International Agency for Research on Cancer

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IARC Interim Annual Report 2014

Contents

Foreword

I am pleased to present this Interim Annual Report, which provides a summary of the activities at IARC during the past year. This short report is in one sense historic as it marks the completion of 50 years since the creation of IARC in 1965. The research activity of IARC took form over the subsequent two years or so as budgets were decided, people were recruited, and buildings were provided. As those familiar resource requirements were debated, the Agency got down to the business of shaping its activities around the priorities outlined in its Statute. In doing so it began to develop the types of collaboration that have characterized its approach over the ensuing decades.

IARC is now 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, as testified for example by the hundreds of scientists who have now benefited from the enduring IARC training experience, the Agency has constantly adapted to the changing knowledge about cancer and the evolving international cancer research landscape. This dynamism at an organizational level is driven in large part by the creativity and dedication of the personnel, representing the heart of IARC's success and further illustrated in the project descriptions that follow.

The current report entails a spectrum of research contributing in different ways to cancer control – from describing the occurrence, through identifying causes, to evaluating and implementing prevention and early detection. It is an ambitious programme. The growing world cancer burden demands that of us. But the depth and breadth of the activities in turn reveal the secret of how IARC is able to achieve so much with so little – by catalysing collaboration and joining with the international cancer research community to achieve common goals. The collaborative projects described in this snapshot report illustrate just how wide the influence of the Agency stretches and how strong is the desire of partners across the world to work with IARC in a partnership of equals. This is a powerful model for success, through cooperation rather than competition, through emphasis on the group rather than the individual.

I commend the work of all IARC personnel to you and trust that the contents of this Interim Annual 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.

Dr Christopher Wild
IARC Director

Section of Cancer Surveillance (CSU)

The Section of Cancer Surveillance (CSU) focuses on global cancer surveillance and the systematic and ongoing pursuit of global cancer data and statistics for cancer control action. CSU collects, analyses, interprets, and disseminates indicators that capture the changing scale and profile of the disease via three essential and complementary areas of activity:

- **Cancer registry support and development.** The long-standing collaborative relationship of CSU with population-based cancer registries (PBCRs) worldwide, members of the International Association of Cancer Registries (IACR), remains vital in improving the availability, validity, and timeliness of cancer data at the national, regional, and global levels. Through the Global Initiative for Cancer Registry Development (GICR), CSU aims to radically increase the quality and availability of cancer incidence data in low- and middle-income countries (LMICs). Advocating for the central role of PBCRs in national cancer control planning, reference centres (IARC Regional Hubs) are operating in six regions to provide targeted support to countries wishing to plan and develop their PBCR programmes.
- **Global cancer indicators: development and dissemination.** The compilation, estimation, and reporting of cancer statistics are performed through CSU's flagship projects and databases *Cancer Incidence in Five Continents* and GLOBOCAN, international compendiums of high-quality registry data and of national estimates of incidence, mortality, and prevalence, respectively. A greater focus is now being placed on the development of interactive and user-friendly web-based tools to better inform cancer control and cancer research.
- **Descriptive epidemiology of cancer: core activities and innovation.** An increasingly diverse and comprehensive set of collaborative studies describe and interpret the changing magnitude and transitional nature of the cancer profile, via the observation of variations by geography and time. A novel additional research area aims to develop indicators that underscore cancer as a major cause of premature death, as a barrier to old age, and as a chronic condition linked to social and economic development.

Cancer registry support and development

The cancer incidence burden is projected to increase from 14.1 million in 2012 to 21.6 million by 2030, with increases of 60–70% forecast in Latin America, Asia, and Africa. The development and implementation of national cancer control plans is imperative in every country, yet planning is impossible without first identifying the scale and the profile of cancer in the community. It is of acute concern that currently only 68 countries (mainly high-income countries) are equipped with high-quality PBCR data for such purposes, while in 62 countries (mainly LMICs), no reliable data are available.

Bolstered by the high-level efforts to combat noncommunicable diseases (NCDs) and by countries agreeing to collect cancer incidence data as a marker of progress, the IARC-led GICR partnership (http://gicr.iarc.fr) aims to change the surveillance landscape, aiding and accelerating the availability of PBCRs for national cancer control. The key instrument through which these ambitions are realized is the formation of six IARC Regional Hubs for Cancer Registration, which provide localized programmes of training, support, and advocacy to targeted countries within defined regions.

The infrastructure and governance of GICR have evolved in 2014 to embrace the dedicated surveillance activities of the international organizations represented (the GICR Partners Group) to provide strategic advice on integrating efforts in fully operationalizing the Hubs. Membership of the GICR Partners Group includes the American Cancer Society (ACS), IACR, the International Atomic Energy Agency (IAEA) Programme of Action for Cancer Therapy (PACT), the Public

Health Agency of Canada, the Union for International Cancer Control (UICC), the United States National Cancer Institute (NCI), the United States Centers for Disease Control and Prevention (CDC), and WHO.

The Hub model is a connected system arranged to link country-level needs with regional support mechanisms. Four Hubs are operational: a Regional Hub for South, East, and South-Eastern Asia, in Mumbai, India (based at Tata Memorial Centre); a Regional Network Hub for Sub-Saharan Africa (in collaboration with the African Cancer Registry Network [AFCRN]); a Regional Hub for North Africa, Central and West Asia, in Izmir, Turkey (based at the Izmir Cancer Registry); and a Regional Network Hub for Latin America, in Buenos Aires (coordinated by the National Cancer Institute, Argentina). Two more Hubs are being implemented: Regional Hubs supporting countries in the Pacific Islands and in the Caribbean. Global coordination and technical development across Hubs is provided through the Hub Executive Group, comprising IARC staff and the Hub Principal Investigators.

An important milestone in 2014 was the definition of a goal and explicit objectives that will provide measurable improvements in PBCRs in 50 countries during the period 2014–2018. The selection of countries is a dynamic process requiring regular strategic input from the GICR Partners Group and regular review as to the technical requirements of Hubs by the Hub Executive Group. Three-year operational plans for each Hub are close to completion, including the identification of priority countries. In concert, a significant area of advocacy and fundraising work is creating a sustainable global fund to advance the Hub and country activities.

Fundamental to GICR are site visits, recommendations, and follow-up. Eight consultancies were undertaken in 2014, and nine more are planned. Several agreements between IARC and individual countries are being implemented. Targeted registries in Asia are working with IARC and the Mumbai Hub to produce first reports of the cancer burden in Indonesia, Mongolia, and Sri Lanka. Training remains a core component, and 11 GICR-led or affiliated Hub regional courses were held in 2014. Highlights include the first Russian-language course, involving participants from 10 countries in central Asia and Europe, held in Astana, Kazakhstan. Priority areas identified in the action plan with the WHO Regional Office for the Eastern Mediterranean led to a registry training workshop being held in Cairo, which included a future needs assessment of 17 Eastern Mediterranean countries. Exploratory workshops in conjunction with the United States NCI in China and with the IACR 2014 conference in Ottawa and in El Salvador have brought together registry-affiliated participants in support of building registration in different regions.

Online training and the development of e-learning modules is being assessed for possible delivery in 2015. To supplement training and provide a reference source for health planners, an IARC Technical Publication has been disseminated and is available online in PDF and e-Pub formats (Bray et al., 2014). Given shared goals, a mutual programme of activities is being developed with IACR via ongoing discussions with the IACR President and Executive Board.

Global cancer indicators: development and dissemination

CSU aims to retain its remit as the definitive reference source and provider of global cancer statistics in adults, children, and adolescents. After the launch of the GLOBOCAN 2012 website, a companion paper described the rationale, data sources, and methods of estimation of the global cancer burden, and introduced an alphanumeric scoring system that indicates the robustness of the national estimates (Ferlay et al., 2014b). A global snapshot of the cancer-specific patterns brought focus to regional and national prioritization of cancer control efforts as well as the need for better surveillance systems in many LMICs. A more formal modelling

framework for estimation, incorporating uncertainty estimates, is being evaluated in collaboration with the University of Washington and the Section of Infections (INF).

Through the online publication of Volume X of *Cancer Incidence in Five Continents* (CI5, http://ci5.iarc.fr) – jointly with IACR – results from all 10 published volumes have been made available through two additional public domain websites and databases: CI5 I–X and CI5*plus*. The CI5 I–X application contains the original data published in each volume. To enable temporal comparisons, the CI5*plus* database (Ferlay et al., 2014a) contains long-term annual data for 118 selected populations from 102 cancer registries published in CI5 for 28 major cancer sites.

Preparation of the third volume of *International Incidence of Childhood Cancer* (http://iicc.iarc.fr) is in its final stages. Data on cancer incidence in children and adolescents (ages, 0–19 years) are being compiled in collaboration with more than 350 cancer registries worldwide. The European Cancer Observatory (http://eco.iarc.fr) estimates national incidence, mortality, and prevalence in 40 major countries of Europe (EUCAN), complemented by recorded incidence, mortality, and survival series from 130 registries (EUREG). With the provision of such data via collaboration with members of the European Network of Cancer Registries (ENCR), geographical and temporal patterns can be elucidated to inform cancer control policies in Europe (Steliarova-Foucher et al., 2014).

The WHO Mortality Database and NORDCAN database (http://www-dep.iarc.fr) have been updated to 2012. The latest version of the NORDCAN database, co-developed with the Association of the Nordic Cancer Registries (ANCR, http://ancr.nu), now includes cancer survival statistics for 2009–2011. In response to growing demand, a new cancer dictionary based on tumour–node–metastasis (TNM) groupings (replacing the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] codes) is being implemented for the next NORDCAN release, and may be adapted for implementation within future CSU projects.

The above-mentioned websites will be superseded by the planned Global Cancer Observatory – a database of global and national cancer statistics and a suite of interactive and user-friendly tools to provide instructive and timely information on a broad range of indicators.

Descriptive epidemiology of cancer: core activities and innovation

Descriptive epidemiological research remains a major component of CSU's activities and has two main areas of focus. First, numerous descriptive studies of the key patterns and trends by cancer type, region, and so on are undertaken, often as ad hoc collaborative efforts with internal or external colleagues; many make direct use of the GLOBOCAN and CI5 data described above. In terms of cancer-specific assessments, articles have described the global patterns and trends of urological cancers as part of a Platinum Priority series in *European Urology*, and in partnership with ACS. Global reports of the incidence and mortality patterns and trends of testicular cancer (Znaor et al., 2014a), bladder cancer (Chavan et al, 2014), and renal cell carcinoma (Znaor et al., 2014c) have been published, as well as a series of testicular cancer incidence papers quantifying the future burden in Europe (Le Cornet et al., 2014), generational trends in 38 countries worldwide (Znaor et al., 2014b), and international variations in seminoma and non-seminoma (Trabert et al., 2014). An international study of bone cancer incidence has examined the descriptive epidemiology of osteosarcoma, Ewing sarcoma, and chondrosarcoma, while lung cancer trends and current oesophageal cancer rates have been explored by histological subtype (Lortet-Tieulent et al., 2014; Arnold et al., 2014c). The latter study estimated 398 000 squamous cell carcinomas and 52 000 adenocarcinomas of the oesophagus in 2012, reporting a relatively high proportion of adenocarcinoma in high-income countries and an excess risk among men, linked to shifts in the tobacco smoking and obesity epidemics.

In terms of regional assessments, a study in Colombia assessed cancer mortality by socioeconomic level, part of the IARC Expertise Transfer Fellowship of Esther de Vries during 2013–2014. In collaboration with Tata Memorial Centre, a study of incidence trends in six Indian registry populations revealed a clear transition from cervical to breast cancer in urban but not rural settings within the country (Badwe et al., 2014). Some studies have explored patterns in subpopulations, linking cancer transition to socioeconomic change. For example, considerable work is under way to highlight and contrast the cancer disparities among Indigenous peoples worldwide (Arnold et al., 2014a; Moore et al., 2014a; Moore et al., 2014b; Moore et al, 2014c; Valery et al., 2014). Another paper provides an appraisal of the cancer situation in Africa in 2012, with comparison of the incidence and mortality profiles in North Africa and sub-Saharan Africa, and the prospects for cancer control on the continent (Parkin et al., 2014).

CSU also aims to provide evidence of the effectiveness of cancer control programmes using population-based data. In collaboration with INF, CSU has assessed the impact of cervical cancer screening in four Nordic countries; up to 49% of the expected cases may have been prevented by screening introduced from the late 1960s (Vaccarella et al., 2014). A novel report with the New South Wales Cancer Council evaluated the long-term impact of the phenacetin ban on upper urinary tract cancer rates in Australia; a significant reduction in renal pelvis cancer incidence was observed (particularly among women) after the widely used analgesic was banned in 1979 (Antoni et al., 2014).

CSU has published several books and chapters in 2014. As well as Volume X of CI5 (Forman et al., 2014) and co-development of the second edition of *The Cancer Atlas* with ACS (Jemal et al., 2014), introductory chapters were written for IARC's *World Cancer Report 2014* and a chapter assessing implications for cancer control of developmental transition was prepared as part of the third edition of Disease Control Priorities (Bray and Soerjomataram, 2014).

A second theme of innovation is emerging, linking cancer with other NCDs and efforts to combat the rising burden. Several studies are assessing the public health utility of measures from a societal burden perspective. One example is a European study of costs related to premature mortality from cancer (Hanly et al., 2014). Overall costs were high (almost 0.6% of European gross domestic product in 2008), with losses greater in the least wealthy European nations. Another major project is quantification of the cancer burden according to major risk factors. A recent report has estimated that 3.6% of cancers worldwide are related to excess weight, with a larger attributable fraction in countries with a higher Human Development Index (HDI) than in countries with a lower HDI (5.3% vs 1.0%) (Arnold et al., 2014b). The impact of tobacco smoking on cancer and other NCDs over the past 30 years indicates that smoking is related to approximately 20% of total adult mortality (work in progress); cardiovascular disease is the most important disease related to smoking, followed by lung cancer. While the share of cardiovascular disease among all smoking-related deaths has decreased over the past 30 years, the proportion of smoking-related lung cancer deaths has grown.

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Section of IARC Monographs (IMO)

The first step in cancer prevention is to identify the causes of human cancer. The IARC Monographs Programme is an international, interdisciplinary approach to carcinogenic hazard identification. Its principal product is the serial publication 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 – since 1987 – 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 300 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. The Handbooks of Cancer Prevention also include public health and research recommendations, thus facilitating translation of evidence into policy. Evaluations have included chemo-preventive 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; IARC will use this advice in making decisions on agents for future evaluations.

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 within low- and middle-income countries, including enhanced retrieval of relevant exposure data for Monographs and increased dissemination of pertinent evaluations (Straif et al., 2014).

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
N,*N*-Dimethyl-*p*-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), *tert*-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
ortho-Phenylenediamine dihydrochloride
Physical inactivity and sedentary work
Red and processed meats
Shiftwork
Styrene
Tetrabromobisphenol A (TBBPA)
Tungsten
Welding and welding fumes

Volume 110: Perfluoro-octanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone (3–10 June 2014)

In June 2014, 20 experts from 9 countries met at IARC to assess 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* in humans that exposure to

1,2-DCP causes cancer of the biliary tract in exposed workers and *sufficient evidence* in experimental animals. The most important human evidence about the carcinogenicity of 1,2-DCP came from studies of workers in a small offset printing plant in Osaka, Japan, where a very high risk of cholangiocarcinoma was reported. The Working Group classified DCM as *probably carcinogenic to humans* (Group 2A), based on *limited evidence* in humans that its use is associated with 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). The Working Group based its classification 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; 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 that exposure to PFOA is associated with testes and kidney cancer and *limited evidence* in experimental animals (Benbrahim-Tallaa et al., 2014).

Volume 111: Fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes (30 September–7 October 2014)

In October 2014, 21 experts from 10 countries met at IARC to assess 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 environmental exposure to fluoro-edenite causes mesothelioma and *sufficient evidence* in experimental animals. The human evidence came from surveillance studies reporting an excess of mesothelioma incidence and mortality in the regional population of Biancavilla, Italy. SiC fibres are unwanted by-products of the manufacture of SiC particles by the Acheson process. SiC whiskers are intentionally produced by other processes. Excesses of lung cancer mortality and incidence were observed in two cohort studies of Acheson process workers. Occupational exposures associated with the Acheson process were classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* 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 (mesotheliomas were observed in exposed rats), and consideration of their physical properties resembling those of asbestos and erionite.

There was no epidemiological study on CNTs in exposed humans. 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 caused peritoneal mesotheliomas in rats and *p53*$^{+/-}$ mice after non-inhalation routes of exposure, and promoted bronchioloalveolar carcinoma in mice. Both types of MWCNTs with dimensions similar to MWCNT-7 caused mesotheliomas in rats in one intraperitoneal study. 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, in both developed and developing countries, and the potential role of primary prevention is limited because most risk factors for breast cancer are directly linked with endogenous hormone levels and choices of childbearing. Therefore, secondary prevention encompassing all forms of screening for breast cancer is a priority.

In 2002, an IARC Working Group developed IARC Handbook Volume 7 on breast cancer screening. Recent improvements in treatment outcomes for late-stage breast cancer and concerns about overdiagnosis called for reconsideration. Therefore, an up-to-date, objective, and independent evaluation of the benefits and harms of mammography screening in different age groups was urgently needed. In addition, new studies on clinical breast examination and breast self-examination warranted a re-evaluation of the efficacy and effectiveness of such screening programmes.

Furthermore, new modalities have become available and needed rigorous scientific evaluation. These include magnetic resonance imaging (contrast-enhanced and non-contrast-enhanced), digital breast tomosynthesis (or 3D mammography), breast-specific positron emission tomography, ultrasound in conjunction with mammography for women with dense breasts, and computer-assisted diagnosis in combination with digital mammography.

Finally, the effectiveness of screening women at increased risk of breast cancer was evaluated, particularly in the context of new data being available on alternative screening modalities. This increased risk may be attributed to the presence of a familial predisposition for breast cancer, with or without a genetic mutation, to a personal history of invasive breast cancer or ductal carcinoma in situ, or to the presence of lobular atypical proliferations.

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Section of Mechanisms of Carcinogenesis (MCA)

The Section of Mechanisms of Carcinogenesis (MCA) conducts studies aimed at elucidating molecular mechanisms by which environmental and lifestyle 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 relevant 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.

Epigenetics Group (EGE)

Advances in epigenomics have dramatically accelerated research on mechanisms of carcinogenesis and biomarker discovery, and have opened up new perspectives in cancer research (Herceg et al., 2013; Nogueira da Costa and Herceg, 2012; Umer and Herceg, 2013; Wild et al., 2013). 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 carcinogens and by the application of cutting-edge epigenomics in conjunction with unique biospecimens from population-based cohorts. 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.

Accelerated epigenetic clock is a predictor of breast cancer in a prospective study

Recent studies on retrospectively collected blood samples in breast cancer patients have underlined the importance of assessing epigenetic (DNA methylation [DNAm]) patterns in peripheral blood of cancer patients and have provided new insights into the pathophysiology of the disease. Peripheral blood serves as a promising non-invasive biofluid of choice for cancer detection. However, there is a strong need to conduct prospective longitudinal epigenome-wide studies for identification of putative causal epigenetic alterations and risk markers. EGE developed a study aimed at testing the hypothesis that the methylome changes associated with breast cancer risk and dietary/lifestyle factors can be identified in peripheral blood cells and that methylation changes can serve as sensitive biomarkers in primary and secondary prevention of breast cancer. The potential of DNAm in peripheral blood as a marker of breast cancer risk was examined in a nested case–control cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) study (collaboration with NEP). The study cohort involved 480 female incident breast cancer cases and 480 matched controls (matched for centre, age, date of blood collection, and menopausal status). DNAm levels were measured across 485 777 CpG sites using the Illumina 450K BeadChip array. Methylation values for all the probes thus obtained were compared between cases and matched controls using logistic regression analysis, adjusting for potential confounders. Differential methylation was found across 185 probes ($P < 0.0005$), and

these probes may serve as potentially useful surrogate markers for identification of individuals with a high risk of breast cancer development. Furthermore, EGE used a recently developed biomarker of ageing (the "epigenetic clock") based on DNAm levels (Horvath, 2013), which can be used as a proxy of epigenetic tissue age. Because DNAm age has a strong linear relationship with chronological age in our data, we were able to define age acceleration as the residual resulting from a linear model that regressed DNAm age on chronological age. By definition, this measure of age acceleration is not correlated with chronological age; therefore, these results suggest that perturbation of the epigenetic stability may underline age acceleration associated with breast cancer risk.

Exposure to aflatoxin B_1 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. Aflatoxin is a contaminant of staple foods in sub-Saharan Africa and is a known human liver carcinogen that has been associated with impairment of growth and development and susceptibility to diseases and cancer. EGE investigated the consequences of early-life exposure to aflatoxin at the epigenome (DNAm) level. Aflatoxin exposure was measured in 115 pregnant women in The Gambia, and the DNAm status of white blood cells from their infants at age 2–8 months (mean, 3.6 ± 0.9 months) was examined. Aflatoxin exposure in women was assessed using an enzyme-linked immunosorbent assay (ELISA) method to measure aflatoxin–albumin adducts in plasma taken at 1–16 weeks of pregnancy. Global DNAm of infant white blood cells 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 such as *FGF12* and *IGF1*, in immune-related genes such as *CCL28*, *TLR2*, and *TGFBI*, and in *AKR7A3*, which is involved in aflatoxin detoxification. Moreover, differential methylation was sex-dependent, with two differentially methylated regions (HOOK2 and FOSB) only present in male infants. This study shows that maternal exposure to aflatoxin during the early stages of pregnancy is associated with changes in epigenome patterns of infants. This reinforces the need for interventions to reduce aflatoxin exposure, especially during critical periods of fetal and infant development.

Development of epigenomic methodologies and bioinformatics 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 IonTorrent) at IARC and external collaborators. These methodologies enabled EGE to move from focused approaches to comprehensive epigenome-wide approaches and to develop several new and original topics in cancer epigenetics (Aury-Landas et al., 2013; Ghantous et al., 2014; Martin et al., 2014; Xu et al., 2012; Aushev et al., 2013). In addition, the diverse tasks of understanding mechanisms of carcinogenesis and their link to environmental exposures, or of defining epigenetic signatures of cancer risk, are all increasingly dependent on our capacity to handle and exploit such multidimensional data sets. The data produced with genome-wide techniques need to be properly processed and integrated with data sets from other assays or from available online repositories. EGE (together with MMB) takes the lead in the integration of different layers of genome-wide data, such as the DNA methylome, gene expression, mutations and genomic variants, and histone marks. To this end, EGE has been involved in the adaptation of available packages and in-house scripts for bioinformatics pipelines dedicated to such integration, with important considerations such as the power/sample size, dimension-reduction

techniques, normalization across data sets, removal of batch effects, and statistical modelling. This includes the development of Galaxy pipelines for the analyses of DNA methylation (Illumina Infinium bead arrays and NGS-based reduced representation bisulfite sequencing [RRBS]), exome sequencing, RNA sequencing, and ChIP-seq. Furthermore, to allow non-developer users to analyse the omics data, pipelines are being developed into the open-source, web-based Galaxy platform and/or other suitable environments. In addition to integration, modularity will be built into the pipelines, which will permit individual users to select the required analytical modules according to the characteristics of their data set.

Molecular Mechanisms and Biomarkers Group (MMB)

The overarching objective of MMB is to establish an evidence base for cancer prevention by elucidating molecular mechanisms and biomarkers of carcinogenesis associated with specific environmental and lifestyle risk factors. MMB characterizes new biomarkers of exposure and tumorigenesis by mutation signature screens in experimental models of carcinogen effects in vitro, as well as in tumour tissues and circulating free DNA (cfDNA) from plasma, taking advantage of existing epidemiological studies and supporting new ones. MMB develops and validates new carcinogen screening methods as well as molecular profiling and bioinformatics tools applicable to population-based and mechanistic studies. Collectively, MMB's projects aim to advance the general understanding of mechanisms of carcinogenesis and to facilitate and strengthen evidence-based cancer prevention strategies.

Modelling mutational signatures of human carcinogens in vitro

MMB devised experimental models recapitulating mutational landscapes of human somatic mutation patterns from public genomics databases. In immortalized cell lines derived from primary murine embryonic fibroblasts, exposed in vitro to mutagenic carcinogens or expressing endogenous mutagenic activity, mutation patterns were shown to recapitulate key features of mutational signatures observed in human cancers, with high genome-wide concordance between human tumour mutation data and in vitro data (Olivier et al., 2014). Primary-cell clonal immortalization is thus a simple and powerful strategy for modelling mutation signatures that facilitates the interpretation of human cancer genome-wide sequencing data. The system is being used in support of IARC's programme on the evaluation and classification of chemicals for their carcinogenic effects.

Mutational signature of carcinogenic aristolochic acid identified in renal cell carcinomas of chronic kidney disease patients

Carcinogenic aristolochic acid (AA) is an established etiological agent underlying severe nephropathies and associated upper urinary tract urothelial cancers. Its genome-wide mutational signature, marked by predominant A:T > T:A transversions, has been identified in upper urinary tract urothelial carcinomas and in experimental systems (Olivier et al., 2014). MMB used whole-exome sequencing performed on DNA from formalin-fixed, paraffin-embedded renal cell carcinomas (RCCs) arising in patients with chronic renal disease from endemic nephropathy regions in Croatia and Bosnia, where the disease results from the consumption of bread made from wheat contaminated by AA-containing seeds of *Aristolochia clematitis*. In 5 of 8 (62%) analysed RCCs, a mutational signature was observed that is consistent with exposure to AA (Jelaković et al., 2014). In addition, MMB contributed to a clear cell RCC whole-genome sequencing study (CAGEKID Consortium), which identified AA signature-containing RCC tumours in Romanian patients (Scelo et al., 2014). By identifying a new tumour type associated with the AA-driven mutagenic process, these results suggest new epidemiological and public health implications for RCC incidence worldwide. The putative causal role of AA in renal cortex carcinogenesis should be broadly addressed in high-risk regions marked by inadvertent exposure to AA or widespread use of AA-containing herbal remedies.

Non-invasive diagnosis of clinically relevant mutations by deep sequencing of cfDNA in lung cancer from never-smokers

Somatic mutation analysis is part of the standard management of metastatic lung cancer to identify mutations enabling gene-targeted therapies. Biopsy samples provide limited amounts of DNA for testing and may not be representative of the entire tumour mass. cfDNA from plasma has emerged as a promising surrogate tissue for accessing the tumour genome non-invasively. MMB used deep sequencing with the IonTorrent Personal Genome Machine (PGM) Sequencer for the detection of low-abundance tumour mutations in cfDNA from non-small cell lung cancers (NSCLC) in non-smokers. Non-smoker lung cancer patients have been chosen because their tumours are expected to be enriched in clinically relevant mutations. Multiplex polymerase chain reaction (PCR) assays covering hotspot mutations in the *EGFR*, *KRAS*, *BRAF*, *HER2/ERBB2*, and *PIK3CA* genes were used to analyse cfDNA samples extracted from plasma collected in the BioCAST/IFCT-1002 lung cancer study (never-smokers cohort). A set of 68 cfDNA samples and matched tumour DNA (tDNA) was sequenced at deep coverage. Mutations were identified by an in-house bioinformatics pipeline. A detection sensitivity of 58% and an estimated specificity of 87% were obtained, taking mutations found in tDNA as the reference and using a modified variant calling strategy (Couraud et al., 2014). NGS is thus a suitably sensitive and specific method for the detection of tumour mutations in cfDNA. This approach is promising both for the diagnosis and follow-up of lung cancer patients, and may be envisioned as a molecular diagnostic tool in cancer epidemiology studies for which only blood samples are available.

Etiology and biology of premenopausal breast cancer in Latin American women

In Latin America, there are a large number of incident breast cancer cases in premenopausal women. This high incidence rate is only partly explained by the population age structure. Behavioural, reproductive, and lifestyle risk factors typical of industrialized populations are becoming increasingly prevalent in Latin America, but their role in the increased breast cancer incidence is unknown. In-depth knowledge of the molecular and pathological characteristics of premenopausal breast cancer is lacking, with consequences for cancer etiology, treatment, and survival. IARC's PRECAMA epidemiological study investigates the molecular, pathological, and risk factor patterns of premenopausal breast cancer in Latin America in a multicentre case–control study. PRECAMA plans to recruit more than 800 women over the next 2 years, administering questionnaires on lifestyle, diet, and environmental factors and collecting blood, urine, and tumour samples. MMB has conducted a feasibility study on 41 PRECAMA formalin-fixed, paraffin-embedded tumour samples and their matched blood pairs, and somatic mutations in genes frequently mutated in breast cancer were screened by targeted resequencing on the Ion Proton Sequencer. The rates of mutations found in the targeted genes (*TP53*, *PIK3CA*, *CDH1*, *RB1*, and *ERBB2*) matched those described in other populations. These results demonstrate the suitability of the samples for advanced genomic analyses. Providing characteristics of the molecular features of premenopausal breast cancer in Latin America and their link to risk factors should help to advance the prevention and management of breast cancer in this world region.

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Section of Molecular Pathology (MPA)

The Section of Molecular Pathology (MPA) conducts original research to elucidate the molecular basis and genetic pathways of human neoplasms. The specific aims of MPA 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 (Ohgaki et al., 2014; Kim et al., 2014; Louis 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, 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 publication of the 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.

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.I827N) 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., 2014).

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 poor prognosis. Other than frequent *TP53* mutations (> 80%), little has been known about their molecular profile. 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%) *IDH1*-mutated 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 deletion of *RRAS* and *ERCC1* were absent in other low-grade diffuse gliomas or 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 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. Thus, 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).

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 polymerase chain reaction (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 DAOY and ONS-76 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

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 has a

high impact not only for the pathology community but also for cancer registration, epidemiological studies, clinical trials, and cancer research in general. IARC has been responsible for this book project since the third edition (2000–2005; 10 volumes). The current (fourth) edition was initiated in 2006, with four new series editors (Dr Fred Bosman, University of Lausanne, Switzerland; Dr Elaine Jaffe, National Institutes of Health, Bethesda, USA; Dr Sunil Lakhani, University of Queensland, Brisbane, Australia; and Dr Hiroko Ohgaki, IARC). So far, six volumes have been published, and for each volume, 20 000–50 000 copies were printed and distributed worldwide.

The sixth volume, Tumours of Female Reproductive Organs, was published in April 2014. The volume editors are Dr Robert J. Kurman, Johns Hopkins University, Baltimore, USA; Dr Maria Luisa Carcangiu, Fondazione IRCCS, Institute Nazionale dei Tumori, Milano, Italy; Dr Simon Herrington, Centre for Oncology and Molecular Medicine, Ninewells Hospital and Medical School, Dundee, United Kingdom; and Dr Robert H. Young, Massachusetts General Hospital, Harvard Medical School, Boston, USA. More than 6000 copies have been distributed worldwide through book sales by WHO Press.

The seventh volume, Tumours of the Lung, Pleura, Thymus, and Heart, is currently being prepared. The volume editors are Dr William D. Travis, Memorial Sloan Kettering Cancer Center, New York, USA; Dr Elisabeth Brambilla, Centre Hospitalier Universitaire de Grenoble, Grenoble, France; Dr Allen Burke, University of Maryland, Baltimore, USA; Dr Alexander Marx, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany; and Dr Andrew Nicholson, Royal Brompton Hospital, London, United Kingdom. The consensus and editorial meeting was held at IARC on 24–26 April 2014, and the book is scheduled to be published in the spring of 2015.

The eighth volume of the fourth edition, Tumours of the Urinary System and Male Genital Organs, is in preparation. The volume editors are Dr Holger Moch, University Hospital Zurich, Zurich, Switzerland; Dr Peter Humphrey, Yale University School of Medicine, New Haven, USA; Dr Thomas Ulbright, IU Health Pathology Laboratory, Indianapolis, USA; and Dr Victor Reuter, Memorial Sloan Kettering Cancer Center, New York, USA. The consensus and editorial meeting will be held in March 2015, and the book is scheduled to be published in the spring of 2016.

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Section of Infections (INF)

The Section of Infections (INF) includes the Infections and Cancer Biology Group (ICB) and the Infections and Cancer Epidemiology Group (ICE). The research of both Groups is focused on the role of infectious agents in human carcinogenesis, including: (i) range of tumours associated with infection, and strength of the association; (ii) monitoring of human papillomavirus (HPV) vaccination and cervical screening in selected countries; (iii) biological properties of different viruses in in vivo and in vitro experimental models; (iv) biological significance of viral variants; (v) role of innate and acquired immunity; and (vi) diagnostic assays for human viruses and bacteria to be used in epidemiological studies. Agents studied are mucosal and cutaneous HPV types; HIV, in combination with other cancer-associated viruses; *Helicobacter* species; hepatitis B and C virus; Epstein–Barr virus (EBV); and Merkel cell polyomavirus. Some topics are exclusive to ICB (e.g. biological properties of different viruses) or ICE (e.g. worldwide distribution trends); many research programmes are collaborations between the two Groups. In 2014, INF personnel published 60 articles.

Infections and Cancer Biology Group (ICB)

ICB's research is focused on establishing a causal role of specific infectious agents in human cancer. Two complementary strategies are currently followed: (i) characterization of biological properties of both well-established and potential oncogenic viruses; and (ii) development and validation of laboratory assays for the detection of infections in human specimens, which can be used in epidemiological studies. ICB's functional studies have been focused on characterizing the impact of viral proteins on key cellular events in carcinogenesis, such as regulation and inactivation of tumour suppressors and evasion of immune surveillance. ICB has established laboratory diagnostic assays for more than 100 infectious agents, which have been used in many collaborative epidemiological studies to evaluate the role of HPV types and other infectious agents in different types of cancers.

Biological studies

In 2014, ICB completed three collaborative studies on HPV16 and EBV (Leitz et al., 2014; Siouda et al., 2014; Bazot et al., 2014). In particular, an EBV mechanism of downregulation of the expression of the tumour suppressor DOK1 was recently dissected. EBV downregulates DOK1 expression in primary human B cells in two steps. The first step is mediated by LMP1, which induces recruitment of two independent inhibitory complexes to the DOK1 promoter, one complex containing E2F1/pRB/DNMT1 and another containing at least EZH2. These events result in trimethylation of histone H3 at lysine 27 (H3K27me3) of the DOK1 promoter and gene expression silencing. In the second step, an additional EBV protein or proteins, as yet unidentified, lead to further repression of DOK1 expression by inducing hypermethylation of the DOK1 promoter (Siouda et al., 2014).

Epidemiological studies

Another activity of ICB is to perform epidemiological studies in collaboration with colleagues at IARC and external researchers, aiming to establish novel associations between infectious agents and cancer, for example between HPV and non-melanoma skin cancer (NMSC). Ultraviolet irradiation is a key risk factor for NMSC. However, the fact that immunosuppressed patients, such as organ transplant recipients, have an increased risk of NMSC development suggests the involvement of an infectious agent in skin carcinogenesis. Biological and epidemiological data indicate that cutaneous β HPV types are the most likely infectious agents involved in this pathological condition. A clinic-based case–control study was conducted to investigate the association between β HPV DNA in eyebrow hairs and skin squamous cell carcinoma (SCC). Eyebrow hairs from 168 SCC cases and 290 controls were genotyped for β HPV DNA. Eyebrow hair DNA prevalence was greater in cases (87%) than in controls (73%) ($P < 0.05$), and the

association with SCC increased with the number of HPV types present (≥ 4 types vs HPV-negative: odds ratio [OR], 2.02; 95% confidence interval [CI], 1.07–3.80; P_{trend} = 0.02). Type-specific associations were observed between SCC and DNA in eyebrow hairs for HPV23 (OR, 1.90; 95% CI, 1.10–3.30) and HPV38 (OR, 1.84; 95% CI, 1.04–3.24). SCC cases were more likely than controls to have eyebrow hairs that were HPV DNA-positive for single and multiple β HPV types, providing additional support for the potential role of these types in SCC development (Iannacone et al., 2014). Several other studies also suggest that β HPV infection may play a role at early stages of carcinogenesis (reviewed in Tommasino, 2014). To further evaluate this hypothesis, screening for β HPV DNA was performed in primary SCCs and their corresponding lymph node metastases in a series of patients. No primary cutaneous SCC or lymphatic metastases were found to share the same HPV DNA. These data support the fact that β HPV types do not play an etiopathogenic role in advanced stages of squamous cell carcinogenesis (Toll et al., 2014).

Infections and Cancer Epidemiology Group (ICE)

ICE's primary goals are to elucidate the contribution of infectious agents, notably HPV and HIV, to cancer etiology and to identify the most sustainable preventive strategies against infection-associated malignancies.

HPV and cervical cancer prevention

Promoting HPV vaccination and cervical screening programmes for the prevention of cervical cancer was an ICE priority in 2014. ICE concentrated on a multiyear project initiated in Bhutan in 2012 and in Rwanda in 2013. The aim is to demonstrate the early impact of vaccination against HPV in two low-resource countries that pioneered the implementation of this intervention. The first data on the prevalence of, and risk factors for, HPV infection in Bhutan have been published (Tshomo et al., 2014), setting a baseline with which to robustly assess the future effectiveness of the HPV vaccination programme. In addition, an estimate of cervical screening coverage in Bhutan has been completed (Baussano et al., 2014c). To anticipate the evaluation of the impact of HPV vaccination among adolescent girls, a novel type of HPV survey has been conducted, based on the collection of urine samples in female students aged 18–19 years in the two countries.

HPV and cancer of the head and neck

The contribution of HPV infection to cancer of the head and neck is still ill-defined and varies substantially by cancer site and world region, depending mainly on the competing importance of tobacco smoking or chewing (Combes and Franceschi, 2014). ICE also reviewed the prevalence of HPV in oropharyngeal cancer by sex and found that it was higher in men than in women in North America and Australia, but that the opposite was true in Asia and in some European countries, like France. The male-to-female ratio of HPV prevalence was negatively correlated with the male-to-female ratio of cumulative lung cancer risk (a proxy of smoking) (Combes et al., 2014). SPLIT (Study of HPV and Precancerous Lesions in the Tonsil) is a multicentre study conducted in France and coordinated by ICE that aims to fill the gap in understanding the prevalence and features of precancerous lesions in cancer-free tonsils according to the presence of HPV markers and smoking. The RACKAm study in France (hospital-based case–control study) and in Sweden (record linkage) was initiated in 2014 and should help to answer the question of the influence of tonsillectomy, mainly in childhood, on the risk of oropharyngeal cancer.

Fraction of cancer attributable to infection worldwide

ICE estimated that 2.2 million cancer cases (17.1% of the global burden) were attributable to infectious agents worldwide. Of these, approximately 610 000 were attributable to HPV (attributable fraction [AF], 4.8%), with 570 000 new cancer cases diagnosed among women (AF, 9.4%) and 39 000 cases among men (AF, 0.6%) (Giuliano et al., 2014). The AF of HPV in

women ranged from 2.5% in North America and Australia to approximately 25% in sub-Saharan Africa and India. ICE also continued updating AF estimates and made progress on new infection candidates, for example *Helicobacter* species other than *Helicobacter pylori*. An ICE meta-analysis showed that, using the improved immunoblot-based data, the worldwide AF for *H. pylori* in gastric cancer increased from 74.7% to 89.0%. This implies approximately 120 000 additional cases attributable to the infection, for a total of about 780 000 cases (6.2% instead of 5.2% of all cancers worldwide) (Plummer et al., 2014).

HIV/AIDS

Cancer risk in people with HIV/AIDS is a very important subject to ICE now that combined antiretroviral therapy (cART) has improved their survival and the cancer burden is set to increase as they age. ICE demonstrated that in Italy the gap in all-cancer survival between people with an AIDS diagnosis and the general population decreased from 5-fold in the pre-ART period to 3-fold thereafter (Maso et al., 2014).

Women living with HIV (WHIV) are at increased risk for HPV infection and HPV-related diseases, including severe cervical intraepithelial neoplasia of grades 2 and 3 (CIN2/3) and invasive cervical cancer. The impact of cART on CIN2/3 or invasive cervical cancer is still unclear. A cross-sectional study on HPV was nested within a cohort of 498 WHIV who underwent cervical screening in Nairobi, Kenya. HPV prevalence was evaluated in cervical exfoliated cells and biopsies. At 6 months after cryotherapy, CIN2/3 had been eliminated in 77% of women (De Vuyst et al., 2014). The performance of methylation markers in the triage of high-risk HPV-positive women was compared with that of Pap smear or visual inspection with acetic acid (VIA) for the first time in WHIV.

Innovative statistical methods for epidemiology

Statistical models in cancer research need to deal with sources of complexity such as repeated measurements, interval censoring, and hierarchical structure. In ICE, the most challenging problems of statistical analyses of infection-associated cancers are addressed using Bayesian hierarchical models (Plummer, 2014). To support this activity, ICE has also developed the statistical software package JAGS (http://mcmc-jags.sourceforge.net).

Modelling applied to HPV and cancer

The use of infection transmission models has entered the field of infection-related cancer epidemiology. In combination with models of carcinogenesis and empirical data, infection transmission models are useful to understand the patterns of transmission and progression of carcinogenic infections (Baussano et al., 2014b). In 2014, ICE developed an age-structured dynamic model of HPV transmission, validated it through between-country comparison, and used it to estimate the parameters that regulate the natural history of the most common HPV types (Baussano et al., 2014a; Baussano et al., 2014b; Franceschi and Baussano, 2014). Different strategies of HPV vaccination, i.e. the inclusion of girls of different ages and boys, were also compared (Baussano et al., 2014b).

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Section of Environment and Radiation (ENV)

The overall objectives of the Section of Environment and Radiation (ENV) are to investigate environmental, lifestyle, occupational, and radiation-related causes of cancer in human populations. ENV investigates these exogenous factors with the aims of contributing to primary prevention of cancer, increasing the understanding of biological mechanisms of carcinogenesis, and assessing the impact of environmental factors in the prognosis and course of disease and how best to implement prevention. These objectives are achieved through collaborative international epidemiological studies using a multidisciplinary approach, or through the initiation of individual analytical epidemiological studies. ENV also coordinates international consortia of epidemiological studies.

With studies related to environmental, lifestyle, occupational, or radiation-related exposures, the scope of the Section is broad. The main areas of environmental, occupational, and lifestyle-related research include pesticides and cancer (in particular, testicular cancer, breast cancer, and haematological malignancies), occupational carcinogens and lung cancer, asbestos and cancer, lifestyle-related and environmental risk factors for oesophageal cancer, lifestyle-related occurrence and survival of breast cancer in Africa, and risk factors for childhood leukaemia. Related to exposure to ionizing radiation, ENV has projects to study the effects of protracted low doses of external ionizing radiation from medical diagnostic examinations and from occupational activities, and studies of populations exposed to Chernobyl fallout and to radiation contamination in the Southern Urals and in the territories adjacent to the former Semipalatinsk nuclear weapons test site in Kazakhstan. With regard to non-ionizing radiation, research continues on possible cancer risks related to mobile phone use. In this regard, in 2014 ENV started to prepare for the launch of the French subcohort of a large European prospective cohort study (Cosmos) of mobile phone users.

Some key findings published during the past year are highlighted below.

Occupational carcinogens and lung cancer risk

The SYNERGY consortium pools data from 16 case–control studies on lung cancer from Europe and Canada with information on occupational history and lifetime smoking history, comprising almost 20 000 cases and more than 23 000 controls. Occupations previously suspected to be related to an increased lung cancer risk are being investigated. There were 473 cases and 501 controls who had ever worked in a baking-related job. No increased risk was observed for men working in baking. No linear trends were observed for duration of employment. Some results suggested increased lung cancer risk for women – for example, for working as a baker for more than 30 years and in never-smokers – but after exclusion of one study these increased risks disappeared. Overall, the findings of this study do not suggest increased lung cancer risk in baking-related professions (Behrens et al., 2013). There were 568 cases and 427 controls who had ever worked as welders, and the odds ratio of developing lung cancer was 1.44 (95% confidence interval [CI], 1.25–1.67), with the odds ratio increasing for longer duration of welding. In never-smokers and light smokers, the odds ratio was 1.96 (95% CI, 1.37–2.79). Overall, the findings of this study lend further support to the hypothesis that welding is associated with an increased risk of lung cancer (Kendzia et al., 2013). There were 695 cases and 469 controls who had ever worked as bricklayers (odds ratio, 1.47; 95% CI, 1.28–1.68). This study provided robust evidence of increased lung cancer risk in bricklayers. Although non-causal explanations cannot be completely ruled out, the association is plausible in view of the potential for exposure to several carcinogens, notably crystalline silica and, to a lesser extent, asbestos (Consonni et al., 2014). In a study based on the SYNERGY consortium and related to occupational risks, findings from this large international case–control consortium indicate that

after accounting for co-occurring respiratory diseases, chronic bronchitis and emphysema have a positive association with lung cancer (Denholm et al., 2014).

Breast cancer in sub-Saharan Africa

The African Breast Cancer-Disparities in Outcomes (ABC-DO) study is a within-Africa, multi-country study of factors that affect breast cancer outcomes for patients at public hospitals across different sub-Saharan African settings. In four public hospital settings in Namibia, Nigeria, South Africa, and Uganda, ABC-DO will examine the full journey of breast cancer patients, from pre-diagnosis right through the post-diagnosis treatment period for up to 3 years. ABC-DO will study both immediate biological factors (prognostic factors, tumour biology, and treatment received) and distal factors that represent barriers to early presentation and diagnosis and to receipt of timely and appropriate treatment. Independently using cancer registry data from some of those countries has already shown intriguing findings on breast cancer occurrence and presentation. In 1218 consecutive women (91% black) diagnosed with invasive breast cancer during 2006–2012 at a public hospital in Soweto, South Africa, it was seen that although a greater proportion of black patients than non-black patients had estrogen receptor (ER)-negative or triple-negative breast cancer, in all racial groups breast cancer was predominantly ER-positive and was being diagnosed at earlier stages over time. These observations provide initial indications that late-stage aggressive breast cancers may not be an inherent feature of the breast cancer burden across Africa (McCormack et al., 2013). In data of 12 361 women with histologically confirmed breast cancer diagnosed during 2009–2011 from South Africa's national cancer registry and diagnosed during 2011–2013 from Namibia's only cancer hospital, ER-positive breast cancer dominated in all Southern African races, but black women had a modest excess of aggressive subtypes. Based on the predominant receptor-defined breast cancers in Southern African, improving survival for the growing breast cancer burden should be achievable through earlier diagnosis and appropriate treatment (Dickens et al., 2014a). Living far from health services is known to delay presentation. In a peri-urban South African setting, the effect of distance from a patient's residence to the diagnostic hospital on stage at diagnosis was examined in 1071 public-sector breast cancer patients diagnosed during 2006–2012. Risk of late stage at diagnosis was 1.25-fold higher (95% CI, 1.09–1.42) per 30 km. Effects were pronounced in an underrepresented group of patients older than 70 years. Studies of women and the societal and health care-level influences on these delays and on the distribution of late stage at diagnosis are needed to inform interventions to improve diagnostic stage and breast cancer survival in this and similar settings (Dickens et al., 2014b).

Cancer burden related to exposure to asbestos

Fieldwork has begun on a retrospective cohort study of employees of one of the world's largest chrysotile mines and mills, situated in Asbest in the Russian Federation. The primary aim of the study is to better characterize and quantify the risk of cancer mortality in terms of: the dose–response relationship of exposure with risk; the range of cancer sites affected, including female-specific cancers; and the effects of duration of exposure and latency periods. This information will expand the understanding of the scale of the impending cancer burden due to chrysotile, including if use of chrysotile were to cease worldwide forthwith (Schüz et al., 2013). Exposure to asbestos remains a health concern. As mesothelioma occurs 30 years or more after asbestos exposure, contemporary rates likely reflect exposures in the 1960s and 1970s. During that period, the political division between western Germany and eastern Germany led to differences in the importation and consumption of asbestos. Therefore, regional, temporal, and sex variations in mesothelioma mortality rates in Germany in 2000–2010 were examined. Rates were higher in western Germany than in eastern Germany. In both regions, mortality rates increased for birth cohorts until the mid-1940s and subsequently declined. Germany's peak mesothelioma burden is predicted to occur by 2020 (Schonfeld et al., 2014).

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. Children are generally more sensitive to the carcinogenic effects of ionizing radiation than are adults. In addition, they may receive even higher radiation doses from a CT procedure than adults. Direct estimation of the health impact of CT radiation remains imprecise, and further large-scale epidemiological studies with more accurate dosimetry and assessment of potential biases and uncertainties are needed. For EPI-CT, a cohort study of more than 1 million children who underwent CT examinations in Europe, accurate estimates of organ-specific doses are essential. A new strategy of individual dose estimation involving CT scanner- and patient-specific data extracted from the archived system of the radiology departments is being developed, while properly accounting for uncertainty in dose estimates (Thierry-Chef et al., 2013).

Promotion of further studies on cancer risks related to nuclear accidents

IARC previously led a European Union-funded project, Agenda for Research on Chernobyl Health (ARCH), the objective of which was to recommend a strategic health research agenda (SRA) after the Chernobyl accident. Further steps leading to the implementation of the ARCH SRA are needed. The new initiative CO-CHER was started in 2014 in order to take the research agenda forward. It emphasizes the need to build partnerships with the three main countries affected by the accident, as well as Japan, the USA, and European countries. The CO-CHER project has the potential to create a coordination mechanism to ensure sustainable research into the health effects of the Chernobyl accident, to improve our understanding of radiation effects and to direct future radiation protection measures, as well as to aid health planning for those exposed after the Chernobyl accident, and after future nuclear accidents.

In late 2013, together with Fukushima Medical University, ENV organized a workshop in Fukushima to discuss with colleagues from Japan what steps are necessary to investigate long-term cancer effects related to the Fukushima Daiichi nuclear accident. In particular, it was pointed out that a population-based cancer registry in the prefecture was needed for surveillance, and that procedures need to be implemented so that data from the various studies in progress, such as the health survey or the thyroid screening, can later be linked to follow the participants.

Risk factors and survival of childhood cancer

Maternal occupational pesticide exposure during pregnancy and/or paternal occupational pesticide exposure around the time of conception have been suggested to increase risk of leukaemia in the offspring. Data from 13 case–control studies participating in the Childhood Leukaemia International Consortium (CLIC), with more than 8000 cases and more than 14 000 controls, were pooled, showing an increased risk of acute myeloid leukaemia (AML) in the offspring with maternal exposure to pesticides and a slightly increased risk of acute lymphoblastic leukaemia (ALL) with paternal exposure around conception (Bailey et al., 2014a). For parental occupational exposure to paints, using the same CLIC database, null findings for paternal exposure for both ALL and AML are consistent with previous reports. Further data on home exposure are needed (Bailey et al., 2014b). Parental exposures to pesticides and other chemicals are also suspected to be related to an increased risk of testicular cancer in the offspring. Current evidence from a literature review is inconsistent. The limitations of the studies may partly explain the inconsistencies observed (Béranger et al., 2013). This should be seen in the light of an increasing incidence of testicular cancer. Despite substantial heterogeneity in the rates, most European countries will have an increasing burden over the next two decades. Estimates predict 23 000 new cases of testicular cancer annually in Europe by 2025, a rise of 24% from 2005 (Le Cornet et al., 2014). Social, family, and environmental factors may also influence survival of childhood cancer. However, socioeconomic determinants did not affect ALL

survival in children in western Germany, in a study of more than 600 cases diagnosed during 1992–1994. The observation of no social inequalities in paediatric ALL survival is reassuring, but continued monitoring is needed to assess the potential impact of evolving treatment options and changes in paediatric health service (Erdmann et al., 2014).

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Section of Nutrition and Metabolism (NME)

Diet, nutrition, metabolic and hormonal imbalances, excess energy consumption, obesity, and physical inactivity are thought to be important contributors to increasing cancer incidence rates worldwide. However, the mechanisms of action of these factors remain poorly understood. In addition, the contributing influence of dietary transitions from traditional diets to those typical of industrialized countries, which is taking place in low- and middle-income countries (LMICs) (e.g. in Latin America), and exposures in fetal life and early infancy have not been 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 (including dietary patterns), nutrition, physical activity, and energy imbalance with cancer risk in high-income countries and LMICs using cohort and case–control designs or human intervention studies. The emphasis is on improving the assessment of dietary exposures, applying biomarkers and metabolomics to study biochemical changes, and considering gene–environment interactions. The translation of findings into public health recommendations for cancer prevention is of major importance to NME. The Section is composed of three Groups: the Biomarkers Group (BMA), the Dietary Exposure Assessment Group (DEX), and the Nutritional Epidemiology Group (NEP).

Biomarkers Group (BMA)

The main goal of BMA is to improve the understanding of the role of environmental and lifestyle factors in carcinogenesis through the application of biomarkers of exposure in population-based studies. Advanced analytical methodologies (mass spectrometry, gas chromatography, immunoassays) and metabolomic approaches are developed to measure the exposome and its fractions in epidemiological and/or intervention studies set up in high-income countries and LMICs. These methods are used to discover novel biomarkers of exposure to dietary, environmental, and metabolic factors, to identify novel risk factors for cancers, and to elucidate mechanisms linking exposures to cancer risk.

Exposome-wide association studies on cancer risk

A workflow for the acquisition of untargeted metabolomic data by high-resolution mass spectrometry and for data processing has been fully validated and applied to the analysis of the exposome in batches of up to 600 plasma or urine samples (Edmands et al., 2014a). Software in the R language has been developed to correct signal drift in large analytical batches and to identify unknown signals of interest based on their mass fragmentation spectra (Edmands et al., 2014b). This workflow is being deployed to explore liver cancer etiology and to identify pre-diagnostic biomarker profiles for early diagnosis using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (collaboration with NEP). The workflow is also geared towards the discovery of biomarkers of environmental pollution (EXPOsOMICS EU project) and the identification of biomarkers of food intake (collaboration with DEX; NutriTech EU project) (Scalbert et al., 2014). More than 80 biomarkers of intake for six polyphenol-rich foods could be identified in urine samples from the EPIC calibration study. In addition, detailed data on more than 400 biomarkers of exposure to dietary and other environmental factors have been collected from the scientific literature and curated in the new web-based Exposome-Explorer database. These data will be used to select panels of biomarkers for future exposome-wide association studies.

Targeted metabolomic approaches have been implemented in several epidemiological studies to evaluate the reliability of metabolic profiles over time and to study the influence of different diets on metabolic phenotypes (collaboration with the University of Oxford, United Kingdom). Similar targeted metabolic analyses are being applied to a case–control study nested in EPIC to evaluate the association of metabolic profiles with liver cancer (collaboration with NEP).

Preliminary findings point towards a positive association of liver cancer risk with blood levels of aromatic amino acids, glutamate, and citrate, and an inverse association with sphingomyelin, lysophosphatidylcholine, branched chain amino acids, glutamine, choline, and polyunsaturated fatty acid.

Hormones and cancer risk

Novel methods for the measurements of steroids (liquid chromatography-mass spectrometry [LC-MS], highly sensitive enzyme-linked immunosorbent assays [ELISAs]) and inflammatory factors (multilabel plate readers) have been tested to improve the validity of measurements and reduce the sample volume needed for the analyses. A study within the EPIC cohort was carried out to explore the association between reproductive and menstrual factors and the risk of differentiated thyroid carcinoma in women (collaboration with ICE); the results did not support a strong role of these factors in the disease (Zamora-Ros et al., 2014a). Several cross-sectional studies have also been carried out in a subsample of the large Mexican ESMaestras cohort (600 premenopausal women) to study the association between circulating levels of C-peptide, leptin, and adiponectin and mammographic density (collaboration with NEP). Statistical analyses are in progress.

Polyphenols and cancer risk

The lack of convincing epidemiological evidence on the role of polyphenols in the prevention of cancers appears to be explained by difficulties in measuring exposures to this highly complex family of dietary constituents (Zamora-Ros et al., 2014b). A new food composition table for the 502 known polyphenols was constructed for the EPIC and EsMaestras cohorts (collaboration with DEX and NEP). Data on polyphenol losses during food processing and cooking were collected from the scientific literature (Rothwell et al., 2013) and integrated into the food composition tables. A mass spectrometry-based method to measure 40 major polyphenols in urine has been developed and is now being used in the EPIC cross-sectional study to validate the new food composition table.

Fatty acids and cancer risk

Measurements of plasma phospholipid fatty acids, as validated biomarkers of dietary intake and metabolism, have been implemented in a large case–control study on breast cancer nested within EPIC, in a case–control study on breast cancer within the Mexican CAMA study, and in a pilot study carried out by the Catalan Institute of Oncology, Spain, on the effect of a diet and physical activity intervention in breast cancer patients on fatty acid metabolism and weight loss. Statistical analyses are in progress within NEP.

Dietary Exposure Assessment Group (DEX)

The overall goal of DEX is to improve the accuracy, understanding, and interpretation of dietary exposure (and changes thereof) in studies of diet and cancer and other intermediate diseases. DEX has a leading role in developing, validating, and implementing standardized dietary assessment methodologies, particularly in international nutrition surveillance and epidemiological study settings.

Global nutrition surveillance implementation

An IARC-WHO Global Nutrition Surveillance initiative has been launched to collect standardized dietary data worldwide (in 25 countries) using the DEX methodologies, to support dietary surveillance, research, and prevention of cancer and other noncommunicable diseases worldwide. Building on its successful implementation in Europe and strong international networks, this initiative aims to pilot its expansion in two to four countries in the other WHO regions worldwide.

The creation of a European GloboDiet consortium, including seven countries (Austria, Belgium, France, Germany, Malta, the Netherlands, and Switzerland), has been initiated as the European branch of this Global Nutrition Surveillance initiative. The main aim of this consortium is to create the legal and managerial framework to use, provide, and analyse the first comparable food consumption data available worldwide, as the proof of principle of the Global Nutrition Surveillance initiative.

Piloting is in progress in Latin America (in Brazil and Mexico) and Asia (in the Republic of Korea). In Africa, an in-depth inventory of the methodological and logistic situation (ASPADAM project, in 22 countries) was performed as a prerequisite to producing a road map for the African-GloboDiet surveillance branch.

Development of international dietary methodologies and (web) infrastructures

Through different EU projects (EuroDISH, PANCAKE, JPI-DEDIPAC, BBMRI-LPC), DEX is pursuing the development and implementation of a comprehensive e-research infrastructure to support the dissemination, maintenance, data access, sharing, and (pooled) analyses of the GloboDiet data across participating countries. A strong information technology network involving academics, centres of excellence, and key stakeholders supports the development and implementation of the research infrastructure and its integration with other complementary research infrastructures such as the EuroFIR eSearch facility, a federated European food concentration database network. In addition, e-training facilities have been successfully pilot-tested as an alternative to traditional face-to-face trainings. These e-trainings were applied under real study conditions in several European countries and LMICs and are complemented by the development, testing, and implementation of new standard operating procedures (SOPs).

To address specific methodological requirements to collect dietary information from children, a GloboDiet data entry version using food diaries, but still compatible with the 24-Hour Dietary Recall GloboDiet software, was developed. This GloboDiet data entry version has been successfully pilot-tested in Belgium and the Czech Republic (Freisling et al., 2014; Ocké et al., 2014).

To develop new nutritional research areas, the DEX standardized European Nutrient Database (ENDB) has been enriched with several new nutrients and/or biological components (folates, polyphenols, plant sterols, methyl group donors, and vitamin K), following SOPs (Nicolas et al., 2014).

DEX also contributed to advanced methodological publications, including book chapters and editorials (Slimani et al., 2014; Illner et al., 2014; Freisling et al., 2013b; Huybrechts et al., 2013; Huybrechts et al., 2014).

Targeted research to better measure and understand dietary exposure (and changes thereof) and its associations with cancer and other intermediate diseases, including obesity

DEX is also involved in projects studying the role of diet and nutritional biomarkers in relation to cancer (the EPIC project) and other chronic diseases, such as obesity and diabetes (the EPIC-PANACEA, INTERACT projects). New holistic measures of dietary exposures through more diet-biomarker integrated and multivariate approaches, specifically nutrient patterns by means of principal component analysis (Moskal et al., 2014) and the treelet transform – an alternative method to derive dietary patterns that produces sparse factors in combination with a cluster tree to visualize related groups of foods/nutrients – have been implemented and related to colorectal cancer, breast cancer, and weight change. Descriptive analyses on acrylamide dietary exposure in EPIC showed that dietary acrylamide intake differed by 3-fold between European

regions, with a clear geographical gradient (Freisling et al., 2013a). Furthermore, a comparison between dietary intake estimates and haemoglobin adduct levels of acrylamide revealed correlation values consistently lower than 0.20 (Ferrari et al., 2013b). Cadmium exposure in Europe was evaluated using probabilistic and deterministic models, where probabilistic estimates were almost consistently larger than deterministic counterparts and should thus be preferably applied (Ferrari et al., 2013a). Furthermore, targeted projects have been initiated on potential health impacts of the consumption of highly processed foods, and on health risks of vulnerable population groups, such as obese people (where obesity was associated with a slightly higher bladder cancer risk in men but not in women; Roswall et al., 2014), children and adolescents, the elderly (where more than 40 factors from different domains such as lifestyle, health, and environment were reviewed and related to diet quality in old age; Freisling et al., 2013b), and people of low socioeconomic status. This work is being performed in collaboration with other researchers in NME.

Nutritional Epidemiology Group (NEP)

The overall objective of NEP, in close interaction with DEX and BMA, is to determine the role of diet, nutrition (under- or over-nutrition), hormonal factors, physical activity, and energy balance on cancer risk and development, particularly considering biomarkers of dietary exposure, metabolic factors, epigenetics, and gene–diet/nutrient/environment interactions.

Studies in high-income countries

NEP has strong coordination and scientific roles in EPIC, with a focus on cancers of the breast, colorectum, and liver. NEP reviewed the association between nutrition and breast cancer (Chajès and Romieu, 2014) and reported inverse associations with breast cancer risk for higher dietary fibre intake (Ferrari et al., 2013c), dietary folate intake (among higher alcohol consumers), and a healthy lifestyle (McKenzie et al., 2014). In addition, NEP is conducting a large epigenetic project to evaluate the role of B vitamins and lifestyle factors on methylation patterns and associations with breast cancer risk in a nested cancer control approach. Analyses of the interaction of circulating fatty acids and antioxidant vitamins with breast cancer risk are under way in EPIC, as observed in the SUVIMAX cohort (Pouchieu et al., 2014), as well as exploration of diet–epigenetic interactions. For colorectal cancer, our findings showed that serum levels of high-density lipoprotein cholesterol, non-high-molecular-weight adiponectin, and soluble leptin receptor had the greatest impact on the observed association with adiposity (Aleksandrova et al., 2014b) and that biomarker patterns associated with metabolic syndrome, inflammation, and oxidative stress each represent important pathways towards development of these tumours (Aleksandrova et al., 2014c). Other observations were inverse associations with selenium and its carrier protein (Hughes et al., 2014) and higher dairy intake (Murphy et al., 2013), a positive association with adult weight gain (Aleksandrova et al., 2013), poorer colorectal cancer survival with higher pre-diagnostic weight (Fedirko et al., 2014b), and an inverse association between long-chain omega-3 polyunsaturated fatty acids and risk of advanced colorectal adenomas (Cottet et al., 2013). For liver cancers, inverse associations were observed with circulating vitamin D (Fedirko et al., 2014a) and higher coffee intake (Bamia et al., 2014), and positive associations with increased inflammation (Aleksandrova et al., 2014a), higher sex hormone-binding globulin (Lukanova et al., 2014), and higher dairy intake (Duarte-Salles et al., 2014). In other work, higher circulating markers of industrial trans-fatty acids showed increased risk of weight gain during a 5-year follow-up. NEP led the review of recommendations for the fourth edition of the European Code Against Cancer regarding diet, obesity, physical activity, alcohol consumption, and breastfeeding.

Studies in low- and middle-income countries

NEP collaborates with the EsMaestras cohort study of teachers in 12 Mexican states, with the goal of assessing the determinants of major female cancers in a population undergoing

nutritional transitions. To date, predictors of mammographic density have been evaluated (Rice et al., 2013a; Rice et al., 2013b; Rinaldi et al., 2014). NEP also collaborates on CAMA, a breast cancer case–control study in Mexico, and has evaluated the role of several dietary factors, anthropometry, and hormone use (Amadou et al., 2013; Amadou et al., 2014; Chajès et al., 2012; Fedirko et al., 2012).

NEP also conducts the PRECAMA multicentre population-based case–control study (in Chile, Colombia, Costa Rica, and Mexico; collaboration with the Fred Hutchinson Cancer Research Center and the MCA Section) to determine major predictors of breast cancer phenotypes among premenopausal women. A similar project is being conducted in the Soweto population in Johannesburg, South Africa (South Africa Breast Cancer [SABC] study; collaboration with the University of the Witwatersrand and the ENV Section). Recruitment of cases and controls is in progress for both.

To track the changing nutritional environment and determine the impact on obesity, the trend of serum fatty acids concentrations over 20 years is being studied in an ongoing cohort in Uganda.

Alcohol and cancer

NEP recently reviewed the role of alcohol in breast cancer (Scoccianti et al., 2014), colorectal cancer (Ferrari et al., 2012), and total/cause-specific mortality (Bergmann et al., 2013). A competing risks framework was also applied (Ferrari et al., 2014).

Determinants of cancer in elderly populations

NEP is investigating the association of various exposures with cancer risks in elderly populations within the CHANCES project, which has brought together and harmonized detailed data from 14 European and international prospective cohort studies, making it one of the largest resources to study the impact of lifestyle and social factors on disease development and multimorbidity in the elderly.

Nutritional metabolomics

NEP published a method to investigate sources of variability in metabolomic data, an important contribution to the field (Fages et al., 2014), and continues its projects of targeted and untargeted metabolomic profiling in liver cancers (in collaboration with BMA).

Early life and metabolic disorders

Using data from the POSGRAD Mexican birth cohort, NEP is evaluating the role of maternal and early nutritional exposures on epigenetic changes in cord blood cells (Lee et al., 2013; Lee et al., 2014), in collaboration with the National Institute of Public Health of Mexico (INSP) and Emory University (USA).

Intervention studies

NEP collaborates with an interventional randomized controlled trial conducted in French cancer centres. The intervention includes an experimental arm with a tailored physical activity programme associated with nutritional counselling during 27 weeks of adjuvant treatment and a control arm with standard care in French cancer treatment centres. The initial phase of this project will enrol 180 women per arm. NEP will evaluate the effect of the intervention on weight loss and fat distribution as well as fatty acid metabolism. Plasma phospholipid fatty acids extracted from blood samples obtained before and after intervention will be measured at IARC through validated gas chromatography methodology. Endogenously synthesized fatty acids will be quantified and levels will be compared before and after intervention.

Methodological work

NEP conducts methodological research on correction procedures for exposure measurement errors, use of multivariate statistics to analyse large data sets, and multilevel techniques for risk models. NEP also coordinates the EPIC Statistical Working Group, which promotes statistical expertise within the EPIC network. Collaborations are in place with statistical experts worldwide.

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Section of Genetics (GEN)

The Section of Genetics (GEN) comprises three Groups, with the overall mission of identifying genes involved in cancer, characterizing the spectrum of pathogenic sequence variants that they harbour, and understanding how they interact with non-genetic factors. These are the Genetic Epidemiology Group (GEP), the Genetic Cancer Susceptibility Group (GCS), and the Biostatistics Group (BST). GEP is mainly involved in the coordination of large population-based epidemiological studies and the analysis of multiple common genetic variants to identify new susceptibility loci. Cancers of primary interest include those of the lung and upper aerodigestive tract (including the nasopharynx) as well as kidney cancer. GCS hosts the Genetic Services Platform and uses a combination of bioinformatics and sequencing approaches to aid the identification of susceptibility variants or mutations. BST provides overall statistical and bioinformatics support to GEP and GCS. GEP is also responsible for two large cohorts that were developed by IARC, the Golestan (Islamic Republic of Iran) cohort of 50 000 individuals and the Russian Federation cohort of 150 000 individuals.

Genetic Epidemiology Group (GEP)

Recent developments indicate that the next few years will be a fundamental time in genetic epidemiology for identifying complex disease genes and assessing how these genes interact with environmental factors. Reasons for this include the availability of genome-wide scans and the increasing availability of large population-based studies. GEP continues to develop infrastructure for future studies while leading large genome-wide and sequencing studies. Notable developments and results from GEP in 2014 include the following.

Renal cancer sequencing and genome-wide analyses

Two large GEP projects aim at investigating the genetic and genomic features of renal cancer. The KIDRISK project, funded by the United States National Cancer Institute (NCI), has assembled germline genome-wide genotyping data on more than 10 000 cases and 15 000 controls. This represents the largest genome-wide association study (GWAS) of renal cancer to date, with results expected by the end of 2014 for disease risk and survival. Whole-genome expression data from tumour and non-tumour renal tissue from a subset of cases will complement the findings, either by inferring potential functional effects of certain polymorphisms or by increasing the statistical power to detect polymorphisms associated with renal cancer risk and survival. In parallel, the CAGEKID project, funded by the European Commission, has investigated the somatic (tumour) mutations occurring in renal cancer. While most previous efforts had been directed towards single-country projects and drug target discovery, CAGEKID has been pivotal in investigating somatic mutational signatures in four European countries (Scelo et al., 2014). Previous publications were based on whole-exome sequencing (i.e. known functional areas of the genome, representing approximately 1% of the total DNA), whereas GEP undertook whole-genome sequencing experiments, revealing a striking genomic pattern in tumours from Romania, thought to be related to exposure to aristolochic acid. GEP is now expanding this work to other geographical areas and investigating perhaps less common mutational patterns and their interaction with modifiable factors.

Renal cancer and metabolic markers of risk and survival

Concurrently with the projects on renal cancer genomics, GEP has made a concerted effort to evaluate the relationship between circulating fat- and water-soluble vitamins and renal cancer. The initial analysis (Johansson et al., 2014) on B vitamins involved in the one-carbon metabolism pathway was based on 550 kidney cancer cases and matched controls from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. This analysis clearly demonstrated that study participants with higher plasma concentrations of vitamin B6 had lower risk of subsequent kidney cancer diagnosis in a dose–response fashion ($P_{trend} = 4 \times 10^{-6}$); the

odds ratio when comparing the fourth and first quartiles (OR_{4vs1}) was 0.40 (95% confidence interval [CI], 0.28–0.57), a result that was independently replicated in the Melbourne Collaborative Cohort Study (MCCS; OR_{4vs1}, 0.47; 95% CI, 0.23–0.99). Another noteworthy finding was that vitamin B6 was also associated with improved renal cell carcinoma survival after diagnosis; the hazard ratio for all-cause mortality in renal cell carcinoma cases when comparing the fourth and first quartiles (HR_{4vs1}) of vitamin B6 was 0.57 in EPIC (95% CI, 0.37–0.87; $P_{trend} < 0.001$) and 0.56 in MCCS (95% CI, 0.27–1.17). Further analyses on newly diagnosed cases from the K2 case series showed that vitamin B6 stood out as an independent predictor of kidney cancer survival when measured at diagnosis, with 3-fold differences in survival rates between the fourth and first quartiles (HR, 0.33; 95% CI, 0.11–0.66) after accounting for disease stage. Together, these analyses strongly implicate an important role of vitamin B6 for renal cancer onset and outcome, and GEP is now initiating studies based on metabolomics and Mendelian randomization to further evaluate the importance of vitamin B6 in renal cancer etiology.

Genome-wide analyses for both lung and oral cancers

In collaboration with NCI, and as part of the TRICL (Transdisciplinary Research in Cancer of the Lung) consortium, the largest GWAS of lung cancer is being completed, involving more than 25 000 lung cancer cases and comparable controls. Initial results are expected by the end of 2014. As well as providing further evidence on novel genetic loci for lung cancer, this initiative should also help to highlight the role of non-genetic factors through focused Mendelian randomization analyses. GEP scientists have also organized a parallel large GWAS of oral and pharyngeal cancers including more than 7000 cases and comparable controls.

Large cohort infrastructure led by GEP

As one of the leading partners in the BBMRI-LPC (Biobanking and Biomolecular Resources Research Infrastructure – Large Prospective Cohorts) consortium, GEP organized the first scientific call providing access for European scientists to a network of population-based cohort studies. This call took place in April–July 2014, and an international scientific committee has been established to review the proposals.

As well as contributing to the coordination of the EPIC cohort, GEP is also responsible for two additional IARC cohorts, based in the Islamic Republic of Iran and the Russian Federation. The first major publication of the Russian Federation prospective cohort, based on more than 150 000 Russian adults, provided strong evidence for the important role of vodka in premature mortality in the Russian Federation (Zaridze et al., 2014).

Genetic Cancer Susceptibility Group (GCS)

GCS carries out work towards two goals within the Agency: (i) the study of how genetic variation, and particularly rare genetic variants, contributes to cancer susceptibility, and (ii) the development and maintenance of much of the Agency's genomics capacity (including the related bioinformatics). In the context of the second goal, GCS has continued the roll-out and optimization of next-generation sequencing at the Agency. Throughout 2014, an Ion Torrent Proton DNA Sequencer has been incorporated into the laboratory to replace the SOLiD5500 system and to complement the existing medium-throughput Ion Torrent Personal Genome Machine (PGM) Sequencer. GCS has installed semi-automated robotic workflows for library preparation, which allow up to 384 samples to be analysed in parallel on a Proton run. In addition, GCS has focused on methods that enable the detection of very rare mutations from very low starting amounts of DNA, such as those found in circulating cell-free DNA. In collaboration with Information Technology Services (ITS), GCS has tripled the computational and memory capacity of the Agency's high-performance computing cluster to ensure an appropriate infrastructure for the analysis of these large, complex genomic data sets. GCS has

also contributed to the development of the IARC Bioinformatics Steering Committee (BISC), tasked with the oversight of the Agency's bioinformatics activities and with providing advice to the Director about their future direction.

In terms of genetic research, with collaborators at the Institute of Cancer Research (United Kingdom), Dartmouth College (USA), and NCI (USA), GCS coordinated a very large imputation-based GWAS of lung cancer, totalling 11 348 lung cancer cases and 15 861 controls, followed by validation in an additional 10 246 cases and 38 295 controls. This study identified robust associations with two rare variants with particularly important risk effects (2.5-fold): one missense variant in the *CHEK2* gene (rs17879961, I157T), which validated our previous findings (Brennan et al., 2007), and a second variant in *BRCA2* (rs11571833, K3326X). Both findings were of note due to their unexpected nature; the *CHEK2* variant was inversely associated with lung cancer but associated with increased risks of other cancers, and susceptibility to lung cancer has not previously been linked to genetic variation in *BRCA2*. Such findings highlight the potential of agnostic genetic approaches to provide novel insights into cancer susceptibility and cancer etiology in general. This study also demonstrated that coordinated imputation protocols and very large studies can be used to identify additional genetic variants from pre-existing GWAS data (Wang et al., 2014). As part of an international effort that identified three likely pathogenic mutations in *RINT1* by exome sequencing in multiple-case breast cancer families, a case–control mutation-screening study of the *RINT1* gene was conducted in 1313 early-onset breast cancer cases and in 1123 frequency-matched controls, and it was concluded that very rare genetic variants in the *RINT1* gene predispose to breast cancer (Park et al., 2014).

In addition, GCS has coordinated a meta-analysis-based GWAS of Hodgkin lymphoma, which identified the genetic variants at 19p13.3, a locus containing *TCF3*, a gene critical to B-cell development. Bioinformatic analysis of this locus identified that the associated variants disrupted putative transcription binding sites within the promoter of *TCF3* and appear to influence expression of *TCF3*. The study also demonstrated an enrichment of expression quantitative trait loci (eQTLs) within variants associated with Hodgkin lymphoma, implying that many additional risk alleles are likely to exist (Cozen et al., 2014). Finally, GCS participated in other GWAS-related projects, for example a large GWAS of diffuse large B-cell lymphoma (Cerhan et al., 2014).

Biostatistics Group (BST)

BST focuses on statistical issues specific to the goals of GEN. In some cases these relate to application of standard statistical techniques, but some areas require more profound involvement and innovation.

One of these areas is the detection of mutational signatures in somatic DNA sequences. These may potentially indicate the action of specific toxins, or reveal a finer-than-anticipated range of cancer phenotypes. The most commonly used technique is non-negative matrix factorization (NMF); however, many choices remain unclear and there is no theoretical guarantee that the resulting decomposition into signatures is unique. Thus, there remain important opportunities to develop techniques in this area.

A second challenging area is the detection of circulating tumour DNA (ctDNA). Potentially this may provide early diagnosis of cancers that are difficult to detect by current techniques. However, concentrations of tumour DNA in plasma are typically less than 1% and are discarded as noise by standard sequence-reading algorithms. The challenge for BST, undertaken with bioinformaticians in GCS, is to develop methods of sufficient specificity to separate ctDNA from various sources of noise generated in the sequencing process.

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Section of Early Detection and Prevention (EDP)

Prevention and early detection interventions are effective ways of reducing cancer burden. The Section of Early Detection and Prevention (EDP) is composed of three Groups, the Prevention and Implementation Group (PRI), the Quality Assurance Group (QAS), and the Screening Group (SCR), which contribute to the evaluation of resource-appropriate interventions and quality assurance inputs for the control of breast, cervical, colorectal, and oral, and gastric cancer globally, with particular emphasis on less developed countries. To achieve this objective, EDP investigates innovative early detection and prevention approaches and addresses the development of quality assurance guidelines and the integration of the different prevention and early detection strategies as part of routine health services. There is a continuing emphasis on developing, updating, and expanding training resources to augment human resources for cancer prevention and early detection initiatives and on scaling up prevention and early detection services by contributing to the development of local health systems within the context of the research studies.

Prevention and Implementation Group (PRI)

PRI conducts studies to evaluate the efficacy, population impact, and feasibility of interventions for the prevention of cervical, anal, oral, and gastric cancer. In addition, PRI collaborates with public health institutions to implement and evaluate cancer prevention interventions.

Cervical cancer vaccine studies in Latin America

The Costa Rica Vaccine Trial is a clinical trial including approximately 7500 women of the efficacy and safety of the bivalent human papillomavirus (HPV) vaccine to prevent infections and lesions in different anatomical sites. During 2014, PRI published the final according-to-protocol efficacy results against cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) (90% against HPV 16/18; 60% against other types) (Hildesheim et al., 2014) and the first efficacy demonstration against vulvar HPV infections (54% against HPV 16/18, intention to treat) (Lang Kuhs et al., 2014a). Several studies evaluating the comparability of different HPV serological methods (Robbins et al., 2014a; Robbins et al., 2014b) and its impact on efficacy assessment (Lang Kuhs et al., 2014b) were published. In another clinical trial in Mexico including 2000 women (Lazcano-Ponce et al., 2014), the response to two doses of the bivalent vaccine in girls 9–10 years old was demonstrated to be non-inferior to the response to three doses in the same age group and among women aged 18–24 years. These results, together with other studies, led to the WHO recommendation of two doses for young girls.

Primary end-points for prophylactic HPV vaccine trials

In September 2013, PRI organized, in collaboration with the United States National Cancer Institute, a meeting of international experts to recommend end-points for future clinical trials of HPV vaccines. For most applications, the use of virological or immunological end-points was considered sufficient (www.iarc.fr/en/publications/pdfs-online/wrk/wrk7/).

Multicentre study of HPV screening and triage (ESTAMPA)

PRI is conducting a multicentre screening study in Latin America to evaluate the performance of visual, cytological, and molecular triage techniques for HPV-positive women. More than 50 000 women aged 30–64 years will be recruited at collaborating centres in Latin America. All HPV-positive women are being referred for colposcopy, biopsy, and final diagnosis, with follow-up at 18 months. Recruitment has begun in two sites in Colombia, one in Paraguay, and one in Honduras, and current recruitment is at more than 3500 women. Centres in Mexico, Costa Rica, and Uruguay will soon initiate recruitment. Another important objective is to evaluate implementation strategies for organized screening and to provide training and transfer of new technologies.

Epidemiology of *Helicobacter pylori* and its eradication for prevention of gastric cancer

The ENIGMA study investigates the prevalence of *H. pylori* and gastric cancer cofactors in high- and low-incidence areas for gastric cancer. Age-stratified random samples of subjects aged 1–69 years are being recruited with an interview and collection of blood, urine, and faecal specimens to investigate age-specific prevalence of *H. pylori* infection and environmental, host, and bacterial cofactors, in addition to predicting future rates of gastric cancer and assessing antibiotic resistance in each area. In collaboration with the University of Latvia, PRI has initiated the pilot phase of a clinical trial (the GISTAR study) to investigate the impact of *H. pylori* eradication on stomach cancer incidence and mortality among 30 000 subjects in several eastern European countries, including assessment of biomarkers of chronic atrophic gastritis (pepsinogens). The study arms are: (1) screening for *H. pylori*, pepsinogen testing, with gastroscopy referral of subjects with serological evidence of chronic gastritis and treatment of *H. pylori*-positive subjects, or (2) no intervention. Follow-up will be 15 years. Pilot work is under way in Latvia. PRI has also initiated a randomized clinical trial (HELPER) to evaluate the impact of *H. pylori* eradication on stomach cancer incidence within the National Cancer Screening Program of the Republic of Korea. Approximately 13 000 subjects aged 40–64 years will be tested for *H. pylori*, and *H. pylori*-positive subjects will be randomized to treatment or placebo, with passive follow-up through the screening programme (endoscopy every 2 years) for 10 years.

In December 2013, PRI organized a meeting of international experts to discuss the role of *Helicobacter pylori* eradication for prevention of gastric cancer. The group called for increased attention to the burden of the disease and its incorporation into cancer control programmes, including demonstration projects of *H. pylori* eradication with progress assessment of its feasibility, impact on gastric cancer, and potential adverse consequences (Herrero et al., 2014; www.iarc.fr/en/publications/pdfs-online/wrk/wrk8/).

Support of HPV vaccination and screening programmes in Latin America

Within the national screening programme of Argentina, a protocol to evaluate the acceptability and performance of self-collected specimens was recently completed, with excellent results. Extension of the screening programme to new areas is starting. The materials developed and the experience gained should be useful for other programmes in the region.

Quality Assurance Group (QAS)

Quality assurance aims to ensure that a given endeavour leads to its intended outcome. It is highly relevant to complex systems, such as screening and primary prevention programmes that are designed to lower the burden of cancer in the population. The activities of QAS aim to expand and effectively disseminate knowledge key to assuring the successful implementation of primary and secondary prevention programmes as a tool for comprehensive cancer control. The focus is on programmes and evidence-based interventions for large segments of the population in which the majority of currently preventable cancer cases and deaths occur. The efforts of QAS are particularly relevant to continuous improvement in comprehensive control of cancer. They cover not only primary and secondary prevention but also tertiary prevention, because the process of screening involves diagnosis, treatment, and also subsequent care of patients identified through screening.

The same principles of quality assurance and successful implementation of cancer prevention programmes apply in all cultural and resource settings. Through coordination of international networks, QAS promotes exchange of experience and collaboration in quality assurance and

successful implementation of programmes in Europe and, increasingly, in other regions of the world.

IARC Handbook of Cancer Prevention on breast cancer screening

QAS staff and visiting scientists have contributed to the development of Volume 15 of the IARC Handbooks of Cancer Prevention, on breast cancer screening, which will update Volume 7, published in 2002.

Guidelines for cancer screening

In 2014, the WHO Assistant Director-General for Noncommunicable Diseases and Mental Health completed work on a position paper on mammography screening. The primary objectives of the guidelines are: (i) to provide policy-makers, health-care managers, and health-care providers with clear, objective, and independent guidance on the balance between benefits and harms of mammography screening in women of different age groups; and (ii) to disseminate the recommendations based on this guidance among policy-makers, health-care providers, health-care managers, women, and the general public to promote informed decisions in this area. The QAS Group Head served on the Guideline Development Group that drafted the recommendations in the position paper.

The second edition of the European guidelines for quality assurance in cervical cancer screening was published by the European Union (EU) in 2008. Supplements to the second edition have been prepared in a project coordinated by QAS and co-financed by the EU Health Programme. These supplements deal with fields that the editors felt warranted an update (primary screening with HPV testing, organization of screening) or inclusion in the guidelines (implementation of HPV vaccination) before preparation of a third edition. The supplements will be published in 2014.

Collaboration with WHO in implementation of cancer screening guidelines

In 2014, QAS continued to collaborate with the WHO Regional Office for Europe, WHO Headquarters in Geneva (DG HQ/CPM Chronic Diseases Prevention and Management, and HQ/NMH/MND/CPM Noncommunicable Diseases and Mental Health), and the WHO Country Office in Belarus and the Ministry of Health of Belarus in planning feasibility and pilot studies and the initiation of nationwide roll-out of population-based breast and cervical screening programmes that fulfil international and European quality standards. QAS also provided technical and scientific support to the WHO regional and country offices and the Ministry of Health of Belarus in preparing applications for financial support from the Russian Federation and the EU for quality-assured implementation of breast and cervical screening programmes in Belarus. Financial support for this activity was provided by the WHO Regional Office for Europe. The projects will begin in the second half of 2014.

Further dissemination of knowledge on successful implementation of cancer screening

In addition to the above-mentioned activities in collaboration with WHO and the Ministry of Health of Belarus, QAS has continued to disseminate knowledge on successful implementation of cancer screening programmes through publications and lectures given by QAS staff and visiting scientists. In 2014, QAS staff and visiting scientists also collaborated with the Petrov Oncology Research Institute in St Petersburg and the Finnish Cancer Society in the scientific coordination of the 2014 Baltic International Oncology Forum, held in St Petersburg in June 2014. The two-day meeting attracted a wide range of stakeholders and specialists, including health officials, general practitioners, oncologists, surgeons, pathologists, epidemiologists, and service providers from the North-western Region of the Russian Federation and from several other regions throughout the Russian Federation and neighbouring countries. Experts highly

experienced in the planning, implementation, quality assurance, and evaluation of population-based cancer screening programmes shared their experience about state-of-the-art approaches to implementation of cancer screening and future prospects for programme implementation in the Russian Federation and neighbouring countries, including the former republics of the Soviet Union. A joint follow-up workshop, the Siberian Screening Forum, will take place on 27 November 2014 in Khanty-Mansiysk.

Revision of the European Code Against Cancer

In 2014, work was completed on the fourth edition of the European Code Against Cancer. The aim of the project, which was co-financed by the EU Health Programme, was to evaluate, revise, and expand, if necessary, the previous recommendations in the Code. The updated and expanded recommendations indicate key lifestyle and public health interventions that if adopted by average-risk members of the population may result in a reduction in cancer incidence and mortality. In addition to 12 main recommendations in the Code itself, additional related information is provided on the IARC website, explaining the recommendations and indicating how individuals can follow them. The website also includes links to the scientific publications that explain the evidence base for each of the recommendations. The project is coordinated by QAS and ENV and involves several other IARC Sections and Groups (CSU, COM, IMO, INF, NME, PRI, and SCR). The new Code was launched on 14 October 2014 with a virtual press conference coordinated by IARC and the European Commission. Additional press conferences and media activities will be conducted in EU Member States and IARC Participating States and coordinated by the IARC Communications Group.

EU screening implementation report

The first report on implementation of the Council Recommendation on cancer screening was published by the European Commission in 2008. In 2014, work has continued on the second report, in a project coordinated by QAS and co-financed by the EU. The data collection instruments have been designed, piloted, and revised, and data collection has begun.

EurocanPlatform

In the framework of the EurocanPlatform project, which is co-funded by the EU Seventh Framework Programme for Research, QAS has convened an international working group that is preparing a report on evidence-based recommendations on breast cancer screening. The recommendations aim to improve the multidisciplinary approach to managing breast lesions by refined characterization and reporting of small (1–14 mm) and diffuse breast cancers.

European Cancer Control Joint Action

In collaboration with the Finnish Cancer Society, QAS provided scientific and technical support to the joint action of the European Commission's European Partnership for Action Against Cancer (EPAAC) by hosting the secretariat of the work package on cancer screening. In the new Comprehensive Cancer Control (CanCon) Joint Action, which follows the EPAAC joint action, QAS is providing scientific and technical support to the project secretariat for the work package on cancer screening hosted at the Finnish Cancer Society. This support will be financed through the EU grant for CanCon. The new joint action will develop guidance for EU Member States on how to develop comprehensive cancer control plans. The work package on screening will develop the guidance applicable to screening, taking into account European quality assurance guidelines.

Screening Group (SCR)

SCR conducts field studies to evaluate the performance characteristics, effectiveness, and service delivery aspects of different early detection methods for breast, cervical, colorectal, and oral cancer control in low- and middle-income countries (LMICs). These initiatives also address the means by which screening services could be scaled up through public health services and

the development of different training resources to catalyse and augment trained human resources through close collaboration with the national institutions and government health services in the countries (Bosch et al., 2013; Denny et al., 2013; Sankaranarayanan et al., 2013a). SCR aims to contribute scientific evidence through its research programme to support the development of resource-appropriate early detection policies and health systems to deliver effective early services (Sankaranarayanan et al., 2014; Khuhaprema et al., 2014). Technical support is also provided to national early detection programmes in selected LMICs.

Cervical cancer prevention and screening

As part of efforts to accelerate the introduction of HPV vaccination in low-resource countries, the efficacy of one, two, and three doses of HPV vaccine in preventing cervical neoplasia is being evaluated in a multicentre observational study involving 17 729 girls and women in India. Preliminary results indicate that vaccination is safe and that even a single dose is immunogenic, with non-inferiority of the immunogenicity of two doses compared with that of the three-dose regimen and similar frequency of incident and persistent HPV 16/18 infection in all the study groups. The study cohorts will be followed up to establish long-term protection against HPV infection and cervical neoplasia after the different dose regimes.

The long-term impact of a single round of screening with HPV testing, cytology, or visual inspection with acetic acid (VIA) on cervical cancer incidence and mortality is being addressed by following up about 230 000 women in the Osmanabad and Dindigul district cervical screening trials in India. The utility of conventional cytology and VIA to triage HPV-positive women is being evaluated in field studies in India (Muwonge et al., 2014). The effectiveness of different screening approaches in preventing cervical neoplasia in HIV-infected women is being addressed in a cohort study in India (Joshi et al., 2014). Technical support is provided to ongoing VIA or HPV screening programmes in Bangladesh, Guinea, India, Morocco, the Republic of the Congo, and Thailand. A meta-analysis of the efficacy of cryotherapy and cold coagulation in curing cervical intraepithelial neoplasia has been completed (Sauvaget et al., 2013; Dolman et al., 2014).

Breast cancer screening

In a randomized controlled trial involving 116 000 women in Trivandrum, India, the second round of screening by clinical breast examination (CBE) has been completed and the third round is in progress. A qualitative study addressing the factors influencing participation in the various levels of the screening trial has been published (Grosse Frie et al., 2013). The role of breast awareness in improving early detection and survival of breast cancer patients is being investigated in Mumbai, India. The performance characteristics of near-infrared as well as tactile imaging are being evaluated in India, China, and Thailand.

Oral cancer screening

Long-term results, after 15 years of follow-up, of the participants in the randomized trial of oral visual screening in Kerala, India, indicate a 25% reduction in mortality among users of tobacco and/or alcohol and a more than 80% reduction in mortality in those who complied with all four rounds of screening (Sankaranarayanan et al., 2013b). The inputs and outcome of “social marketing” to increase awareness for early detection are being evaluated in Sri Lanka. A manual for visual screening has been published (Ramadas et al., 2013).

Colorectal cancer screening

A pilot programme based on immunochemical faecal occult blood testing (iFOBT) and triage colonoscopy in the government health services in Lampang Province, Thailand, was successfully completed (Khuhaprema et al., 2014). The cost–effectiveness of colorectal cancer screening in

Thailand is being evaluated, and technical support is currently being provided in the integration and scaling up of colorectal cancer screening in five provinces.

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Office of the Director

The Office of the Director comprises a small team that supports the Director in the implementation of the Agency's scientific strategy and programme and in the coordination of contacts with IARC's networks of scientific collaborators and institutional partners involved in research and policy development for cancer prevention and control. The Director's Office is also responsible for assisting the Director and the Section of Support to Research in relations with the Scientific and Governing Councils and with current and potential Participating States. Finally, the Director's Office team supports the activities of several internal advisory groups and committees, most notably the Senior Leadership Team and the IARC Ethics Committee, and supports the coordination of cross-cutting scientific initiatives involving multiple research Groups.

Over the past year, the Director's Office coordinated several strategic activities supporting the implementation of the global agenda for the prevention and control of noncommunicable diseases, in collaboration with WHO Headquarters, WHO Regional Offices, and other United Nations agencies, for example through the IARC-Noncommunicable Diseases and Mental Health (NMH) Coordination Group, and coordination of IARC's contributions to the update of the WHO *Global Status Report on Noncommunicable Diseases 2014*. Also in this area, the Director's Office hosted in October a meeting with the International Atomic Energy Agency (IAEA) Programme of Action for Cancer Therapy (PACT) and WHO to discuss and develop the IAEA-IARC-WHO Joint Project on Cancer Control, an initiative integrated with the United Nations Inter-Agency Task Force on the Prevention and Control of Noncommunicable Diseases.

Dr Rengaswamy Sankaranarayanan was assigned a new role as Special Advisor to the Director on the topic of Cancer Control, and the Director's Office supported the development of activities in this area by coordinating IARC's participation in the International Cancer Control Partnership (ICCP) and collaborative activities with the Union for International Cancer Control (UICC).

In terms of the development of relations with potential new Participating States and international partners, the Director undertook several official visits. He visited Morocco in January, for discussions with the Moroccan Ministry of Health and with the Lalla Salma Foundation (LSF), and again in May, when he attended the LSF's general assembly and signed a Memorandum of Understanding to develop a programme of collaboration on cancer prevention and research. In March, the Director attended a meeting of the Asian National Cancer Centers Alliance (ANCCA) in Seoul, Republic of Korea, where he held discussions with officials from several countries in the region. In June, the Director visited the Kuwait Cancer Control Center and held discussions with the Kuwait Ministry of Health, and in October he attended the Conference on the Burden of Cancer in the Gulf Region in Riyadh, Saudi Arabia.

The Director's Office hosted the IARC Medal of Honour awardee, Dr Harold Varmus, Director of the National Cancer Institute, USA, who presented the 21st Roger Sohier Lecture, "*Promoting the discovery and application of knowledge about cancer*", in January 2014. In addition, Professor Sir Michael Marmot, Director of the University College London Institute of Health Equity, United Kingdom, presented the second IARC Cancer and Society Lecture, "*Fair society, healthy lives*", on World Cancer Day (4 February).

Finally, several key reports resulting from Working Group meetings promoted by the Director's Office were published in 2014, including *Primary End-points for Prophylactic HPV Vaccine Trials*, Helicobacter pylori *Eradication as a Strategy for Preventing Gastric Cancer*, and *Aflatoxin Control Measures: A Basis for Improved Health in Developing Countries*.

Section of Support to Research (SSR)

The Section of Support to Research (SSR) contributes to the achievement of IARC's scientific objectives through efficient and effective management of the Agency's resources and provision of administrative services, ensuring accountable risk mitigation and implementing strategies to strengthen IARC's capacities.

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

During 2014, SSR teams began implementation of a work plan covering 2014–2015, as agreed upon with the Director and the Senior Leadership Team at the beginning of the year. The two-year work plan aims to: explore new mechanisms for increasing extrabudgetary financial support to IARC's scientific programme; strengthen and simplify the existing financial tools, systems, and processes; develop a sustainable staff development platform; and implement tools to facilitate knowledge sharing and project management. Good progress was achieved in all areas of the work plan in 2014:

- Support was provided to the Director in a full redesign of the presentation and management of IARC budgets. The introduction of the Project Tree and the related financial reporting implications provide the Agency with new tools for broader outreach to potential funders outside the traditional grant-issuing institutions. The new presentation of the budget will also improve transparency for the Governing Council with regard to IARC's allocation of resources to priority areas.
- The upgrade of the IARC Enterprise Resource Planning (ERP) system for management of financial data will ensure compliance with prevailing standards and ensure simplified financial reporting both for internal needs and for IARC stakeholders. Considerable strides continue to be made in revamping the Agency's administrative policies and procedures with the aim of streamlining and simplifying, including automation of several such processes.
- As a first step towards putting in place a role-based learning platform, concentrated efforts were put into supporting IARC managers in developing important competencies towards ensuring a high-performance culture in the Agency. These efforts followed a comprehensive 360-degree feedback review for senior managers and the introduction of a new electronic Performance Management and Development System.
- During 2014, IARC began implementation of the SharePoint platform for improved knowledge sharing across the Agency and for management of projects with external collaborators. Within this project, a portal was developed to provide IARC personnel with clear information on the Agency's procedures related to their needs in implementing scientific activities.

Communications Group (COM)

The Communications Group (COM) consists of several teams: the IARC Knowledge Management Centre, which comprises both the IARC publications programme and library services; the web services team; the editing and translation services team; and the media team. Below are some highlights of COM's activities in 2014.

COM renegotiated the commercial agreement with the distributor of IARC publications, WHO Press. The commercial dissemination activity was divided into two parts: WHO Press will continue to sell print products, and IARC has taken over all distribution of e-products, thus endorsing the policy decision to foster e-information products. The e-preferred option will allow faster, cheaper dissemination of cancer research results. The focus on electronic dissemination includes not only the development of IARC's own web platforms for providing access to publications, but also open access initiatives such as depositing IARC monographs in the National Library of Medicine's PubMed Bookshelf (for which a deposit agreement is in place). IARC has also joined the HINARI programme, whereby low- and middle-income countries can access IARC products at no or very low cost. Support from a consultant for several months helped COM and IARC to define priorities for the future marketing and dissemination of publications, resulting in recommendations that are currently being implemented.

In 2014, with the arrival of the new Knowledge Manager, and following the restructuring of the COM teams, the **Knowledge Management Centre** has focused on efforts to develop an open access policy for the Agency. In addition, the Knowledge Management Centre has continued to coordinate publication efforts across the Agency, and took the lead for streamlining processes, screening and selection of a manuscript submission system and editorial management tool, and project planning and rationalizing. IARC will be issuing volumes of the WHO Classification of Tumours in e-Pub format for the first time during 2015, an important step in the development of electronic resources in this area by the time the last volume of the fourth edition of the Blue Books is published.

The **web services team** continued to develop a range of new websites for the Agency's various projects, including the following: Low- and Middle-Income Countries (LMICs) Biobank and Cohort Building Network (BCNet); IARC Handbooks of Cancer Prevention; EPIC; PRECAMA study; The African Breast Cancer - Disparities in Outcomes study; and Education and Training Programme. The web team also orchestrated a number of events, including World Cancer Day and the launch of *World Cancer Report 2014* in February, and the launch of the new European Code Against Cancer in October. It also continues, on a daily basis, to distribute high-quality information, optimized for slow-speed, narrow-band access, and to constantly update cancer information. In addition, a special effort has been made to continue providing online access to IARC publications in PDF format, and the following publications were made available in PDF format during 2014: IARC Scientific Publication No. 154: Biomarkers in Cancer Chemoprevention; IARC Handbook of Cancer Prevention Volume 3: Vitamin A; IARC Handbook of Cancer Prevention Volume 7: Breast Cancer Screening; and IARC Handbook of Cancer Prevention Volume 14: Effectiveness of Tax and Price Policies for Tobacco Control. The web team also took part in the revamping of the IARC Intranet, which was successfully launched by the administration in late October.

The **editing and translation services team** edited dozens of articles, book chapters, reports, and grant proposals, and translated official documents from English into French and Spanish. Training sessions on writing scientific manuscripts were provided for Summer School participants as well as for IARC personnel.

The **media team** issued 55 IARC news items published on the web, and released 9 international news releases. It coordinated media efforts for World Cancer Day alongside WHO and UICC, with a major press conference in London in February to launch *World Cancer Report 2014*. It also organized the launch of the new European Code Against Cancer in October with a global virtual press conference, participated in the launch of the American Cancer Society's *The Cancer Atlas* (second edition) in Melbourne in early December, and publicized the outcome of the first meeting after the relaunch of the IARC Handbooks of Cancer Prevention (on breast cancer screening) in mid-December.

In addition, COM developed and produced a set of multipurpose institutional brochures, in English, French, and Spanish, to be used as IARC's calling card in various venues, and as a support for more specific presentations, including for funding and sponsorship.

After testing and presenting a new format and design for IARC book collections, the **IARC publications team** has helped prepare the following volumes.

IARC Monographs in PDF online:

- Volume 105 (2013) Diesel and Gasoline Engine Exhausts and Some Nitroarenes
- Volume 106 (2014) Trichloroethylene, Tetrachloroethylene and Some Other Chlorinated Agents.

IARC Monographs in print:

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

Other publications:

- World Cancer Report 2014
- WHO Classification of Tumours of Female Reproductive Organs, 4th edition
- Planning and Developing Population-based Cancer Registration in Low- and Middle-income Settings, IARC Technical Publication No. 43
- Primary End-points for Prophylactic HPV Vaccine Trials, IARC Working Group Report No. 7
- *Helicobacter pylori* Eradication as a Strategy for Preventing Gastric Cancer, IARC Working Group Report No. 8.

Website:
European Code Against Cancer, 4th edition (http://cancer-code-europe.iarc.fr/)

Electronic resource:
International Classification of Diseases for Oncology: ICD-O-3 online (http://codes.iarc.fr/)

Education and Training Group (ETR)

Education and training in cancer research has been one of the statutory functions of the Agency since its inception, complementing and supporting IARC's research activities. Priority is given to scientists from, or with a research interest relevant to, low- and middle-income countries (LMICs).

It should be noted that whereas the Education and Training Group (ETR) oversees IARC's education and training activities and leads some of them, many initiatives are led by IARC research groups.

IARC Training and Fellowship Programme

The Agency welcomed more than 100 Early Career and Visiting Scientists in 2014, supported by IARC Fellowships or project funds from IARC research groups.

In 2014, 11 new IARC Postdoctoral Fellowships were awarded and seven were extended for a second year. Fellows came from 15 different countries, of which 10 were LMICs. Three Return Grants were awarded to fellows from LMICs. This high number of awards resulted from the fact that ETR successfully obtained a second competitive grant from the EC-FP7 Marie Curie Actions-People-COFUND programme, which is contributing 40% of the postdoctoral fellowship costs for 2014–2018.

Under the bilateral agreement with Cancer Council Australia, one IARC-Australia fellowship was awarded in 2014 and one extended for an additional year. The first IARC-Ireland postdoctoral fellowship was awarded under the bilateral agreement with the Irish Cancer Society. Other, similar partnerships are currently under discussion with several institutions.

Within the framework of the IARC Postdoctoral Fellowship Charter, during 2014 seven generic courses were organized at IARC, to equip postdoctoral researchers with essential cross-cutting skills. An ongoing dialogue with the Early Career Scientists Association enabled ETR to refine needs for future courses as well as to support some of the association's activities.

Senior Visiting Scientist Awards for 2014 were made to Professors Walter Prendiville (Ireland), Michael Leitzmann (Germany), and Kyle Steenland (USA).

The Union for International Cancer Control (UICC)-IARC Development Fellowship, which was launched in 2012 and allows one participant in the IARC Summer School to return to IARC for a period of 3 months for further training and collaborative work, was awarded to a cancer registry professional from Sri Lanka. A joint proposal with UICC was developed to raise funds to sustain and expand this initiative.

IARC Courses

The IARC Summer School in Cancer Epidemiology is organized in Lyon each year in June and July. In 2014, more than 280 applications were received, of which 64 were accepted, with approximately 80% of the participants from LMICs. Additional financial support for the Summer School was provided by the United States National Cancer Institute (NCI) as well as by the Nordic Cancer Union (NCU) and the Klinik und Poliklinik für Gynäkologie, Martin Luther University, Halle, Germany.

Specialized courses were also organized by IARC scientific groups, sometimes with the support of ETR. For example, 10 courses related to cancer registration were organized in partnership with the IARC Regional Hubs of the Global Initiative for Cancer Registry Development.

A partnership with the Institut Català d'Oncologia (ICO), Spain, was established to organize a joint IARC/ICO online course in cancer epidemiology targeting Latin American countries. Initial support was provided by the United States NCI, and additional funds are being raised to launch the activity. As the first component of a future IARC online learning platform that will bring such resources to IARC's target audiences, a new dedicated Education and Training Programme website (http://training.iarc.fr/) was launched in early 2014.

The Gambia Hepatitis Intervention Study (GHIS)

The Gambia Hepatitis Intervention Study (GHIS), now in its third decade, is a collaborative project undertaken by IARC, the government of the Republic of The Gambia, and the Medical Research Council, United Kingdom. GHIS was initiated in 1986 to evaluate the efficacy of hepatitis B virus (HBV) vaccination in childhood for the prevention of infection, chronic liver disease, and hepatocellular carcinoma (HCC) in adulthood in a high-risk population. Led by the Director's Office, GHIS is a 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 Ramou Njie, the hepatologist managing the project, together with a team of tumour registration officers, carries out enhanced surveillance of chronic liver disease and cancer in hospitals and health centres around the country. She is assisted by junior doctors from the local Edward Francis Small Teaching Hospital (EFSTH), whom she has trained in ultrasonography and liver biopsy techniques. Suspected cases of liver cancer are assessed by ultrasonography and computed tomography (CT) scans, by quantitative α-fetoprotein assays, and, in some cases, by histological confirmation from liver biopsy samples. Histopathology reporting is carried out by two independent pathologists: in The Gambia by Professor O. Khalil at EFSTH, and in London by Professor Rob Goldin at Imperial College London. All confirmed cases of liver cirrhosis and cancer are recorded in the NCR.

A European Union-funded multicentre collaborative project, PROLIFICA (Prevention of Liver Fibrosis and Cancer in Africa), aimed at preventing liver cancer through screening and treating individuals who are chronically infected with HBV, is now in its third year. Additional histopathology support is obtained through collaboration with Imperial College London, the coordinating centre.

Current status

- Testing the record linkage of confirmed cases of HCC and chronic liver disease with the original GHIS vaccination database is yet to start. The approach for this is being evaluated by Dr Sir Andrew J. Hall, former Head of GHIS, with Mr Morten Ervik at IARC in Lyon.
- To further strengthen the histological diagnoses, slides have been sent for validation by the histopathology team at IARC.
- Recruitment and training of two additional tumour registration officers was undertaken last year in order to strengthen the NCR and ensure coverage of the whole country.

Laboratory Services and Biobank Group (LSB)

The focus of the Laboratory Services and Biobank Group (LSB) is on operational and quality control issues, which are important in shaping the future of the Agency's laboratories and the IARC Biobank as well as supporting the establishment and upgrading of biobanks in low- and middle-income countries (LMICs).

LSB was established in 2010, and the expectations of the Group have since changed in view of the increasing services provided to IARC scientific groups and external collaborators, as well as the realization of the envisioned substantive support that the Group is beginning to provide to LMICs. Specifically, LSB requires a stronger process management role for the services provided and needs to boost data management capacity to manage the changing landscape of biobank management and to face the increasing demand for substantive services. In response to this need, the Group's structure was revised. The new structure, in place since October 2014, caters for the new expectations while aligning the resources and capabilities of the Group accordingly.

Laboratory Services

Health and safety

Health and safety issues are addressed in close collaboration with the Occupational Health and Safety Committee (OHSC). Several suggested improvements to the cryogenic rooms were brought to the committee's attention to provide a safer working environment, including installation of cameras for surveillance when personnel are working alone and installation of an emergency button to stop the liquid nitrogen supply in case of an emergency.

A new authorization for handling radioisotopes has been granted for the next 5 years. For the use of genetically modified organisms (GMOs), the renewal process is under way. Training sessions are organized regularly to keep laboratory staff informed and to provide reminders on safety issues.

IARC Biobank

Infrastructure

Expansion of the storage facilities: To cater for the increasing demand for storage facilities for samples collected through IARC-led studies and for the provision of safe storage conditions requested by LMIC collaborators, funds have been made available to secure two new liquid nitrogen tanks and several −80 °C freezers. Floor space to accommodate an additional 20 new freezers has been made available in collaboration with the Administrative Services Office (ASO). The newly installed automatic temperature monitoring system, SIRIUS, continues to provide an efficient means of managing storage conditions.

Sample management: The in-house sample management information system (SAMI) is currently being upgraded and improved to cater for new attributes. In particular, the program now has the facility to record data on the quality of samples received and stored at IARC. The inventory and cataloguing of IARC-based samples is progressing well; more than 1 million of the IARC-based samples (excluding those from the European Prospective Investigation into Cancer and Nutrition [EPIC] study) have now been uploaded into SAMI. Plans are under way to migrate the EPIC database into SAMI.

Centralization of IARC biological samples: Standard protocols for reception, archiving, storage, and distribution of biological samples are being developed to manage these processes. This includes the online registration of new projects and samples and their associated data and documents for central archiving. Standard operating procedures (SOPs) and Working Instructions are being prepared for transfers of samples (incoming and outgoing).

International collaborations

BBMRI-ERIC: The Agency was admitted to the pan-European Biobanking and Biomolecular Resources Research Infrastructure-European Research Infrastructure Consortium (BBMRI-ERIC) under the category of international organization as an observer. IARC will share with the consortium its expertise in international networking and interoperability issues to ensure that the compatible structures that are developed within Europe will be accessible to wider international communities.

Support to LMIC biobanks: IARC, in collaboration with several international organizations and biobanking societies, notably with support from the United States National Cancer Institute (NCI), established the LMICs Biobank and Cohort Building Network (BCNet) in 2013. To facilitate the sharing of resources and information between members and to increase the visibility of BCNet, the network's website (http://bcnet.iarc.fr/) was launched in September 2014. LSB is providing bilateral support for the establishment of biobanks, in particular the national biobank in India, which is being hosted by the Tata Memorial Centre in Mumbai. On-site training programmes for colleagues from Poland and Lithuania are being planned, and this initiative will be extended to other countries that have requested similar support.

Biobank catalogue: The biobank centralization programme has resulted in the creation of a catalogue of IARC's biological samples available for sharing with the international community. This information is available on the website dedicated to the biobank (http://ibb.iarc.fr/), together with the established Sample Access Policy, which provides information on how to access the Agency's biological material. In 2014, BCNet, in collaboration with the BioBanking and Molecular Resource Infrastructure of Sweden (BBMRI.se), began the process of developing a computer program to catalogue the resources of the network. This catalogue aims to facilitate the sharing of members' resources with the network members and with the international community. A needs assessment survey was conducted in 2014 to identify areas to target development programmes, including training and technology transfer to LMIC members.

Governing Council and Scientific Council

The International Agency for Research on Cancer (IARC) was established in May 1965 through a resolution of the XVIIIth 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 prior to the WHO World Health Assembly. The Governing Council elects IARC's Director, who normally serves for a five-year term. The Council 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.

Scientific Council

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

Budget

For the biennium 2014–2015, the IARC Governing Council voted a regular budget of €40 424 491. A number of projects are also funded by extrabudgetary sources, both national and international. In 2013, approximately 31% of the Agency's overall expenditure was financed by extrabudgetary funds.

Participating States and Representatives at IARC Governing Council 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 of Molecular and Cellular Medicine, Medical Research Council
London

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

M. 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
Berne

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
M. 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
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Ms Lucero Hernandez
Senior Policy Advisor, Multilateral Relations Division
Office of International Affairs for the Health Portfolio
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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 (DBRAIRCH)
All India Institute of Medical Sciences (AIIMS)
New Delhi

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Incoming Chairperson, Scientific Council
Professor Cornelia (Neli) Ulrich

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IARC Publications 2014

Abbas S, Linseisen J, Rohrmann S, Beulens JW, Buijsse B, Amiano P, et al. (2014). Dietary vitamin D intake and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition: the EPIC-InterAct study. Eur J Clin Nutr. 68(2):196–202. http://dx.doi.org/10.1038/ejcn.2013.235 PMID:24253760

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