day, corresponding to the 99th percentile of the alcohol intake distribution. Reprinted with permission from Romieu et al. (2015).



predictors of mammographic density (Rinaldi et al., 2014a; Rice et al., 2015). Results from a multicentre case–control study conducted in Mexico show increased breast cancer risks with increasing body shape silhouette over the life course (Amadou et al., 2014a), high carbohydrate intake (Amadou et al., 2015), and lower scores on a healthy lifestyle index (Fanidi et al., 2015).

NEP leads a World Cancer Research Fund (WCRF)-funded study of dietary/lifestyle determinants of breast cancer in the understudied population of Soweto, South Africa, with structured collection of individual, clinical, and pathological information, biological specimens, and detailed anthropometry (DEXA/ultrasound). This study will provide relevant information on tumour subtype frequencies and specific risk factors for breast cancer incidence and survival.

MOLECULAR SUBTYPES OF PREMENOPAUSAL BREAST CANCER IN LATIN AMERICAN WOMEN (PRECAMA): A MULTICENTRE POPULATION-BASED CASE–CONTROL STUDY

NEP coordinates the PRECAMA project to explore risk factors for premenopausal breast cancer among Hispanic women in four Latin American countries (Chile,

Colombia, Costa Rica, and Mexico). The standardized protocols (refined phenotyping, identification of endogenous or exogenous risk factors) and structured collection of individual, clinical, and pathological information and biological specimens were successful in the feasibility study (<http://precama.iarc.fr>). The main study is now under way, with Brazil also joining.

COLORECTAL CANCER

Inverse associations with risk of colorectal cancer were observed with higher circulating selenoprotein P levels (a selenium status indicator) (Hughes et al., 2015), higher plasma alkylresorcinols (biomarkers of whole-grain intake), for the distal colon cancer only (Kyrø et al., 2014a), and lower endogenous energy excess, for rectal cancer only. Post-diagnosis survival of colorectal cancer patients was improved with lower pre-diagnostic general/abdominal adiposity (Fedirko et al., 2014a) or concordance with the WCRF/American Institute of Cancer Research (WCRF/AICR) cancer prevention guidelines (Romaguera et al., 2015).

HEPATOCELLULAR CARCINOMA

Associations with decreased risk of hepatocellular carcinoma were observed

with higher consumption of monounsaturated fats (Duarte-Salles et al., 2015), vegetables (Bamia et al., 2015a), or coffee/tea (Bamia et al., 2015b) and with lower consumption of sugary drinks and of milk/cheeses (Duarte-Salles et al., 2014). Multiplatform metabolomic analyses identified distinct profiles between cases and matched controls (Fages et al., 2015), particularly with respect to levels of some amino acids.

METHODOLOGICAL RESEARCH

NEP has developed statistical techniques to correct for measurement errors in episodically consumed foods (Agogo et al., 2014) and to evaluate individual-level and aggregate-level evidence of diet–disease associations using multilevel modelling (Sera and Ferrari, 2015). Analytical frameworks were conceptualized to explore major sources of variability in large-dimensional data (e.g. metabolomics; Fages et al., 2014) and to model the “meeting-in-the-middle” principle linking dietary/lifestyle exposures and cancer risks through metabolomics (Assi et al., 2015). The treelet transform was identified as an informative technique to investigate dietary patterns in breast cancer etiology.

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SECTION OF GENETICS (GEN)

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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 AND GENETIC PROFILES THAT CONTRIBUTE TO THE DEVELOPMENT OF CANCER AND ELUCIDATE HOW THEY EXERT THEIR EFFECT ALONG WITH ENVIRONMENTAL FACTORS. THE SECTION ALSO TRIES TO IDENTIFY INDIVIDUALS WHO ARE AT HIGH ENOUGH RISK THAT THEY ARE LIKELY TO BENEFIT FROM EXISTING RISK REDUCTION STRATEGIES.

GEN's projects usually involve extensive fieldwork in collaboration with external investigators in order to develop large-scale epidemiological studies with appropriate clinical and exposure data, as well as biosample collection. 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 genotyping studies, 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 genome-wide association genotyping arrays. GCS's 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 within GEN and more widely across research Sections of the Agency.

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The Biostatistics Group (BST) continued to collaborate with several Sections at IARC. In some cases this involved the development of novel techniques, in others the identification of appropriate standard approaches, and in all cases with the goal of ensuring the reliability of scientific findings at the Agency.

Methodological highlights included the modelling contribution to the estimation of global cancer burden due to overweight and obesity (Arnold et al., 2015a), the identification of somatic mutation patterns suggesting that aristolochic acid may be an important factor in hepatocellular carcinoma in Romania

(Scelo et al., 2014), the development of an approach to epigenetic analysis of childhood cancer risk (Ghantous et al., 2015), and the exploration of the “meeting-in-the-middle” approach to multi-omics analysis (Assi et al., 2015).

Other contributions included refining the use of multiple data types to identify germline genetic factors associated with risk of aerodigestive tract cancers (Delahaye-Sourdeix et al., 2015a, 2015b).

Routine statistical oversight also contributed to some articles on risk factors for thyroid cancer (e.g. Zamora-Ros et al., 2015a).

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The Genetic Cancer Susceptibility Group (GCS) has two equally weighted roles within IARC. First, GCS acts as a laboratory, bioinformatics, and pathology resource for genomic research at the Agency. Second, in close collaboration with its Section partners the Genetic Epidemiology Group (GEP) and the Biostatistics Group (BST), GCS undertakes genetic and genomics research to identify cancer-related genes and explore their mechanisms of action. Through this knowledge, GCS aims to provide insights into cancer etiology, early detection, and prevention.

During the 2014–2015 biennium, GCS has welcomed three scientists into the Group: Dr Matthieu Foll, Dr Lynnette Fernandez-Cuesta, and Dr Behnoush Abedi-Ardekani. Their joining the Group has strongly reinforced its scientific profile in bioinformatics, somatic mutations, and genomic-related pathology, respectively.

GENOME-WIDE ASSOCIATION STUDIES

One of GCS's key scientific findings during the biennium was through a very large imputation-based genome-wide association study (GWAS) of lung cancer. This was undertaken through a collaboration between IARC, the Institute of Cancer Research (United Kingdom), Dartmouth College (USA), and the United States National Cancer Institute (US NCI) (Wang et al., 2014a). It included 21 594 cancer cases and 54 156 controls, making it one of the largest genetic studies of lung cancer carried out to date. This analysis identified three novel

variants: one small-effect, common allele (rs13314271, located near *TP63*) and two large-effect, rare alleles (rs17879961, a missense variant [I157T] in *CHEK2*, and rs11571833, a truncating variant that results in the loss of the final 93 amino acids of *BRCA2*). Also, rs11571833 was observed to be similarly strongly associated with upper aerodigestive tract cancer (Delahaye-Sourdeix et al., 2015a). The association noted with the *CHEK2* variant validated GCS's previous observation of an inverse association with lung cancer and contrasts with the well-described increase in risk described for this variant in other cancers. In the case of *BRCA2*, susceptibility to lung and upper aerodigestive tract cancer had not been previously linked to genetic variation in this well-studied gene. Both findings suggest that alternative susceptibility mechanisms are at work and highlight how unexpected findings from agnostic genetic studies inform cancer etiology.

GCS also coordinated a meta-analysis-based GWAS of Hodgkin lymphoma that identified a susceptibility locus near *TCF3*, a gene critical to B-cell development (Cozen et al., 2014), and GCS was involved in the validation of rare variants linked with breast cancer in *RINT1* (Park et al., 2014a) and the MRE11A-RAD50-nibrin (MRN) complex (Damiola et al., 2014a). GEN has completed recruitment of a multicentre case–control study of 2535 nasopharyngeal cancer (NPC) cases and 2652 controls from centres in Malaysia (Sarawak), Thailand, Singapore, and Indonesia. Linkage analysis of 17

NPC cases from an extended pedigree recruited from Malaysia identified 6p22.1 as an area of interest. This region contains the *HLA-A* gene, previously implicated in NPC. In collaboration with the US NCI, GCS identified that allele HLA-A*24:07 segregates with NPC in this pedigree. The HLA-A*24:07 allele is relatively common to Sarawak and very rare elsewhere. Work is in progress to determine whether this allele is associated with NPC in the case–control study.

GENETIC SERVICES PLATFORM

The Genetic Services Platform has overseen the installation of an additional liquid-handling robot to assist in GCS's laboratory protocols and the management of the almost 100 000 DNA samples, originating from about 75 studies, that are housed within GCS. In addition, an Ion Torrent Proton next-generation sequencer has been installed, and collaborative links have been maintained with local service providers to access additional genomic techniques, such as Illumina (HiSeq/HiScan technology). In bioinformatics, GCS has overseen two technical updates of IARC's high-performance computer cluster and data management systems, and has placed particular emphasis on the development of algorithms able to detect low-allele-frequency variants in the context of targeted next-generation sequencing-based resequencing. GCS has played a key role in the development of the Bioinformatics Steering Committee, a group that monitors bioinformatics across the Agency.

GCS is grateful to the following for their collaboration:

Professor Gilles Thomas and his team at Synergy Lyon Cancer (Lyon, France) for high-performance computing support. Professor Thomas was an inspiration to GCS and is deeply missed. Other collaborators include: Melissa C. Southey, Melbourne, Australia; Henrik Hjalgrim, Copenhagen, Denmark; Francesca Damiola, Charles Dumontet, Uzma Hasan, Joel Lachuer, Lyon, France; Fabienne Lesueur, Paris, France; Jajah Fachiroh, Dewajani Purnomosari, Yogyakarta, Indonesia; Beena Devi, Kuching, Malaysia; Anke van den Berg, Groningen, The Netherlands; Tam Ha, Singapore; Suleeporn Sangrajrang, Bangkok, Thailand; Ruth Jarrett, Glasgow, United Kingdom; Chris Amos, Hanover, USA; Wendy Cozen, Los Angeles, USA; David E. Goldgar, Sean V. Tavtigian, Salt Lake City, USA; Allan Hildesheim, Bethesda, USA.

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La Ligue contre le Cancer Rhône-Alpes, France
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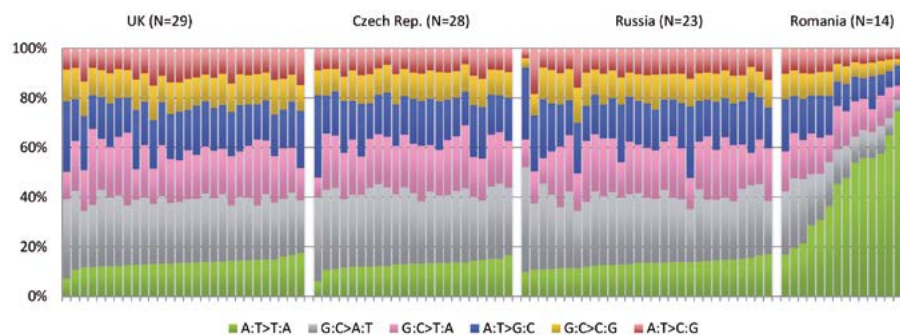
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The overall goal for the Genetic Epidemiology Group (GEP) is to identify genetic susceptibility variants of various cancer sites and study their interaction with environmental factors. An additional goal is to develop accurate risk prediction models 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 (lung and aerodigestive tract cancers) and cancers with moderate incidence rates (such as kidney and pancreatic cancers). GEP devotes substantial resources to extensive fieldwork, with the goal of recruiting large series of cases and controls, comprising extensive questionnaire information and biological samples. Genetic analyses usually comprise 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 of data that have been collected during fieldwork. Some prominent examples of the Section's work over the 2014–2015 biennium are described here.

GENETICS OF KIDNEY CANCER

The first phase of the CAGEKID study (part of the International Cancer Genome Consortium) has been completed, with complete whole-genome sequencing of 100 tumour–germline DNA pairs collected through the IARC central European study and in the United Kingdom. Initial important findings included the observation of a large majority of patients from Romania who

Figure 1. Mutation patterns from whole-genome sequencing of 94 conventional renal cell carcinomas from four different countries, showing a notable excess in the proportion of A:T > T:A mutations in cases from Romania. Reprinted with permission from Brennan P, Wild C (2015). Genomics of cancer and a new era for cancer prevention. PLoS Genet. <http://dx.doi.org/10.1371/journal.pgen.1005522>.

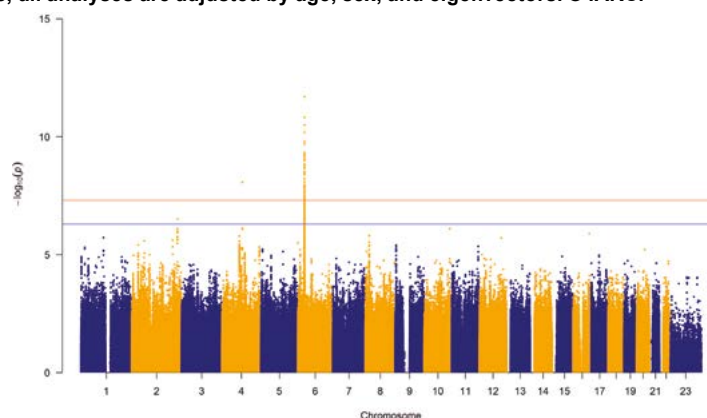


had an unexpectedly high frequency of A:T > T:A transversions, consistent with exposure to aristolochic acid (Scelo et al., 2014). These results show that the processes underlying clear-cell renal cell carcinoma (ccRCC) tumorigenesis may vary in different populations and suggest that aristolochic acid may be an important ccRCC carcinogen in Romania, a finding with major public health implications (Figure 1). In parallel, the genome-wide analysis of renal cancer susceptibility has been completed, in a large study comprising germline genetic data on more than 10 000 renal cancer cases and 20 000 controls. This work is being undertaken in collaboration with the United States National Cancer Institute, and initial analyses point to several new genetic loci for this cancer.

GENOME-WIDE ANALYSIS OF TOBACCO-RELATED CANCERS

GEP has coordinated a large OncoArray analysis of more than 7000 cancers of the oral cavity or oropharynx, along with a similar number of controls. A prominent finding from this study is the important role of the HLA region for oropharyngeal cancer, suggesting an important interaction with HPV (Figure 2). GEP has identified specific HLA loci that are associated with multiple forms of HPV antibody expression (Chen et al., 2015). In addition, GEP is contributing a large series of cases to the genome-wide study of lung cancer that is due to report its findings at the end of 2015.

Figure 2. Manhattan plot of oropharyngeal OncoArray genome-wide association studies (GWASs). The vertical axis shows $-\log_{10}(P\text{-values})$ for 7.5 million single-nucleotide polymorphisms (SNPs), 432 220 genotyped sites (OncoArray platform), and 7 099 472 imputed sites. The red horizontal line represents $P = 5 \times 10^{-8}$, and the blue horizontal line represents $P = 5 \times 10^{-7}$. Noticeably, there is a strong genome-wide significant signal at 6p21.32 in the MHC region (leading SNP, rs3828805; $P = 2.03 \times 10^{-12}$). Also noticeable is rs1229984 at 4q23 ($P = 8.53 \times 10^{-9}$), a previously known locus, and there is a suggestive signal for rs1961637 at 2q36.1 ($P = 3.03 \times 10^{-7}$). P -values are the result of a fixed-effect meta-analysis of three GWASs by region (Europe, North America, and South America), comprising 2666 cases and 6585 controls; all analyses are adjusted by age, sex, and eigenvectors. © IARC.



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(until June 2015)

PREVENTION AND EARLY DETECTION, INCLUDING INTERVENTIONS TO REDUCE EXPOSURE, SCREENING, AND EARLY DIAGNOSIS, CAN DECREASE CANCER INCIDENCE AND MORTALITY AND IMPROVE QUALITY OF LIFE. UNTIL MARCH 2015, THE SECTION OF EARLY DETECTION AND PREVENTION (EDP) WAS COMPOSED OF THREE GROUPS: THE PREVENTION AND IMPLEMENTATION GROUP (PRI), THE QUALITY ASSURANCE GROUP (QAS), AND THE SCREENING GROUP (SCR). THE SECTION WAS SUBSEQUENTLY RESTRUCTURED AND NOW CONSISTS OF ONLY TWO GROUPS: PRI AND SCR. THE ACTIVITIES OF QAS DURING THE 2014–2015 BIENNIUM ARE REPORTED HERE UNDER SCR.

EDP carries out research on resource-appropriate public health policies and feasible, quality-assured, and cost-effective prevention and early detection strategies for the control of common cancers such as breast, cervical, colorectal, oral, oesophageal, and stomach cancer globally, with an emphasis on low- and middle-income countries (LMICs). Prevention offers the most cost-effective long-term strategy for cancer control. The Section's main focus areas in primary prevention are the development and implementation of safe, effective, and affordable vaccination schemes for human papillomavirus (HPV)-related cancers and the evaluation of the impact of *Helicobacter pylori* eradication on stomach cancer. The major focuses of EDP's early detection research are assessing new technologies and alternative screening approaches, as well as the impact of improved awareness and access to health services for the early detection of major cancers such as breast, cervical, oral, and colorectal cancer.

The Section designs and conducts research studies in collaboration with investigators in national cancer organizations, health services, universities, and other key groups within and outside the Agency. EDP works closely with other international organizations to develop, implement, and promote effective strategies for preventing and controlling cancer in the context of national cancer control programmes. In the Section's studies, there is a continuing emphasis on developing training resources, augmenting capacity for cancer prevention and early detection initiatives, and scaling up of prevention and early detection services within local health systems. The establishment of cancer research networks in LMICs to exchange experiences and enhance the local capacity is among EDP's priorities. The Section continues to expand its activities to implementation research, to support the efforts of national health systems to translate scientific findings into the well-being of the population.

PREVENTION AND IMPLEMENTATION GROUP (PRI)

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The Prevention and Implementation Group (PRI) investigates cancer epidemiology and prevention with a focus on human papillomavirus (HPV) vaccines, *Helicobacter pylori* eradication for gastric cancer prevention, triage methods for HPV-positive women, and the promotion and evaluation of cervical cancer control programmes. Recently, PRI began to include implementation research objectives in ongoing projects and national implementation activities.

CERVICAL CANCER STUDIES IN GUANACASTE, COSTA RICA

The Costa Rica Vaccine Trial (CVT) recruited approximately 7500 women aged 18–25 years into a randomized trial of bivalent HPV vaccine (HPV 16/18). The final results confirmed efficacy of the vaccine against HPV 16/18-related lesions and those related to other HPV types. Follow-up is continuing, and after cross-over vaccination, a new unvaccinated control group was recruited for long-term assessment of vaccine efficacy and safety (Gonzalez et al., 2015; Panagiotou et al., 2015). A combined analysis confirmed protective efficacy regardless of the number of doses (Kreimer et al., 2015a). Plans are under way for a randomized trial of one versus two doses of the bivalent and nonavalent vaccines. The efficacy of the vaccine to prevent vulvar HPV 16/18 infections was also evaluated (Lang Kuhs et al., 2014a).

MULTICENTRE STUDY OF HPV SCREENING AND TRIAGE (ESTAMPA)

The ESTAMPA study investigates emerging cervical cancer screening and triage techniques in Latin America. About 50 000 women aged 30–64 years will be screened with HPV testing; all HPV-positive women will be referred for colposcopy, biopsy, and treatment as needed, and recalled for a second screening after 18 months. The main outcome is advanced cancer precursors. The performance of visual, cytological, and molecular methods to identify HPV-positive women at higher risk of disease will be evaluated, contributing towards the establishment of organized screening in the region. The study began in Colombia, Paraguay, Honduras, and Uruguay (recruitment, ~8000) and will

Figure 1. ESTAMPA study: participants in the cervical pathology training course held in Cuernavaca, Morelos, Mexico, on 11–13 February 2015. © IARC/Roland Dray.



soon start in Costa Rica, Argentina, Peru, Mexico, and Bolivia (Figure 1).

EPIDEMIOLOGY AND PREVENTION OF *H. PYLORI* INFECTION AND GASTRIC CANCER

The ENIGMA study investigates the worldwide epidemiology of *H. pylori* infection and gastric cancer. The prevalence of infection, precancer, and cofactors are investigated in population samples from high- and low-risk areas. A multilevel analysis (ecological, cross-sectional, and analytical) will assess age-specific infection prevalence to predict cancer trends, as well as bacterial (including microbiome), host, and environmental factors explaining geographical patterns. ENIGMA has been completed in low- and high-risk areas in Chile (700 people each), and there are plans to expand the study to all continents.

In collaboration with the National Cancer Center of the Republic of Korea, PRI is conducting a randomized controlled clinical trial of *H. pylori* eradication for gastric cancer prevention (the HELPER study), which aims to recruit 11 000 subjects aged 40–65 years who are attending endoscopy within the National Cancer Screening Program. *H. pylori*-positive subjects are randomized to quadruple eradication therapy or placebo. All participants (current recruitment, ~1200) will be routinely screened within the National Cancer Screening Program every 2 years for 10 years.

PRI has also initiated a randomized trial with the University of Latvia to determine whether combined *H. pylori* and pepsinogen screening followed by eradication therapy in *H. pylori*-positive subjects and endoscopic follow-up of those with atrophic gastritis reduces gastric cancer mortality compared with standard care. The study aims to recruit 30 000 subjects aged 40–64 years in Latvia, Belarus, and the Russian Federation (current pilot recruitment, ~3000).

In December 2013, PRI convened a Working Group of experts to review the evidence regarding *H. pylori* eradication strategies for gastric cancer prevention. The experts recommended consideration of programmes in high-risk areas in the context of scientific assessment of the value of such interventions (Herrero et al., 2014a) (Figure 2).

CERVICAL CANCER PREVENTION IN AFRICA

PRI is collaborating with the World Health Organization (WHO) Department of Reproductive Health and Research (RHR) and the United Republic of Tanzania in a study with more than 2000 women to build HPV testing capacity and to assess the reproducibility, feasibility, and acceptability of rapid HPV testing at different levels of the health care system (the AISHA study). Also with RHR, PRI is planning a large trial of three screen-and-treat algorithms currently recommended by WHO (the CESTA study).

Figure 2. *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. The Working Group met at IARC in Lyon on 4–6 December 2013. © IARC/Roland Dray.



SUPPORT OF HPV VACCINATION AND SCREENING PROGRAMMES IN LATIN AMERICA

In the context of the National Cervical Screening Programme of Argentina, which is implementing HPV-based screening, extensive political and educational meetings have been held

and the development of guidelines and educational materials and the setting up of laboratories have been completed for the first province to implement the programme, Jujuy Province (Arrossi et al., 2015a). A cluster randomized trial within this programme demonstrated a 4-fold increase in screening participation when community health workers invited

women to self-collect their HPV tests compared with an invitation to attend a clinic (Arrossi et al., 2015b). Expansion to other provinces in Argentina is well under way. The materials developed and the experience gained should be useful for other programmes in the region, most of which also collaborate with PRI.

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The Screening Group (SCR) conducts studies of the early detection of common cancers, predominantly in low- and middle-income countries (LMICs), evaluating the accuracy, acceptability, feasibility, safety, and cost-effectiveness of early detection methods for breast, cervical, colorectal, and oral cancers and addressing how the evidence generated can influence early detection policies in LMICs (Khuhaprema et al., 2014; Krishnan et al., 2015; Parham et al., 2015; Rajaraman et al., 2015). The Group contributes scientific evidence to support the development of resource-appropriate policies to deliver effective early detection services (Sankaranarayanan et al., 2014a). SCR evaluates selected primary prevention

initiatives and explores pragmatic ways of integrating both primary and secondary prevention strategies into cervical cancer control (Sankaranarayanan et al., 2015). SCR engages substantially in developing training resources and educational programmes.

CERVICAL CANCER CONTROL

The effectiveness of one and two doses of human papillomavirus (HPV) vaccine was compared with that of three doses among girls aged 10–18 years in preventing cervical neoplasia in a multicentre study involving 17 729 women in India. Results after 4 years of follow-up indicate that the immunogenicity of two doses was non-inferior to that of

three doses. Although the single dose evoked lower antibody levels, they are much higher than natural infection and are as avid as three-dose antibodies (Figures 1 and 2). One dose provided similar protection against incident and persistent HPV 16/18/6/11 infections as two and three doses.

The long-term impact of screening with HPV testing, cytology, or visual inspection with acetic acid (VIA) on cervical cancer is being addressed by following up about 230 000 women in India. SCR evaluated the triaging options for HPV- and VIA-positive women (Muwonge et al., 2014; Basu et al., 2015). Cytology or VIA triage of HPV-positive women substantially reduced colposcopy

Figure 1. Mean fluorescence intensity (MFI) values for HPV 16, 18, 6, and 11 L1 antibodies at different time points among girls who completed vaccination per protocol (vaccination at days 1, 60, and 180 for the 3-dose group or at days 1 and 180 for the 2-dose group) and those who did not have their complete vaccine schedules (vaccination at days 1 and 60, or a single dose). Reprinted from Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R, et al., for the Indian HPV vaccine study group (2015). Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicenter prospective cohort study. *Lancet Oncol.* [http://dx.doi.org/10.1016/S1470-2045\(15\)00414-3](http://dx.doi.org/10.1016/S1470-2045(15)00414-3).

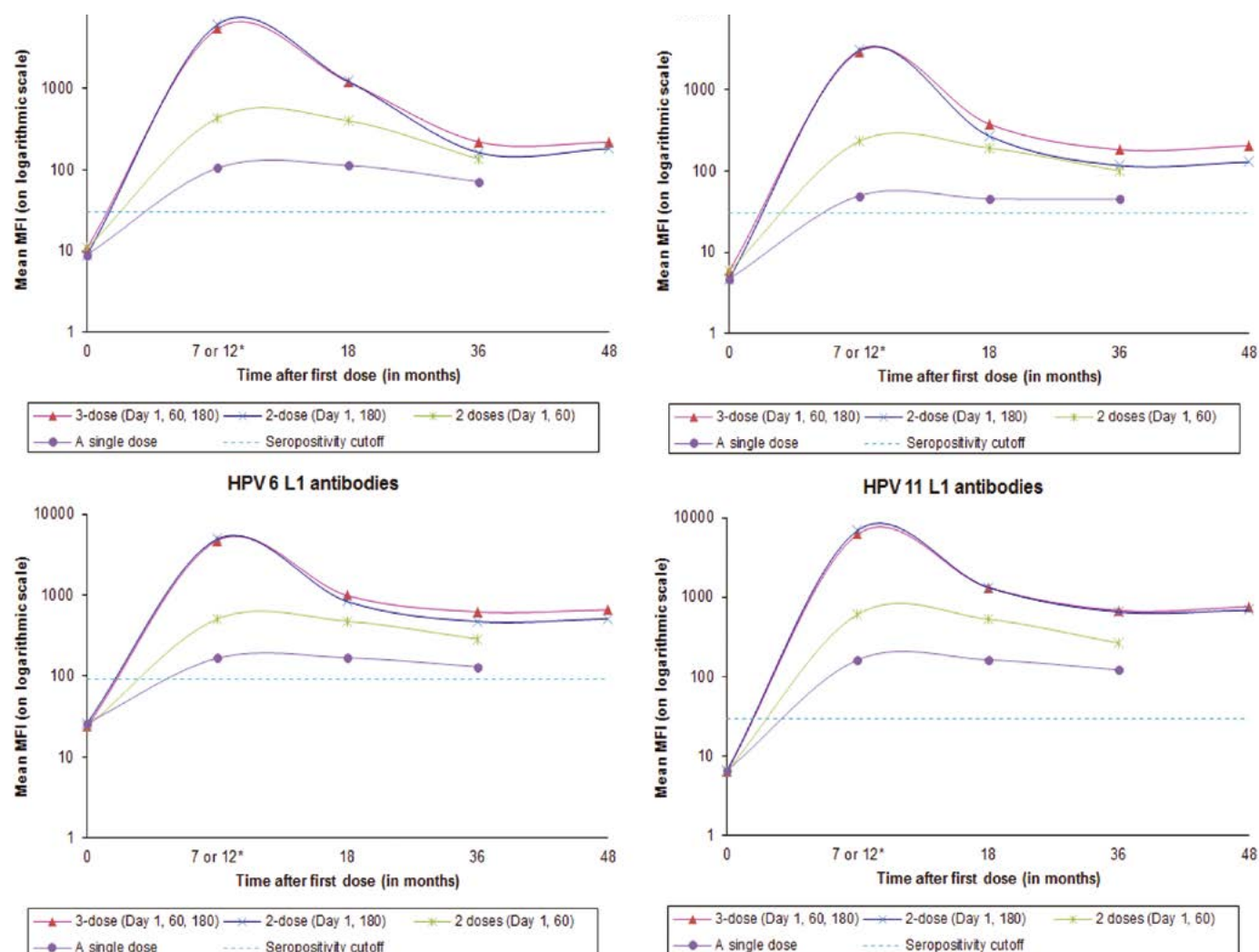
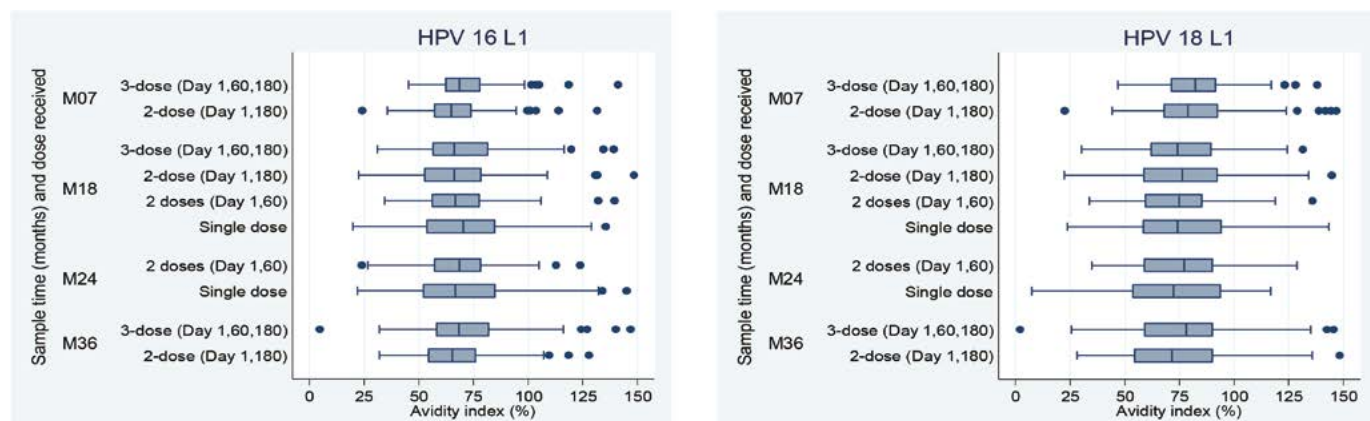


Figure 2. Geometric mean fluorescence intensity (MFI) avidity index of HPV 16, 18, 6, and 11 L1 antibodies at 18 months after the first dose among girls who completed vaccination per protocol and those who did not have their complete vaccine schedules. Reprinted from Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R, et al., for the Indian HPV vaccine study group (2015). Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicenter prospective cohort study. *Lancet Oncol.* [http://dx.doi.org/10.1016/S1470-2045\(15\)00414-3](http://dx.doi.org/10.1016/S1470-2045(15)00414-3).



referral, although 16–18% of cases of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) were missed. HPV testing could triage VIA-positive women very efficiently, with an insignificant drop in sensitivity (Basu et al., 2015). The validity of colposcopy by nurses was addressed in a follow-up study (Thulaseedharan et al., 2015a). A study among 1109 HIV-positive women in India observed 41.0% high-risk HPV positivity (Joshi et al., 2014). Meta-analysis of the efficacy of cold coagulation demonstrated a 95% cure rate for CIN2/3, comparable to that of cryotherapy or excision (Dolman et al., 2014). Scaling up of the VIA screen-and-treat programme in Zambia was evaluated (Parham et al., 2015). HPV viral load was observed to have a key role in colposcopy.

A pilot study involving 6000 women to implement HPV screening and triage by liquid-based cytology and HPV genotyping in Thailand has been completed. A study involving 592 midwives in Government Health Services in Côte d'Ivoire indicated that despite sufficient knowledge about cervical cancer prevention, the attitudes and practices of midwives need improvement by capacity-building activities (Tchounga et al., 2014).

BREAST CANCER SCREENING

In a randomized trial involving 130 000 women in Trivandrum, India, the second

round of screening by clinical breast examination (CBE) has been completed and the third round is in progress. The role of breast awareness in improving early detection and survival of breast cancer patients is being investigated at other sites in India.

ORAL CANCER SCREENING

The natural history of oral precancerous lesions is being addressed in the randomized trial of oral visual screening in Kerala, India. The cohort has substantially contributed to addressing mortality related to cardiovascular disease, tobacco, and obesity in South Asia (Zheng et al., 2014). The inputs and impact of “social marketing” to increase awareness for early detection are being evaluated in Sri Lanka.

COLORECTAL CANCER SCREENING

A pilot study in Thailand involving 130 000 people indicated that colorectal cancer screening with immunochemical faecal occult blood testing (iFOBT), triage colonoscopy, and treatment of adenomas and early cancers by endoscopic resection can be implemented successfully in government health services (Khuhaprema et al., 2014). SCR is currently providing technical support in scaling up colorectal cancer screening in five provinces in Thailand.

TECHNICAL SUPPORT TO NATIONAL CANCER CONTROL PROGRAMMES

SCR provided technical support to national cancer control programmes in Albania, Algeria, Bosnia and Herzegovina, Cambodia, China, Fiji, Georgia, Lebanon, Madagascar, Mauritania, Morocco, Myanmar, Papua New Guinea, Sri Lanka, Thailand, Timor-Leste, Tunisia, and Uzbekistan in collaboration with national governments, World Health Organization (WHO) headquarters and regional offices, the International Atomic Energy Agency (IAEA), and the United Nations Population Fund (UNFPA).

CONTINUED ACTIVITIES OF THE QUALITY ASSURANCE GROUP (QAS)

SCR is contributing to the preparation of the European Screening Report, which will describe the current coverage and status of breast, cervical, and colorectal cancer screening programmes in 28 European countries. The supplements to the second edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening have been published (Anttila et al., 2015; von Karsa et al., 2015). The European Code Against Cancer, a collection of key recommendations to promote primary and secondary prevention of cancer, was launched in October 2014.

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National Cancer Institute, Bangkok, Thailand
National Cancer Control Programme, Ministry of Health and Indigenous Medicine, Colombo, Sri Lanka
National Institutes of Health, National Cancer Institute, Bethesda, USA
Union for International Cancer Control (UICC), Geneva, Switzerland

EPSON

PRACTICAL INFORMATION

- Connection to the wireless network (WIFI)
SSID: TARC_Visitors
Password:
- Should you need an adapter for French electric plugs, please ask the Reception. Please make sure you give it back! Thank you.
- To use the headset for translation:
English: press 1 French: press 2 Russian: press 3



OFFICE OF THE DIRECTOR

Director

Dr Christopher P. Wild

Director's Office team

Scientific officer

Dr Eduardo Seleiro

Personal assistant to the Director

Ms Margot Geesink

Administrative assistant

Ms Susan Haver-Legros
(until September 2014)

Secretary

Ms Laurence Marnat

Senior visiting scientists

Dr David Forman
Dr John Grooman
(until September 2014)
Sir Andrew J. Hall
(until May 2014)

Special advisor (Noncommunicable Diseases)

Dr Silvia Franceschi

Special advisor (Cancer Control)

Dr Rengaswamy Sankaranarayanan

THE OFFICE OF THE DIRECTOR COMPRISES A SMALL TEAM THAT SUPPORTS THE DIRECTOR IN THE IMPLEMENTATION OF IARC'S STRATEGY AND PROGRAMME, AS WELL AS THREE GROUPS WHOSE ACTIVITIES SPAN ACROSS THE AGENCY – THE COMMUNICATIONS GROUP (COM), THE EDUCATION AND TRAINING GROUP (ETR), AND THE LABORATORY SERVICES AND BIOBANK GROUP (LSB) – TOGETHER WITH THE GAMBIA HEPATITIS INTERVENTION STUDY (GHIS), A LONG-TERM SCIENTIFIC PROJECT OF IARC, WHICH IS MANAGED BY THE DIRECTOR. THE ACTIVITIES OF THESE FOUR GROUPS ARE DESCRIBED IN THE FOLLOWING SECTIONS.

The team in the Office of the Director is responsible for assisting in the coordination of specific scientific initiatives, particularly cross-cutting projects involving multiple research Sections; for supporting the establishment and development of strategic partnerships with IARC's network of scientific, governmental, and nongovernmental institutional collaborators; and for assisting in exchanges with the Scientific and Governing Councils and with current and potential Participating States. The Director's Office also supports the activities of several advisory groups and committees, notably the Senior Leadership Team and the IARC Ethics Committee.

Several high-level partnership agreements were signed during the 2014–2015 biennium to formalize and promote institutional collaborations in cancer research and in cancer prevention and control, including with the Lalla Salma Foundation for Cancer Prevention and Treatment in Morocco, with the Health Ministers' Council for the Gulf Cooperation Council States and the Gulf Centre for Cancer Control and Prevention, and with the United States National Cancer Institute's Center for Global Health (NCI-CGH).

In addition, the Director's Office, together with a small working group comprising Dr Silvia Franceschi, Special Advisor on Noncommunicable Diseases (NCDs), and Dr Rengaswamy Sankaranarayanan, Special Advisor on Cancer Control, supports and advises the Director in the coordination of collaborations with a number of key partners in global policy development for cancer prevention and control, including the World Health Organization (WHO) headquarters and regional offices, the International Atomic Energy Agency's Programme of Action for Cancer Therapy (IAEA-PACT), the NCI-CGH, and the Union for International Cancer Control (UICC).

An important focus is the ongoing collaboration with WHO and other partners supporting the planning and implementation of the Global Monitoring Framework for the Prevention and Control of NCDs. Agency staff members participated in numerous planning meetings in the context of the various WHO initiatives in this area, and contributed to the updates of the Global Status Report on NCDs 2014 and of the Global Action Plan for the Prevention and Control of

NCDs. More broadly, IARC continues to work alongside other United Nations (UN) agencies in the UN Interagency Task Force on the Prevention and Control of NCDs, supporting the development and implementation of the global response to NCDs. IARC contributes in particular to the areas of improved surveillance of cancer, through the Global Initiative for Cancer Registry Development (GICR), and of cervical cancer control, including through collaborative research with the WHO Human Reproduction Programme.

A major undertaking for the Director's Office over the biennium was supporting the development of the IARC Medium-Term Strategy for 2016–2020. The process for the development of the Medium-Term Strategy involved broad internal consultation and reflection at all levels of the Agency's personnel, as well as external consultation with the Agency's stakeholders, structured in two stages, the first aimed at key opinion leaders in cancer research, public health, and international cooperation, and the

second aimed at the broader community of IARC's collaborators. Another novel component in the development of the Medium-Term Strategy was the creation of the IARC Project Tree, a framework linking the contribution of each individual project, presented in the Programme and Budget, with the strategic priorities of IARC articulated through the Medium-Term Strategy.

COMMUNICATIONS GROUP (COM)

Group head

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Ms Teresa Lee

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Dr Karen Müller

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Mr Ussama Anas
Ms Natacha Blavoyer
Ms Latifa Bouanzi
Mr Roland Dray
Ms Sylvia Lesage
Mr Othman Yaqoubi

Consultant

Ms Mary Roark
(until June 2014)

The objective of the Communications Group (COM), as an integral part of the Director's Office, is to present a clear and coherent image of IARC and its work to the scientific community, the media, and the general public. COM also provides information- and publication-related services to the research Sections.

KNOWLEDGE MANAGEMENT SERVICES

The Knowledge Management Centre comprises the IARC Library and the IARC Publications Programme. After the restructuring of COM in 2013, knowledge management activities during the 2014–2015 biennium focused on establishing the workflows, policies, frameworks, and technical infrastructure needed to forward IARC's digital publishing and dissemination strategy.

AGREEMENT WITH WHO PRESS

The commercial agreement with the distributor of IARC publications, WHO Press, was renegotiated in 2014, dividing responsibilities for sales into two parts, print and electronic. WHO Press retained rights to sell IARC titles in print, while IARC became responsible for distribution of titles in electronic formats.

DIGITAL DISTRIBUTION CHANNELS

As part of the transition to electronic formats, COM increased its channels of online dissemination, by establishing its own license and workflows to service academic and research institutions directly, and by entering into contracts with major electronic book aggregators that service those markets.

In addition to focusing on diversifying business models, the Knowledge Management Centre sought reputable channels through which to disseminate publications freely. IARC became a participating publisher in HINARI, a programme created by WHO together with major commercial publishers to enable institutions in low- and middle-income countries to access one of the world's largest collections of biomedical and health literature. IARC also entered into an agreement with the United States National Library of Medicine to deposit full-text content in PubMed Bookshelf, a free digital repository of life sciences books.

COM continued its support of PubCan, an integrated online database that brings together IARC publications content in a dynamic and cross-searchable format. May 2014 saw the launch of ICD-O-3 Online, one of the three main components of PubCan, and in April 2015 the PubCan web architect took up a temporary post to continue development of the platform under COM supervision.

DIGITAL STRATEGY

COM continued to develop its strategic vision, engaging a consultant from November 2013 to June 2014 to review IARC's publications activities in the light of current global media trends and practices, and to articulate actionable steps for IARC publishing. Key recommendations from the consultancy were: improved marketing by better aligning IARC publishing activities with external scientific events and through strategic alliances; the streamlining and standardization of publishing workflows in concert with careful technology selection; a strategy for the increased output and digital dissemination of the WHO Classification of Tumours series; raising of awareness within the Agency about publishing trends and business models; and investment in producing and outputting flexible electronic content.

OPEN ACCESS

IARC's Open Access Policy was launched in January 2015. As approved by the Governing Council in May 2015, the IARC Open Access Fund was established, whereby a maximum of €50 000 per annum for 3 years can be spent in support of open access publishing.

During the 2014–2015 biennium, IARC published several key reference publications:

WHO CLASSIFICATION OF TUMOURS

[WHO Classification of Tumours of Female Reproductive Organs, 4th edition](#) (print)
[WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 4th edition](#) (print)

IARC MONOGRAPHS

[Volume 104, Malaria and Some Polyomaviruses \(SV40, BK, JC, and Merkel Cell Viruses\)](#) (print)

[Volume 105, Diesel and Gasoline Engine Exhausts and Some Nitroarenes](#) (print)

[Volume 106, Trichloroethylene, Tetrachloroethylene and Some Other Chlorinated Agents](#) (print)

[Volume 107, Polychlorinated Biphenyls and Polybrominated Biphenyls](#) (PDF)

[Volume 108, Some Drugs and Herbal Products](#) (PDF)

[Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos](#) (Monograph on Glyphosate, PDF)

IARC WORKING GROUP REPORTS

[Primary end-points for prophylactic HPV vaccine trials, IARC Working Group Report No. 7](#) (PDF)

[Helicobacter pylori eradication as a strategy for preventing gastric cancer, IARC Working Group Report No. 8](#) (PDF)

[Mycotoxin control in low- and middle-income countries, IARC Working Group Report No. 9](#) (print, PDF, and EPUB)

[Lutte contre les mycotoxines dans les pays à revenu faible et intermédiaire, Rapports des Groupes de travail du CIRC N° 9](#) (print, PDF, and EPUB)

[Control de las micotoxinas en los países de ingresos bajos y medios, IARC. Informes de grupos de trabajo N° 9](#) (print, PDF, and EPUB)

IARC SCIENTIFIC PUBLICATIONS

[Cancer Incidence in Five Continents, Vol. X, IARC Scientific Publication No. 164](#) (print and PDF)

[Air Pollution and Cancer, IARC Scientific Publication No. 161](#) (PDF)

IARC TECHNICAL PUBLICATIONS

[Planning and developing population-based cancer registration in low- and middle-income settings, IARC Technical Publication No. 43](#) (print, PDF, and EPUB)
[Planification et développement des registres du cancer basés sur la population dans les pays à revenu faible ou intermédiaire, Publications techniques du CIRC N° 43](#) (PDF)

[Planificación y desarrollo de registros de cáncer de base poblacional en los países de ingresos bajos y medios, IARC. Publicaciones técnicas N° 43 \(PDF\)](#)
[The Origin of the International Agency for Research on Cancer, IARC Technical Report No. 6 \(PDF\)](#)

NON-SERIAL PUBLICATIONS

[World Cancer Report 2014](#) (print and EPUB)
[The Cancer Atlas, 2nd edition](#) (print; joint publication with the American Cancer Society)
[International Agency for Research on Cancer: The First 50 Years, 1965–2015](#) (print, PDF, and EPUB)

ELECTRONIC RESOURCES

[International Classification of Diseases for Oncology: ICD-O-3 Online](#) (<http://codes.iarc.fr/>)
[Cancer Incidence in Five Continents, CI5plus. IARC CancerBase No. 9](#) (<http://ci5.iarc.fr/CI5plus/Default.aspx>)
[Cancer Incidence in Five Continents, Vol. I–X](#) (<http://ci5.iarc.fr/CI5I-X/Default.aspx>)
[European Code Against Cancer, 4th edition](#) (<http://cancer-code-europe.iarc.fr/>)

EDITING, LANGUAGE, AND TRANSLATION SERVICES

COM provides English editing services to all IARC Groups, for manuscripts of book chapters, of peer-reviewed journals, or for publication in one of the established IARC Publications series, and administers external translation services for longer documents. COM also organizes successful language courses for the Agency's personnel in both working languages plus Spanish.

MEDIA SERVICES

Media services play a pivotal role in communicating IARC's mission and work clearly and coherently to the world at large. During the 2014–2015 biennium, the Agency's visibility in the media was reinforced and played a key role in promoting the work of IARC to the general public, the scientific community, and a wider range of stakeholders, including policy-makers. Interaction with strategic media outlets was increased, and a database of more than 4500 contacts was developed and updated. A wide range of communication tools and activities were also developed to

ensure that IARC research was featured regularly in mainstream and scientific media.

During the biennium, 17 IARC press releases were issued, more than 140 IARC news items were published, and two international press conferences were organized by IARC: in February 2014 (on World Cancer Day) in London, to launch *World Cancer Report 2014*, and in October 2014, to launch the fourth edition of the European Code Against Cancer, with the collaboration of the European Commission. Several Monograph evaluations were the focus of media outreach, such as the Monographs on Glyphosate and on Consumption of Red Meat and Processed Meat. Other communication materials produced included Q&As, a video on IARC's research in Latin America to improve cervical cancer screening in the region, and several web interviews of participants in the IARC Summer School. Continual contact with key media outlets was maintained, and regular interviews were set up with IARC experts throughout the biennium. Media training was provided to IARC scientific spokespeople on an ad hoc basis.



WEB SERVICES

The Web services team ensures that all IARC websites and subsites present a unified look and feel and a consistent information architecture. During the 2014–2015 biennium, the Web services team successfully developed and launched the following websites:

PUBLIC WEBSITES

Education and Training Programme (<http://training.iarc.fr/>)

ABC-DO: The African Breast Cancer – Disparities in Outcomes study (<http://abc-do.iarc.fr/>)

ICD-O-3 Online: International Classification of Diseases for Oncology (<http://codes.iarc.fr/>)

PRECAMA study: Molecular Subtypes of Premenopausal Breast Cancer in Latin American Women (<http://precama.iarc.fr/>)

EPIC: European Prospective Investigation into Cancer and Nutrition (new release) (<http://epic.iarc.fr/>)

IARC Handbooks of Cancer Prevention (<http://handbooks.iarc.fr/index.php>)

BCNet: Low- and Middle-Income Countries Biobank and Cohort Building Network (<http://bcnet.iarc.fr/>)

European Code Against Cancer, 4th edition (<http://cancer-code-europe.iarc.fr/index.php/en/>)

GICR: Global Initiative for Cancer Registry Development (<http://gicr.iarc.fr/>)

CO-CHER: Cooperation on Chernobyl Health Research (<http://co-cher.iarc.fr/>)

BBMRI-LPC: Second Scientific Call for Access (<http://bbmri-lpc.iarc.fr/>)

EPICentre: The lifestyle and cancer blog (<http://blogs.iarc.fr/epicentre/>)

ESCAPE: The Oesophageal Squamous Cell Carcinoma African Prevention Effort (<http://esccape.iarc.fr/>)

MEETING WEBSITES

Emerging Issues in Oncogenic Virus Research (<http://www.iarc.fr/oncogenicviruses2016/>)

Global Cancer: Occurrence, Causes, and Avenues to Prevention (<http://www.iarc.fr/conference2016>)

EDUCATION AND TRAINING GROUP (ETR)

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Ms Susan Anthony

Responsible officer, fellowship programme

Dr Zdenko Herceg

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Ms Eve El Akroud
(until January 2015)
Ms Isabelle Battaglia

Secretary

Ms Mira Delea

As a core statutory function of the Agency, IARC's education and training programme has made a substantial contribution to the development of human resources for cancer research in many countries and has also helped to shape the Agency's research strategy and widen its network of collaborators.

Key achievements of IARC's education and training programme during 2014–2015 are presented here. Whereas the Education and Training Group (ETR) coordinates the Agency's activities in these areas, many initiatives are led by the research Groups.

POSTDOCTORAL FELLOWSHIPS

During 2014–2015, new IARC Postdoctoral Fellowships were awarded to 23 postdoctoral fellows from 17 different countries (Figure 1). Research Return Grants were awarded to six fellows from low- and middle-income countries (LMICs) to establish their research activity in their own country. Most fellowships were co-funded by the European Union under the Marie Skłodowska-Curie Actions–People–COFUND Programme.

Under the bilateral agreement with Cancer Council Australia, one new IARC-Australia Postdoctoral Fellowship

Table 1. Senior Visiting Scientist Awards, 2014 and 2015

2014	
Professor Michael Leitzmann	University of Regensburg, Regensburg, Germany
Professor Walter Prendiville	University of Pittsburgh Medical Center, Pittsburgh, USA, and Beacon Hospital, Dublin, Ireland
Professor Kyle Steenland	Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, USA
2015	
Professor Fanghui Zhao	Department of Cancer Epidemiology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

was awarded and two were extended for an additional year. Under the bilateral agreement with the Irish Cancer Society, the first IARC-Ireland Postdoctoral Fellowship was awarded in 2014.

SENIOR VISITING SCIENTIST AWARD AND EXPERTISE TRANSFER FELLOWSHIP

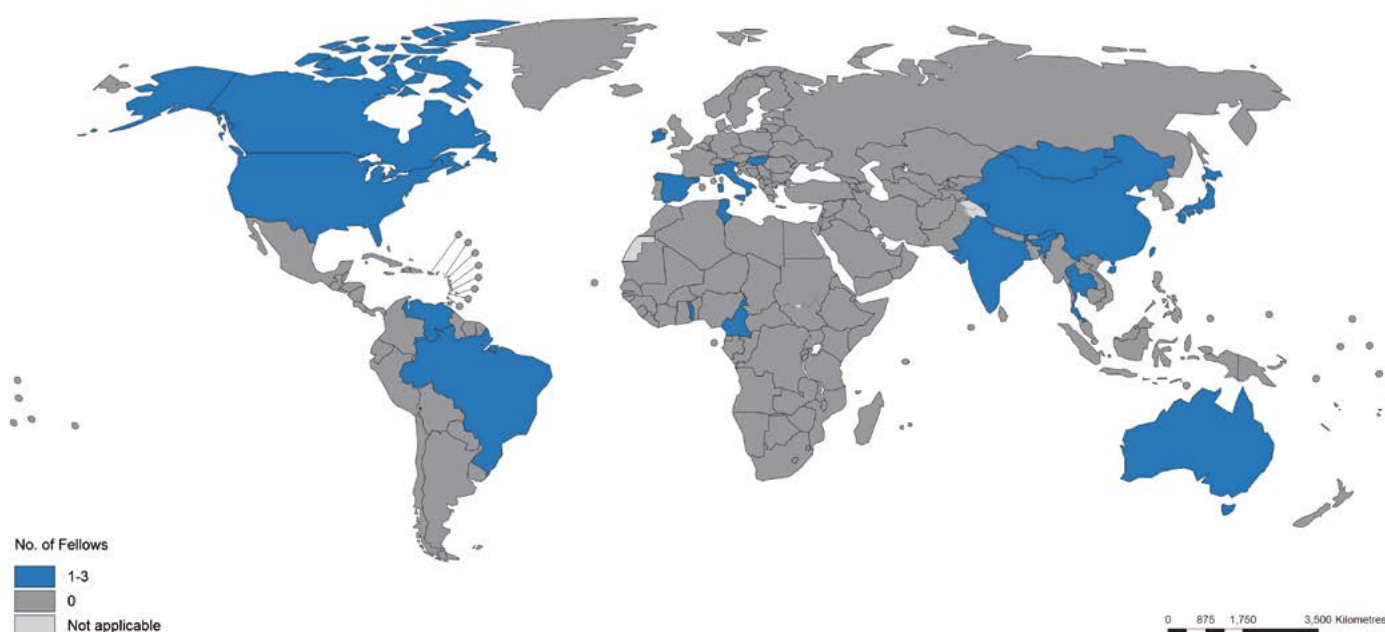
Four Senior Visiting Scientist Awards were conferred in 2014–2015 (Table 1). Beyond the development of collaborative research projects, the Senior Visiting Scientist Award often leads to the expansion of important research initiatives or the joint production of key resources for capacity-building.

Activities carried out in 2014 by Dr Esther de Vries (The Netherlands), who was awarded an Expertise Transfer Fellowship in 2013, enabled the evaluation and improvement of cancer registry data in Colombia as well as the running of training activities.

SHORT-TERM FELLOWSHIPS

In collaboration with the Union for International Cancer Control (UICC), the UICC-IARC Development Fellowship enables one participant of the IARC Summer School to return to IARC for a period of 3 months for further training and collaborative work. In 2014, this fellowship was awarded to a researcher

Figure 1. IARC Postdoctoral Fellowships awarded in 2014 and 2015, by country of origin. © IARC.



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: IARC
Map production: IARC
World Health Organization

from Sri Lanka. In 2015, this initiative was expanded thanks to the increased contribution of UICC, which allowed the support of three researchers, from Ethiopia, Ukraine, and Serbia.

HOSTING ENVIRONMENT

The Agency also hosts a number of trainees, students, postdocs, and visiting scientists supported by project funds from the research Groups. A total of 270 Early Career and Visiting Scientists worked at IARC during the biennium.

The Agency continued to support the Early Career Scientists Association (ECSA), which was created in 2013. Among other activities, ECSA successfully held its first Scientific Day in April 2014, followed by a Scientific and Career Day in April 2015. Within the framework of the IARC Postdoctoral Fellowship Charter, which allows a more structured approach to postdoctoral training at IARC, and in collaboration with ECSA, ETR continued to develop the programme of generic courses for Early Career Scientists (Table 2).

Relationships with universities have been strengthened or developed. At the local level, links with two doctoral schools

Table 2. Generic courses for Early Career Scientists, 2014 and 2015

Research skill development

Epidemiology for non-epidemiologists: a short introduction

Biostatistics: generalized linear models using Stata

BioConductor for integrative genomic analyses

Responsible conduct of research

Biomedical research ethics

Communication skills

Presentation skills

Effective scientific posters

Leadership and management

Project management (twice)

Grant writing (three times)

Financial management (twice)

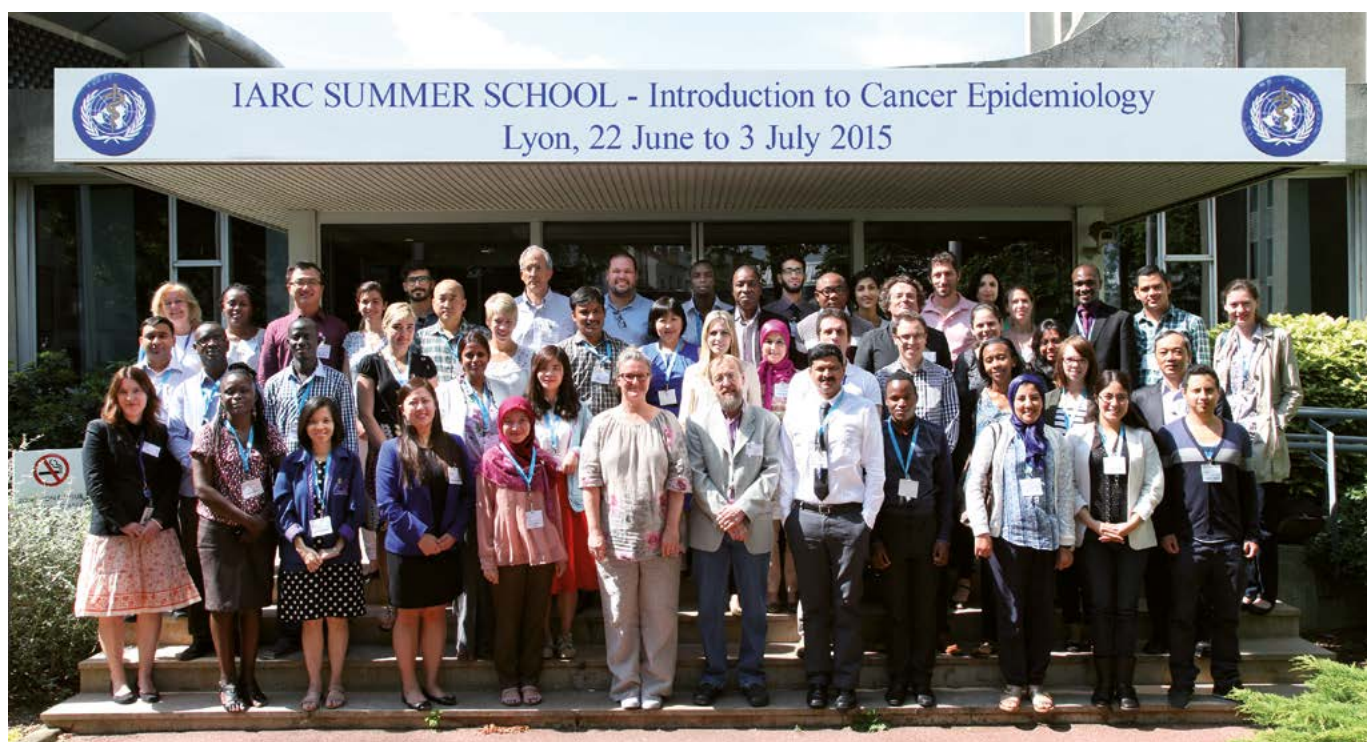
Task management (twice)

of the University of Lyon have been reinforced. At the international level, a collaboration with the University of Warwick (United Kingdom) has been set up for the hosting of doctoral students.

IARC SUMMER SCHOOL IN CANCER EPIDEMIOLOGY

The IARC Summer School in Cancer Epidemiology was held in Lyon in June–

Figure 2. IARC Summer School 2015, Module 2: Introduction to Cancer Epidemiology. © IARC/Roland Dray.



July in 2014 and 2015, with the goal of improving the methodological and practical skills of cancer researchers and health professionals. Modules on cancer registration (Cancer Registration: Principles and Methods in 2014 and Cancer Survival Methods for Cancer Registries in 2015) and cancer epidemiology (Introduction to Cancer Epidemiology) were organized each year (Figure 2).

During the biennium, the Summer Schools enabled the training of a total of 133 researchers and health professionals from 63 countries, 112 of them (84%) from 50 different LMICs. The Summer School modules were very well received by the participants.

Additional financial support for the Summer School came from the United States National Cancer Institute (NCI) as well as from the Nordic Cancer Union (NCU) and the Klinik und Poliklinik für Gynäkologie, Martin Luther University, Halle, Germany.

SPECIALIZED AND ADVANCED COURSES

Specialized or advanced courses are organized by IARC's scientific Groups, sometimes with the support of ETR. The majority of these courses are associated with collaborative research projects, where IARC is transferring skills needed to conduct the projects and to enable the subsequent implementation of

the research findings in the countries concerned. In some instances, specialized courses are co-organized with external partners and held at diverse locations throughout the world (Table 3). During the biennium, these courses enabled the training of a total of about 1100 scientists and health professionals.

E-LEARNING

Complementing its redesigned website (<http://training.iarc.fr/>), ETR launched an IARC Education and Training Newsletter in 2014, aimed at former Early Career and Visiting Scientists at IARC as well as course participants.

IARC is seeking to expand the production of e-Learning resources. A system to record and disseminate presentations, training courses, workshops, and other materials online was set up by the Agency in 2014. The system was used to capture some sessions of the Summer School and of the first Russian-language cancer registration course, held in Kazakhstan. The materials are available from the websites of ETR and the Global Initiative for Cancer Registry Development (GICR).

Partnership initiatives have been pursued to develop e-Learning materials and courses. Collaborations have been established with the Institut Català d'Oncologia (ICO), Spain, leading to the launch of a joint

Figure 3. Flyer for the joint IARC-ICO online course in cancer epidemiology.



online course in cancer epidemiology aimed at Latin American countries (<http://www.e-oncologia.org/cursos/postgrado-fundamentos-metodologicos-investigacion/#.VjO5lNKrTIU>; Figure 3), and with the London School of Hygiene & Tropical Medicine (United Kingdom), involving IARC's contribution to the contents of an e-Learning module, Introduction to Cancer Epidemiology (http://dl.ishtm.ac.uk/download/open-access/gn09/EPM307_GN09_010_010.html).

Table 3. Specialized and advanced courses, 2014 and 2015

Course title	Location	Number of participants	External collaborations
2014			
Cervical cancer screening and treatment with cold coagulation	Fez, Morocco	11	Fondation Lalla Salma – Prévention et Traitement des Cancers
Course on visual inspection with acetic acid (VIA), colposcopy, and treatment of cervical neoplasia	Barshi, India	15	Tata Memorial Centre Rural Cancer Project, India; National Cancer Control Programme, Sri Lanka; Bill & Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention (ACCP)
Training course on screening and treatment of cervical neoplasia	Kigali, Rwanda	14	National Cancer Institute Rwanda; UICC
Training course on colposcopy and LEEP procedures in the management of abnormal cytology	Bangkok, Thailand	57	National Cancer Institute Thailand; Thai Society for Colposcopy and Cervical Pathology
Master Trainers course on cervical cancer screening and treatment of precancerous lesions	Barshi, India	17	Tata Memorial Centre Rural Cancer Project, India
GoToWebinar training on EPIC-Soft GloboDiet	Online courses (4)	45	
Cancer survival methods for cancer registries	Chennai, India	29	UICC; GICR
Building blocks for cancer system performance measurement and evaluation (Spanish)	Ottawa, Canada	18	GICR; IARC Regional Hub for Latin America
Basic training in cancer registration	Mozambique	5	AFCRN (IARC Regional Hub for Sub-Saharan Africa)
Cancer registration (for Francophone countries)	Abidjan, Côte d'Ivoire	11	AFCRN (IARC Regional Hub for Sub-Saharan Africa)
Cancer registration	Cairo, Egypt	25	WHO EMRO
Cancer registration	Yangon, Myanmar	80	IARC Regional Hub for Southern, Eastern and South-East Asia; NCI Bangkok
Cancer registration workshop	Shanghai, China	80	United States National Cancer Institute; GICR
IARC cancer registration course (for Russian-speaking registries)	Astana, Kazakhstan	28	IARC Regional Hub for Northern Africa, Central and Western Asia; National Institute for Postgraduate Medical Education, Kazakhstan; Central Asian Cancer Institute, Kazakhstan
Principles of cancer registration and CanReg	San Salvador, El Salvador	52	IARC Regional Hub for Latin America
Uses of cancer registry data in cancer control research	Ankara, Turkey	25	IARC Regional Hub for Northern Africa, Central and Western Asia; GICR; MECC; NCIC; UC Irvine
2015			
Cancer registration	Russian Federation	34	IARC Regional Hub for Northern Africa, Central and Western Asia; GICR; WHO EURO; European Network of Cancer Registries (ENCR); Petrov Research Institute of Oncology, Saint Petersburg, Russian Federation
Second training course on cervical pathology – ESTAMPA study	Cuernavaca, Mexico	20	Instituto de Salud Publica de Mexico (INSP); WHO Department of Reproductive Health and Research; UICC; Pan American Health Organization (PAHO)
Reunión de Consenso de Colposcopia – Estudio multicéntrico de tamizaje y triaje de cáncer de cuello uterino usando pruebas del virus del papiloma humano (ESTAMPA)	Bogotá, Colombia	26	San José Hospital, Bogotá, Colombia
Colposcopy and LEEP procedures in the management of abnormal cytology	Myanmar	34	National Cancer Institute Thailand; TSCCP, Thailand; University of Medicine, Magway, Myanmar; AOGIN
Training course on early detection of breast, cervical, colorectal, and oral cancer	Sri Lanka	110	National Cancer Institute Sri Lanka; WHO Country Office; UICC

Table 3. Specialized and advanced courses, 2014 and 2015 (continued)

Course title	Location	Number of participants	External collaborations
Cervical cancer screening and management of preinvasive lesions	Thailand	20	National Cancer Institute Thailand; TSCCP, Thailand
Workshop on colposcopy	Morocco	30	African Organisation for Research and Training in Cancer (AORTIC)
GloboDiet reference manager application training: Malta	Online course	5	EU-MENU
GloboDiet train-the-trainers course: Malta	Online course	7	EU-MENU
GloboDiet train-the-trainers course: Malta	Lyon, France, and online course	7	EU-MENU
GloboDiet introduction training – organization of the work: Ireland and Africa	Lyon, France, and online course	3	EU-MENU
GloboDiet training for Latin America (Brazil and Mexico): specific procedures to develop GloboDiet-related files	Online courses (continuous)	7	EU-MENU
Evaluation of GloboDiet in the African context	Online courses	37	EU-MENU
CanReg5 course	The Gambia	5	MRC Gambia; AFCRN (IARC Regional Hub for Sub-Saharan Africa)
CanReg5 training	Mexico	4	IARC Regional Hub for Latin America; INCAN Mexico
Cancer registry workshop	Islamic Republic of Iran	20	Iran University of Medical Sciences; Ministry of Health, Islamic Republic of Iran; IARC Regional Hub for Southern, Eastern and South-East Asia
Cancer registry, basic data analysis	Thailand	35	National Cancer Institute Thailand; IARC Regional Hub for Southern, Eastern and South-East Asia; GICR; IACR
Population-based cancer registry workshop	Indonesia	70	United States National Cancer Institute; Jakarta Cancer Registry; IARC Regional Hub for Southern, Eastern and South-East Asia
CanReg5 course, Pre-meeting Workshop, 37th IACR Meeting	India	20	IACR; Tata Memorial Centre; CDC
Examining solutions for cancer registration in low- and middle-income countries, Pre-meeting Workshop, 37th IACR Meeting	India	30	IACR; Tata Memorial Centre; CDC
Population-based cancer registry workshop	Panama	22	PAHO/INC
Cancer registration in the Gulf countries: principles and updates	Kuwait	19	GICR; Gulf Centre for Cancer Control & Prevention (GCCP); Kuwait Ministry of Health
BCNet training	Lyon, France	25	LMICs Biobank and Cohort Building Network (BCNet)

LABORATORY SERVICES AND BIOBANK GROUP (LSB)

Group head

Dr Maimuna Mendy

Secretary

Ms Sally Moldan

Data management assistant

Mr Ny Haingo Andrianarisoa

Biobank process management assistant

Dr Elodie Caboux

Laboratory services management assistant

Ms Brigitte Chapot

Biobank technicians

Mr Thomas Cler
(until January 2015)

Ms Elodie Colney

Mr José Garcia

Ms Sophie Guillot

Mr Christophe Lallemand

Ms Gertrude Tchoua

Laboratory aides

Ms Marcelle Essertel
(until April 2014)

Ms Nicole Farina

Ms Maria Maranhao
(until November 2014)

Students

Mr Edwin Bouchet
(until March 2014)

Ms Ninon Guichard
(until March 2015)

Mr Tadinho Spencer

The Laboratory Services and Biobank Group (LSB) was formed in 2010 to manage the IARC Biobank facility and the common laboratory platforms. The Group was reorganized in 2014 to address the growing complexity of its workload, which has changed because of the increasing services provided to IARC scientific Groups as well as external collaborators and the growing support that LSB provides to low- and middle-income countries (LMICs). The Group required a stronger process management role and data management capacity.

To ensure that biospecimens are kept under optimal conditions, LSB liaises closely with the Administrative Services Office (ASO), and the two Groups were reorganized simultaneously to address overlapping and complementary responsibilities. LSB now has 10.5 positions (reduced from 13); one post was moved to ASO, two posts were eliminated, and a data management assistant position was created.

LABORATORY SERVICES

COMMON LABORATORY PLATFORMS

Laboratory Services has continued, in conjunction with the Laboratory Steering Committee, to oversee the common laboratory platforms and the maintenance of equipment. Efforts to reinforce interactions between laboratory-based and epidemiological research include the upgrading, updating, and acquisition of state-of-the-art scientific instruments. During the biennium, the shared platforms acquired new equipment, including a benchtop next-generation sequencer of medium capacity, a nucleic acid small-volume extractor, upgraded liquid-handling instruments to provide high-throughput facilities, an enzyme-linked immunosorbent assay (ELISA) plate reader, a vacuum concentrator, a modular high-throughput thermal cycler and real-time detection system, and a digital droplet polymerase chain reaction (PCR) system.

HEALTH AND SAFETY

Health and safety issues are managed in collaboration with the Occupational Health and Safety Committee. Improve-

ments include the installation of an emergency button to stop the liquid nitrogen supply from the main tank in case of an emergency and the installation of cameras for surveillance when personnel are working alone in the cryogenic rooms. During the biennium, advice was provided to several Groups on the relocation of their offices and laboratories.

The 5-year authorization for handling radioisotopes was renewed, and permission to use genetically modified organisms (GMOs) was also granted for another 5 years.

IARC BIOBANK

The IARC Biobank maintains biological sample collections from international collaborative studies and operates a service platform for sample retrieval, DNA extraction, and shipment of biological material worldwide. IARC's facilities also serve as a custodian for collections from LMICs.

Sample location records for 5 million of the more than 7 million biological specimens in the Biobank have been uploaded into the IARC sample management system (SAMI) database. Data about the European Prospective Investigation into Cancer and Nutrition (EPIC) study's collection, which were managed by a commercial program (Tetraed), were also migrated into SAMI.

New samples arrive at IARC with a set of minimum data, which are managed centrally and recorded in SAMI using newly developed standard operating procedures and working instructions. Standard practices are implemented across the Agency for the efficient management of the reception, shipment, and storage of biological samples under optimal conditions to provide reliable material.

A revision of the [Common Minimum Technical Standards and Protocols for Biological Resource Centres](#), first published in 2007, was started in 2015.

BIOBANK SERVICES

The Biobank continues to provide pre-analytical services and operates on

a cost-recovery basis, with a major contribution from the central IARC Regular Budget for infrastructure and salaries. During the biennium, a total of 16 projects were conducted relating to 24 requests from international institutions. This resulted in more than 12 540 sample retrievals from liquid nitrogen, 9280 DNA extractions, 22 000 DNA aliquots, and the shipment of 122 parcels to 21 countries worldwide. In addition to the implementation of stringent quality control measures, the Biobank participated in international proficiency schemes and scored very highly in the DNA extraction and DNA quantification programmes.

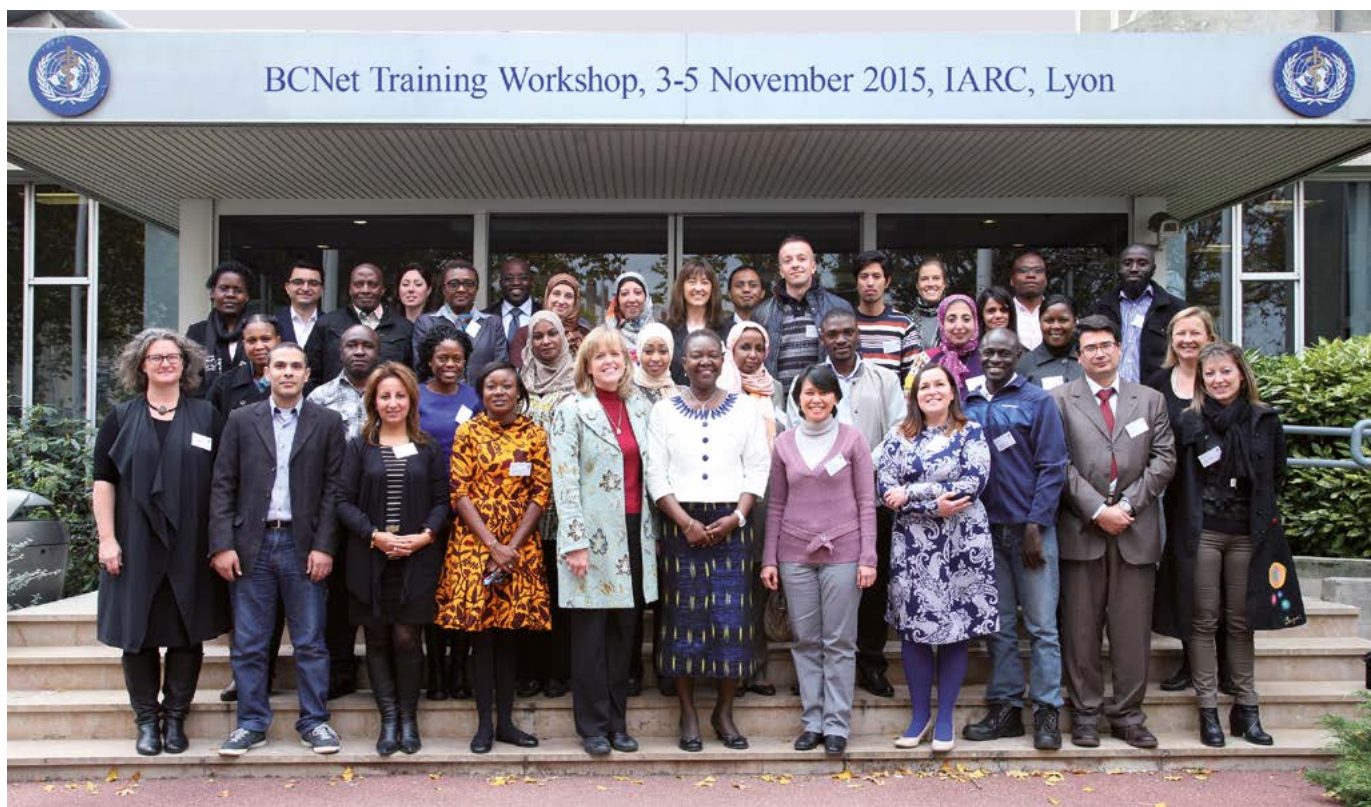
BCNET

Activities to establish the LMICs Biobank and Cohort Building Network (BCNet) continued, and the network is developing into a focal point for LMIC biobanking. A report of the situational analysis, conducted in 2013, was published during the biennium (Mendy et al., 2014). Four additional organizations have joined BCNet (Breast Care International, Ghana; the Centre for Infectious Disease Research in Zambia; Gadjah Mada University, Indonesia; and Institut Pasteur, Tunisia), bringing the membership to 29 institutions from 18 countries. The network's website (<http://bcnet.iarc.fr/>) was launched in September 2014.

TRAINING

With funding and support from the United States National Cancer Institute's Center for Global Health (NCI-CGH) and other partners, the first BCNet Training Workshop was held at IARC in November 2015, covering ethical, legal, and social issues (ELSI); quality; and information technology.

LSB continues to provide on-site training for colleagues from LMICs. During the biennium, LSB hosted students from Ghana, Indonesia, Lithuania, and The Gambia. Training is organized in collaboration with Centre Léon Bérard to include training in the handling and processing of fresh tissue.



COLLABORATIONS

In collaboration with the McCabe Centre for Law and Cancer and Melbourne Law School (Australia), IARC is contributing to the training of future professionals in the field of cancer research with a project to examine ELSIs associated with cancer biobanking in LMICs. A master's student spent 8 weeks at IARC to research issues including informed consent and access to data and samples; conduct an analysis of international, regional, and national laws and policies; and assist in writing and editing generic templates (consent forms, access policies, and access agreements). The report will be published soon.

In 2014, IARC joined the pan-European Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium ([BBMRI-ERIC](#)) as an observer. IARC will share its expertise in international networking and interoperability issues to ensure that compatible structures developed within Europe will be accessible to the wider international community.

LSB continues to support the African Organisation for Research and Training in Cancer (AORTIC), linking the organization with BBMRI and BCNet and other biobanking organizations in Europe.

GRANTS

Two grant awards were received, within the European Union's Horizon 2020 programme: (i) ADOPT BBMRI-ERIC, which aims to expand BBMRI beyond Europe (October 2015–September 2018), and (ii) B3Africa (Bridging Biobanking and Biomedical Research across Europe and Africa), for which IARC is leading the Training and Dissemination work packages (July 2015–June 2018).

THE GAMBIA HEPATITIS INTERVENTION STUDY (GHIS)

Group head

Dr Ramatoulie Njie

Acting head of cancer registry

Mr Lamin Bojang

Trainee hepatologist

Dr Sheikh Omar Bittaye

Tumour registration officers

Mr Yusupha Bah

Mr Ebrima Bojang

Mr Modou Musa Sisawo

Mr Lamin Sanneh

Data entry clerk

Ms Mariatou Rahman

PA/administrator

Ms Mama Cham

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 (MRC), 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 a junior

doctor from the local Edward Francis Small Teaching Hospital (EFSTH), who has been seconded to the MRC liver clinic and is 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 Lyon by Dr Behnoush Abedi-Ardekani at IARC. All confirmed cases of liver cancer are recorded in the NCR, and cases of chronic liver disease are recorded in a linked database.

Dr Freddie Bray, head of the Section of Cancer Surveillance (CSU) at IARC, together with Mr Morten Ervik, IT development manager in CSU, made a comprehensive site visit to The Gambia on 10–13 March 2015. All major health facilities and sources of data capture were visited. An on-site training

programme was held for the tumour registration officers, and a number of recommendations were made about measures to improve the quality of the NCR to the highest possible standard. These measures are currently being implemented and are expected to improve the identification of liver cancer cases and enable record linkage to the vaccine trial database.

The statistical analysis plan for GHIS was discussed at a special one-day meeting held at IARC in Lyon on 13 April 2015. The meeting was attended by Professor Hazel Inskip of the MRC Statistical Epidemiology Unit at the University of Southampton (United Kingdom) and Sir Andrew Hall, formerly of the London School of Hygiene & Tropical Medicine (United Kingdom), both of whom were instrumental in setting up the project three decades ago. A series of action points were detailed, and these are also being implemented.

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

Assistant (Documents)

Ms Agnès Meneghel

Secretary

Ms Anne-Magali Maillol

ADMINISTRATIVE SERVICES OFFICE

Administrative services officer

Ms Elisabeth Françon

Administrative assistant

Ms Sophie Servat

Assistants (Procurement)

Ms Fabienne Lelong

Mr Didier Louis

Ms Sandrine Macé

Assistant (Registry)

Mr François Deloche

Assistant (Security and building management)

Mr Jean-Alain Pedil

Secretary

Ms Valérie Rut

Support staff

Mr José Cardia Lima (Technician) (until October 2014)

Mr Thomas Cler (Laboratory maintenance)

Mr José Garcia (Laboratory and administration)

Mr William Goudard (Space maintenance)

Mr Antoine Hernandez (Driver)

Mr Michel Javin (Reprography)

Mr Hafed Lamouchi (Electronic maintenance)

Mr Ludovic Ripert (Storekeeper) (until October 2014)

Ms Séverine Sarboni (Reception)

GRANTS, BUDGET, AND FINANCE OFFICE

Administration and finance officer

Ms Angkana Santhiprechachit

Resource mobilization and grant officer

Dr Olaf Kelm

Budget officer

Ms Editta Odame

Finance officers

Ms Julie Goux

Mr Rommel Nidea

Assistants (Budget)

Mr Thomas Odin

Ms Madeleine Ongaro

Mr Franck Rousset

Assistants (Accounts)

Mr Pascal Binet

Ms Laurence Piau

Ms Adèle Séguret

Ms Christine Abou-Rizk (Temporary)

Assistants (Resource mobilization)

Ms Nathalie Lamandé

Ms Claire Salignat

Secretary

Ms Lobna Boulegroun

Support staff

Ms Belinda Annibaldi (Finance)

(Temporary) (until December 2014)

HUMAN RESOURCES OFFICE

Human resources officer

Ms Dina D'Amico

Assistants (Human resources)

Ms Catherine Bassompierre

Ms Isabelle Battaglia

(until December 2014)

Ms Maud Bessenay

Ms Julianna Soos (Training) (Temporary)

Secretary

Ms Sophie Sibert

Central Secretarial Services (CSS)

Ms Dominique Bouchard

Ms Nandini Deleu

Ms Marieke Dusenberg

Ms Carole Lastricani (until August 2014)

Staff physician

Dr Michel Baduraux (until April 2014)

Dr Pierre-Olivier Dondoglio

Secretary to IARC Staff Association Committee and Staff physician

Ms Isabelle Poncet

Relocation assistant

Ms Christine Astier

Consultant

Mr Rommel Arca (Training)

(until February 2015)

INFORMATION TECHNOLOGY SERVICES

System analyst

Mr Philippe Damiecki

IT officers

Mr Philippe Boutarin

Mr Christopher Jack

Assistants (Informatics)

Ms Lucile Alteyrac

Mr Nicolas Tardy

Support staff

Mr Sébastien Agathe (Informatics technician)

Mr Rémi Valette (SharePoint and .Net developer) (Temporary)

The role of the Section of Support to Research (SSR) is to support 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 capacity.

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: Resource Mobilization, Budget, and Finance; Human Resources; Procurement, 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.

In addition to the regular provision of services, during 2014–2015 the SSR team's achievements in five areas have contributed substantively to the continued efforts to maintain IARC's

status as a leader in the ever-changing international research environment.

During the biennium, SSR spearheaded the introduction of a new IARC intranet, with the aim of providing more complete and accessible information on the workings of the Agency. As part of this major project, a review of IARC's key administrative processes was carried out, resulting in the issuance of updated and new policies and procedures organized in a modern electronic interface for ease of use. In the continued effort towards streamlining, the re-engineered processes are being automated to increase efficiency and reduce workload across the Agency.

Notable progress was made with our host country's agreement to build a new IARC building and the commitment for the corresponding funding. During the biennium, IARC was fully engaged in the preparation of complete detailed specifications setting forth the anticipated requirements over the next 25 years, with highly appreciated support from Scientific Council members with recent experience in similar projects. Alongside looking at the future "Nouveau Centre", SSR

continued to ensure that IARC's scientific activities were not interrupted by the continued technical failings experienced in the current premises. In view of several incidents with various degrees of severity, a formal IARC Business Continuity Plan is now in place to ensure a smooth response to anticipated and unexpected events. In addition, in view of the escalating international terrorist threat and specifically events in France during 2014–2015, enhanced understandings were reached with local authorities and several investments were made towards heightening IARC's security measures.

In parallel with the preparation of the IARC Medium-Term Strategy for 2016–2020, major efforts were made towards ensuring full funding of the ambitious goals set forth in the document. Most importantly for current and potential donors, SSR continues to ensure effective management of resources entrusted to IARC, as consistently recognized by the WHO external auditors. To better communicate how the ongoing activities at the Agency contribute to the overall strategic goals, the IARC Project Tree was introduced as a framework for the 2016–2017 budget



approved by the Governing Council, and several investments were made to enhance support to project management and reporting to improve the visibility of the efficiency and effectiveness of our projects. The enhancement of the IARC enterprise resource planning (ERP) system to render it compatible with the International Public Sector Accounting Standards (IPSAS) will further support transparency, effective oversight, and financial reporting.

Several made-to-measure and sustainable programmes aimed at enhancing staff development, motivation, and productivity were put in place. Principal among these is the IARC Learning and Development Framework, which sets forth an innovative means to ensure that IARC staff members are equipped

with the right competencies to meet the current and future needs of the Agency within the limited resources available. Efforts continue towards supporting IARC supervisors in carrying out their staff management functions through discussion sessions and targeted training, and an electronic platform to manage the yearly performance management and development process was implemented. In addition, the restructuring of several Groups within the Agency was supported in efforts to ensure alignment within the context of continuously evolving scientific and operational expectations.

The new IARC intranet was the first project implemented at IARC on the Microsoft SharePoint platform, introduced with the purpose of more

effectively managing and sharing knowledge across the Agency and with collaborators. Subsequent projects have introduced templates to capture and facilitate different types of collaborations within the Agency and with external collaborators. This is an exciting new area, which will continue in the next biennium with the implementation of modern document retention and management tools across IARC.

SSR strives to continually improve the Agency's processes and support services by collecting feedback through a yearly services survey. SSR also holds biannual town hall meetings to communicate the Section's objectives and planned activities, and holds information sessions when required to explain new policies and procedures.

COMMITTEES

LABORATORY STEERING COMMITTEE (LSC)

Laboratory research directly involves seven Groups or Sections at IARC (BMA, EGE, GCS, ICB, LSB, MMB, and MPA). The IARC Laboratory Steering Committee (LSC) oversees the IARC core laboratory facilities and advises the Director on their most efficient use. Significant tasks of the LSC over the biennium have concerned the reallocation

of laboratory space and the move of the Biomarkers Group (BMA) to the 6th and 13th floors of the tower building, as well as the purchase of new laboratory equipment, including four robots for handling liquid biospecimens, two mass spectrometers, a pyrosequencer, and a next-generation sequencer of medium capacity. An inventory of current needs

for equipment maintenance and a plan for replacement of old items of equipment were prepared. The LSC also played an active role in the reclassification of laboratory technician posts, the definition of space requirements for laboratory activities in the “Nouveau Centre”, and the organization of Laboratory Technical Watch seminars.

BIOBANK STEERING COMMITTEE (BSC)

The IARC Biobank Steering Committee (BSC) continues to support biobanking activities at the Agency and advises the Director regarding the strategic development of the Biobank both internally and with external collaborators and projects, including the growing involvement in international biobanking capacity-building in low- and middle-income countries.

Following the establishment of a sample Access Policy for the Agency

during the 2012–2013 biennium, the BSC has supported the Biobank in the development of standard operating procedures and working instructions to ensure that samples are received and shipped from the Agency in optimal condition and according to strict international regulations.

The BSC also approved the proposal for a revision of the Common Minimum Technical Standards and Protocols for Biological Resource Centres, first

published in 2007, which was started in 2015.

The BSC also participated in discussions about plans for the Biobank of the new IARC building, according to the future needs of the Agency, and proposed the development of contingency plans for different types of events that could threaten the integrity of the current biospecimen collections.

The biennium witnessed the formation of the new Bioinformatics Steering Committee (BISC), which is tasked with overseeing matters related to bioinformatics in support of the Agency's own and collaborative projects. The BISC, led by chair Dr James McKay (GCS) and vice-chair Dr Jiri Zavadil (MMB), consists of 14 members representing all Groups with bioinformatics needs. The BISC oversees two working groups.

The Bioinformatics Working Group, led by Dr Magali Olivier (MMB), is responsible for facilitating interaction in bioinformatics within the Agency and with collaborative partners. This group holds biweekly sessions attended by about 30 participants from IARC and local bioinformatics groups. With the Education and Training Group (ETR), the Bioinformatics Working Group has also developed courses in bioinformatics for

IARC staff members. The Informatics Working Group, led by Mr Christopher Jack (ITS), is responsible for the information technology aspects of the Agency's scientific activities and has overseen two major technical expansions of IARC's high-performance computing capacity, ensuring that the computing environment matches the Agency's current demand.

ETHICS COMMITTEE (IEC)

The IARC Ethics Committee (IEC) ensures that research conducted or supported by IARC conforms to international ethical standards for research involving humans, and that measures are in place to safeguard the rights and welfare of participants. The IEC ethical review is complementary to local/national ethical approval. The committee is composed of

15 senior members of diverse nationalities with complementary expertise in epidemiology, genetics, oncology, law, and bioethics. Dr Jean-Pierre Boissel (chair, 2010–2013) terminated his mandate in 2014, and Dr Béatrice Fervers was appointed to the role of chair, supported by Dr Paolo Vineis as vice-chair. During the period 2014–2015 (up to September

2015), the IEC evaluated 74 new projects and 13 resubmissions of projects previously reviewed by the IEC. In addition, the IEC regularly considers specific ethical issues on a broader level to advise the Agency. An example is the discussion document on the ethical issues raised by incidental findings in genomic studies, prepared in 2014.

OCCUPATIONAL HEALTH AND SAFETY COMMITTEE (OHSC)

The mission of the IARC Occupational Health and Safety Committee (OHSC) is to ensure, in close collaboration with the Staff Physician and the IARC administration, that excellent working conditions are provided to all IARC personnel. In support of the process of the conception of the new IARC building, the OHSC produced a report in 2014 outlining recommendations on office spaces and optimal physical

working conditions, including social space and dedicated recreational areas. The report also took into consideration the expectations of IARC personnel who were interviewed through a questionnaire developed by the OHSC and the Staff Association. The activities of the OHSC also included (i) the revision of the procedures to be followed in case of an accident with biological samples and in the event of a colleague feeling

faint or dizzy, (ii) regular and specific safety trainings, and (iii) implementation of measures and controls to improve laboratory safety. In collaboration with the Laboratory Services and Biobank Group (LSB), the OHSC has started to work on management of exposure to chemicals and biological hazards in the Agency and is currently exploring the options for developing a risk assessment methodology.

GOVERNING AND SCIENTIFIC COUNCILS

THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC) WAS ESTABLISHED IN MAY 1965, THROUGH A RESOLUTION OF THE EIGHTEENTH WORLD HEALTH ASSEMBLY, AS AN EXTENSION OF THE WORLD HEALTH ORGANIZATION, AFTER A FRENCH INITIATIVE. IT IS GOVERNED BY ITS OWN GOVERNING BODIES: THE IARC GOVERNING COUNCIL AND THE IARC SCIENTIFIC COUNCIL.

GOVERNING COUNCIL

IARC's general policy is directed by a Governing Council, composed of the representatives of Participating States and of the Director-General of the World Health Organization. It meets every year in ordinary session in Lyon, usually the week before the World Health Assembly. The Governing Council elects IARC's Director for a five-year term. The Council re-elected Dr Christopher P. Wild in May 2013 to serve for a second five-year term as from 1 January 2014. The chairperson of the Governing Council prepares the meetings together with the Secretariat and advises the Director throughout the year. In May 2015, Morocco was admitted as the first IARC Participating State from the African continent, bringing the total number of IARC Participating States to 25.



SCIENTIFIC COUNCIL

The Scientific Council consists of highly qualified scientists selected on the basis of their technical competence in cancer research and allied fields. Members of the Scientific Council are appointed as experts and not as representatives of Participating States. When a vacancy arises on the Scientific Council, the Participating State that nominated the departing member may nominate up to two experts to replace that member. Scientific Council members are appointed for four-year terms by the Governing Council. The Scientific Council reviews the scientific activities of the Agency and makes recommendations on its

programme of permanent activities and priorities. The Scientific Council meets every year in ordinary session in late January/early February.

BUDGET

IARC activities are partially funded by the regular budget contributions paid by its Participating States. In addition, substantial funding comes from extrabudgetary sources, mainly grant awards, both national and international. The regular budget for the 2014–2015 biennium was approved in May 2013 at a level of €40 424 491.

PARTICIPATING STATES AND REPRESENTATIVES AT IARC GOVERNING COUNCIL'S FIFTY-SIXTH SESSION, 15–16 MAY 2014

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Dr Mark Palmer, Chairperson
Director, International Strategy
Medical Research Council
London

Dr Nathan Richardson
Head, Molecular and Cellular Medicine
Medical Research Council
London

FRANCE

Professor Agnès Buzyn,
Vice-Chairperson
Présidente, Institut national du Cancer
(INCa)
Boulogne-Billancourt

Mr Armel T'Kint De Roodenbeke
Ministère des Affaires étrangères
Paris

SWITZERLAND

Dr Diane Steber Büchli, Rapporteur
Collaboratrice scientifique, Division
internationale, Office fédéral de la
Santé publique
Bern

AUSTRALIA

Professor Chris Baggoley
Chief Medical Officer
Department of Health
Canberra

AUSTRIA

Dr Hemma Bauer
Austrian Federal Ministry of Science,
Research and Economy
Vienna

BELGIUM

Mr Lieven De Raedt
Attaché Relations Internationales
SPF Santé publique, Sécurité de la
Chaîne Alimentaire et Environnement
Brussels

BRAZIL

Dr Luiz Antonio Santini (unable to
attend)
Director General, Brazilian National
Cancer Institute (INCA)
Rio de Janeiro

Dr Marisa Dreyer Breitenbach
Research Coordinator, Brazilian
National Cancer Institute (INCA)
Rio de Janeiro

CANADA

Dr Stephen M. Robbins
Scientific Director, Institute of Cancer
Research
Canadian Institutes of Health Research,
University of Calgary
Calgary, Alberta

Ms Lucero Hernandez
Senior Policy Advisor, Multilateral
Relations Division
Office of International Affairs for the
Health Portfolio
Ottawa, Ontario

DENMARK

Professor Herman Autrup
University of Aarhus School of Public
Health
Aarhus

FINLAND

Professor Juhani Eskola
Director-General, National Institute for
Health and Welfare (THL)
Helsinki

Professor Harri Vainio
Director-General, Finnish Institute of
Occupational Health
Helsinki

GERMANY

Dr Chariklia Balas
Advisor, Division of Global Health
Federal Ministry of Health
Bonn

INDIA

Professor G.K. Rath (unable to attend)
Chief, Dr B.R. Ambedkar Institute
Rotary Cancer Hospital (DBAIRCH)
All India Institute of Medical Sciences
(AIIMS)
New Delhi

IRELAND

Mr Keith Comiskey
Department of Health
Dublin

ITALY

No Representative

JAPAN

Dr Yousuke Takasaki
Deputy Director, Division of International
Affairs
Ministry of Health, Labour and Welfare
Tokyo

Mr Kenji Okada
Ministry of Health, Labour and Welfare
Tokyo



NETHERLANDS

Dr Jack Hutten
Acting Head, Division of Public Health
Care
Ministry of Health, Welfare and Sport
The Hague

Mr Jeroen Hulleman
Senior Policy Advisor, Public Health
Directorate
Ministry of Health, Welfare and Sport
The Hague

NORWAY

Dr Edgar Rivedal
Scientific Coordinator, Norwegian
Scientific Committee for Food Safety
Oslo

Dr Karianne Solaas
Senior Adviser, The Research Council
of Norway
Oslo

QATAR

Dr Faleh Mohamed Hussain Ali
Assistant Secretary General for Policy
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