International Agency for Research on Cancer

World Health Organization

Biennial Report

18/19

International Agency for Research on Cancer

World Health Organization

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Biennial Report

2018–2019

International Agency for Research on Cancer

Lyon, France

2019

About the cover: IARC has partnered with the GBH American Hospital in Udaipur, India, to develop an innovative comprehensive model to screen and educate people about noncommunicable diseases such as diabetes, hypertension, breast cancer, oral cancers, and cervical cancer. © IARC/V. Terrasse.

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A New Director for IARC

On 17 May 2018, the International Agency for Research on Cancer (IARC) Governing Council, which is composed of the Representatives of the IARC Participating States and of the Director-General of the World Health Organization (WHO), elected Dr Elisabete Weiderpass as the new Director of the Agency. Dr Weiderpass took office as IARC Director on 1 January 2019.

IARC Directors are elected for a five-year term and are eligible for one further five-year term. The Director is responsible for the leadership of the Agency by providing: the general framework for attainment of the Agency's mission in accordance with the IARC Statute, Rules and Regulations; the development of a Strategy and Implementation Plan that sets out the overall vision, direction, and focus of the Agency's research programme; and oversight of the day-to-day operations of the Agency.

Elisabete Weiderpass, MD, MSc, PhD, is a Brazilian cancer researcher who is a naturalized Swedish and Finnish citizen. She is an expert in cancer epidemiology and cancer prevention.

Dr Weiderpass previously served as leader of the Department of Research at the Cancer Registry of Norway, and of the Genetic Epidemiology Group at the Folkhälsan Research Center in Finland. She was a Professor of Medical Epidemiology at the Karolinska Institutet in Stockholm, Sweden, and a Professor of Cancer Epidemiology at the Arctic University of Norway. She held Adjunct Professorship positions in Cancer Epidemiology in Brazil, China, and the Islamic Republic of Iran, and was a Visiting Professor in Kuwait. She is the author of more than 700 scientific publications in peer-reviewed international journals.

Dr Weiderpass took over as IARC Director from Dr Christopher P. Wild, who served two five-year terms after taking office on 1 January 2009. Dr Wild supported the development of several major global initiatives aimed at developing the capacity and infrastructure for research, particularly in low- and middle-income countries, and he oversaw an increase in the number of IARC Participating States.

On her election, Dr Weiderpass stated, "I am delighted to have been selected as the next Director of the Agency, and I look forward to bringing my expertise to IARC and contributing to the important work of the Agency. IARC will increasingly focus its activities on producing cancer research of the highest quality and potential public health impact: producing evidence-based knowledge to support public health policy decision-making processes. IARC must remain the global reference for regulatory agencies, governments, and international organizations to propose evidence-based prevention strategies at the global level, with a particular focus on low- and middle-income countries. IARC must be a trusted organization in producing relevant science for public health policy and for public good, independent from vested interests. IARC will continue to work closely with WHO and other international organizations to maximize the public health impact of the knowledge produced."

Dr Elisabete Weiderpass. © IARC/Nicholas O'Connor.

Introduction – from the IARC Director

Having been the Director of IARC since January 2019, this is the first opportunity I have had to introduce the Agency's Biennial Report. I am pleased to present this account of the relevance, scope, and depth of research and coordinating activity undertaken by IARC scientists and their support teams during the past 2 years. As has been the record over decades, the work of IARC is focused on all matters that directly contribute to cancer prevention.

We know that worldwide, 30–50% of all cancer cases are potentially preventable. We know which interventions work, we know which of these are cost-effective, and we know that such prevention programmes may be implemented at both national and local levels. However, the best possible cancer prevention across populations worldwide is far from the norm, partly because key research is lacking. Undertaking and facilitating cancer prevention research is the mission of IARC, the specialized cancer arm of WHO.

Cancer prevention depends on background knowledge, education and training, and the implementation of key strategies to raise awareness and to ensure that individuals around the world have the information and support they need to reduce exposure to carcinogens such as tobacco smoke and alcoholic beverages, to avoid an unhealthy diet and lack of physical activity, and to be protected against dangerous levels of pollution.

This report showcases the research work conducted by IARC in collaboration with its global network of experts during 2018–2019. Three main areas are covered: describing the distribution of cancer across populations, identifying the causes of cancer, and evaluating preventive interventions and their implementation. Each of these areas contributes vitally to cancer prevention and identifies the role of capacity-building through education and training activities, strategic leadership and partnerships, coordinated communications, administrative support, and resource mobilization.

Cancer has a growing, global burden. However, cancer incidence, risk factors, and optimal strategies for implementing preventive interventions differ according to region or country. An increasing proportion of the burden is falling on low- and middle-income countries (LMICs), not only because of demographic changes but also because of a transition in the relevant cancer-causing agents, from those predominantly linked to infections to those related to personal behaviours, particular carcinogens, and obesity. Furthermore, future increases in cancer incidence will disproportionately affect LMICs, thereby becoming a major health, social, and economic burden. IARC is unique among the leading cancer research institutes for its focus on LMICs, collaborating with 141 LMICs around the world. IARC's engagement to further advance joint research and share knowledge and experience with LMICs is of crucial importance to improve knowledge, build capacity, and increase expertise for cancer control, with the ultimate goal of saving lives and making a difference.

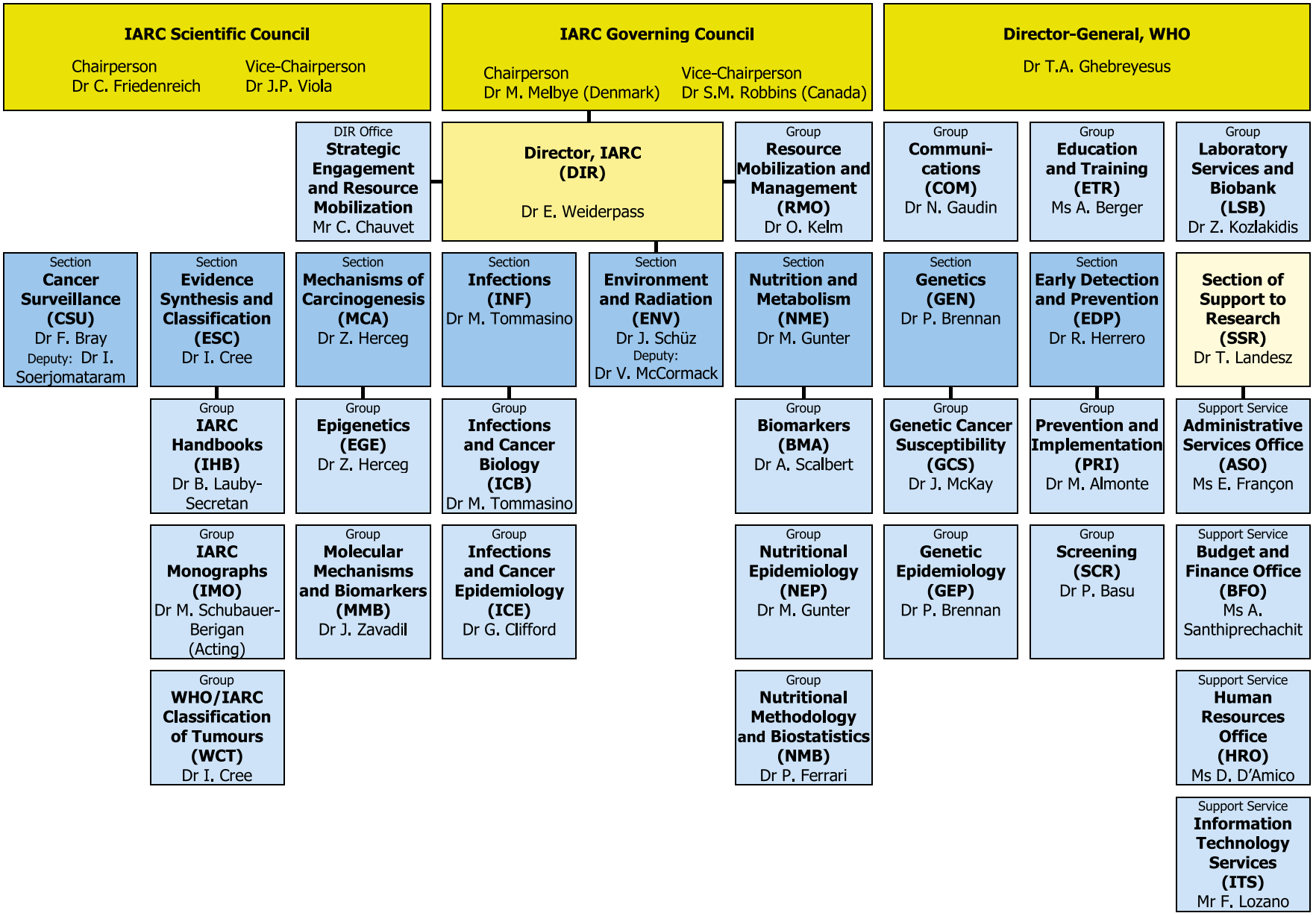
Research is progressively revealing that, whether assessed nationally or locally, social inequalities adversely affect the benefits of cancer control. Social inequalities in cancer are a global problem, as documented in the recent IARC publication titled *Reducing Social Inequalities in Cancer: Evidence and Priorities for Research.* Indeed, there is clear evidence that the risk of overall cancer mortality and survival differs according to socioeconomic status: the lower the socioeconomic status the greater the risk of mortality, and the higher the socioeconomic status the greater the chances of survival.

The efficacy of cancer prevention measures will be critically dependent on action to address the social determinants of health. Cancer inequalities have major economic implications and are largely avoidable, although this requires concerted action at many levels. Through expert workshops and its wider role in convening international cancer leaders and promoting cooperation in research, IARC today reinforces WHO's commitment to keep social inequalities high on the global agenda through the development of new research priorities: expansion of surveillance of social determinants of cancer incidence and mortality, expansion of research focused on prevention, and a focus on social equality when implementing cancer control strategies.

I look forward to continuing this mission with the ultimate goal of reducing the global cancer burden, avoiding unnecessary suffering, and saving as many lives as possible.

International Agency for Research on Cancer
World Health Organization

1 September 2019



IARC Medals of Honour

The IARC Medals of Honour are awarded to acknowledge and reward the work of scientists whose research has made an outstanding contribution to advancing our understanding of the biology or of the epidemiology of cancer.

On 9 January 2018, the IARC Medal of Honour was awarded to Dr Reza Malekzadeh (Tehran University of Medical Sciences, Islamic Republic of Iran), who presented the 11th Richard Doll Lecture, on "Opium as a carcinogen: new insights from the Golestan Cohort Study".

During the Sixtieth Session of the IARC Governing Council (16–18 May 2018), the IARC Medal of Honour was awarded to Dr Christopher P. Wild, in deep appreciation of the services rendered to the Agency by Dr Wild during his Directorship of IARC from 2009 to 2018. In addition, the title of Director Emeritus was bestowed upon Dr Wild, in gratitude for his outstanding contributions to the Agency, which have enhanced its role in and reputation for promoting and coordinating international collaboration in cancer research.

The Agency also invites outstanding speakers to present the IARC Cancer and Society Lecture to address the ways in which cancer research has a broad relevance for society, in a style that is accessible to all IARC personnel, both scientists and non-scientists.

Professor Daniel R. Fagin (New York University, USA) presented the fifth IARC Cancer and Society Lecture, on "From *Toms River* to today: science, spin, and storytelling in dark times", on 6 February 2018, timed to mark World Cancer Day (4 February).

Dr Groesbeck Parham (University of North Carolina at Chapel Hill, USA) presented the sixth IARC Cancer and Society Lecture, on "Catalysing a shift in cancer control in a low-resource setting by using what's available", on 4 February 2019 (World Cancer Day).

Dr Reza Malekzadeh

Dr Groesbeck Parham

Roger Sohier Lecture

1993 Gérard Orth (Institut Pasteur, Paris) – Papilloma virus and human cancer
1994 Guy Blaudin de Thé (Institut Pasteur, Paris) – Epidémiologie moléculaire des rétrovirus oncogènes
1995 Richard Peto (Oxford University, United Kingdom) – Avoidance of premature death
1996 Dirk Bootsma (Erasmus University, Rotterdam, The Netherlands) – DNA repair: maintaining nature's perfection
1997 Luca Cavalli-Sforza (Stanford University, USA) – Gènes, peuples, langues, cultures
1998 Charles Weissmann (University of Zurich, Switzerland) – Biology and transmission of prion diseases
1999 Jan Pontén (Uppsala University, Sweden) – Sunlight and skin cancer: new insights
2000 Richard Klausner (National Cancer Institute, Bethesda, USA) – The war on cancer: where we are and where research is taking us
2001 Oliver Brüstle (Institut für Neuropathologie, University of Bonn, Germany) – Embryonic stem cells: basic concepts and therapeutic applications
2002 Jeffrey Koplan (Centers for Disease Control, Atlanta, USA) – Bioterrorism and public health preparedness
2003 Paul Kleihues (Director, IARC) – Poverty, affluence and the global burden of cancer
2004 Umberto Veronesi (European Institute of Oncology, Milan, Italy) – Breast cancer management and care: current results and future perspectives
2005 David Lane (University of Dundee, United Kingdom) – p53 and human cancer: the next 25 years
2006 Georg Klein (Karolinska Institutet, Sweden) – Viral contributions to tumorigenesis
2007 Mariano Barbacid (Centro Nacional de Investigaciones Oncológicas, Spain) – Ras genes, Ras oncogenes and cancer
2008 Jan Hoeijmakers (Rotterdam, The Netherlands) – Genome maintenance and the link with cancer and ageing
2009 Harald zur Hausen (German Cancer Research Center, Heidelberg) – The search for infectious agents in human cancers
2010 Gerald N. Wogan (Massachusetts Institute of Technology, Cambridge, USA) – Aflatoxins and human liver cancer
2011 Robert A. Smith (American Cancer Society, USA) – The challenge and potential of early detection to reduce the global burden of cancer
2012 John D. Potter (University of Washington, Seattle, USA and Massey University, Wellington, New Zealand) – Nutrition, environment, development, and cancer: casting a wider net
2013 Harold Varmus (National Cancer Institute, Maryland, USA) – Promoting the discovery and application of knowledge about cancer

Richard Doll Lecture

2004 Richard Doll (London, United Kingdom) – Fifty years follow-up of British doctors
2005 Brian MacMahon (Needham, Massachusetts, USA) – Epidemiology and the causes of breast cancer
2006 Joseph Fraumeni Jr (National Institutes of Health, USA) – Genes and the environment in cancer causation: an epidemiologic perspective
2007 Dimitrios Trichopoulos (Harvard School of Public Health, USA) – Breast cancer: epidemiology and etiology
2008 Sir Richard Peto (Oxford, United Kingdom) – Halving premature death
2009 Nubia Muñoz (National Cancer Institute of Colombia) – From etiology to prevention: the case of cervical cancer
2010 Julian Peto (London School of Hygiene & Tropical Medicine and the Institute of Cancer Research, United Kingdom) – Future cancer mortality due to past and continuing worldwide asbestos use
2011 You-Lin Qiao (Chinese Academy of Medical Sciences & Peking Union Medical College, China) – Implementation of cancer screening and prevention in China – evidence and reality
2012 Walter C. Willett (Harvard School of Public Health, USA) – Diet and cancer: a three-decade follow-up
2013 Pelayo Correa (Vanderbilt University Medical Center, Nashville, USA) – The gastric precancerous cascade
2018 Reza Malekzadeh (Tehran University of Medical Sciences, Islamic Republic of Iran) – Opium as a carcinogen: new insights from the Golestan Cohort Study

IARC Lecture

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

IARC Cancer and Society Lecture

2012 David Michaels (Department of Labor and Occupational Safety and Health Administration, USA) – Research is necessary but not sufficient: challenges in preventing occupational and environmental cancer
2014 Michael G. Marmot (University College London, United Kingdom) – Fair society, healthy lives
2015 W. Philip T. James (London School of Hygiene & Tropical Medicine, United Kingdom) – Cancer prevention: the challenge of dietary change and obesity
2017 Karin Holm (Patient Advocates for Cancer Research & Treatment) – Patient power for better research: I can, we can
2018 Daniel R. Fagin (New York University, USA) – From *Toms River* to today: science, spin, and storytelling in dark times
2019 Groesbeck Parham (University of North Carolina at Chapel Hill, USA) – Catalysing a shift in cancer control in a low-resource setting by using what's available

IARC 50th Anniversary Celebrations, 15 May 2015

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

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

IARC 50th Anniversary Scientific Conference, 7–10 June 2016

Elizabeth Blackburn (Salk Institute for Biological Studies, USA) – Telomeres, biology, and cancer

Lynette Denny (Groote Schuur Hospital and the University of Cape Town, South Africa) – Screening and early detection of cervical cancer in Africa

Sixtieth Session of IARC Governing Council, 16–18 May 2018

Christopher P. Wild (IARC Director) was honoured with the title of Director Emeritus


Eskisehir
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Kollam
Lampang
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Khon Kaen
Addis Ababa
Eldoret
Nairobi
Trivandrum
Chennai
Dindigul
Songkhla
Penang
Seychelles
Mauritius
Kampala
Bulawayo
Maputo
Eastern Cape
Harare
Blantyre
Bamako
Abidjan
Republic of Korea
Manila
Rizal
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Zhongshan
Dalian
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Feicheng
Lianyungang
Ganyu
Linzhou
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Lima
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Biobio
Concepcion
Valdivia
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Jau
Cordoba
Uruguay
Bahia Blanca
Mendoza

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Deputy section head
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Mr Jérôme Vignat

Visiting scientists
Dr Therese Andersson
(until December 2019)
Dr Marianna de Camargo Cancela
(until November 2019)
Dr Tor-Aage Myklebust
(until December 2019)
Dr D. Maxwell Parkin
Dr Gholamreza Roshandel
(until December 2019)
Dr Brian Rous (until May 2019)
Dr Mark Rutherford
Dr Anton Ryzhov (until June 2019)
Dr Shama Sheikh

Postdoctoral fellows
Dr Marzieh Araghi (until May 2019)
Dr Citadel Cabasag
Dr Bochen Cao (until October 2018)
Dr Miranda Fidler
(until September 2018)
Dr Ivana Kulhanova (until June 2018)
Dr MengMeng Li
Dr Adalberto Miranda-Filho
Dr Eileen Morgan
Dr Sophie Pilleron
(until November 2018)
Dr Joannie Tieulent

Students
Ms Harriet Rumgay
Mr Raphaël Simon
(until October 2019)

With a global mandate to collect, analyse, and disseminate cancer data to inform cancer control action, the Section of Cancer Surveillance (CSU) seeks new ways to interact, innovate, and expand across its interlinked core areas of activity. The founding principles of CSU remain: to ensure that locally recorded high-quality cancer data are of benefit to governments in informing priorities for national cancer control, and to serve as a reference to the global cancer community in the provision of national cancer surveillance indicators, developed through our collaborative research programme.

The Global Initiative for Cancer Registry Development (GICR, http://gicr.iarc.fr) has made consolidated efforts during this biennium to put into practice a train-the-trainer approach to building local cancer registry capacity within each defined IARC/GICR Regional Hub. CSU's estimates of cancer incidence and mortality on the Global Cancer Observatory website (http://gco.iarc.fr) were updated to 2018, and a new module compiling local estimates of cancer survival was added to the website. The high-impact research of the Section, evaluating the potential contribution of specific interventions, lifestyle, and environmental risk factors to the current and future burden of cancer, is of direct relevance to global cancer control. In accordance with a globally increasing awareness and prioritization of childhood cancer, CSU has further developed its childhood cancer research programme, together with international collaborators.

Cancer registry support and collaboration

Support to cancer registries worldwide remains a priority for CSU, and the GICR serves to strengthen capacity in low- and middle-income countries (LMICs). Six

IARC Regional Hubs provide resources to nearby countries in the Caribbean; Latin America; Northern Africa, Central and Western Asia; the Pacific Islands; South, East and South-Eastern Asia; and Sub-Saharan Africa. The overall aim of the GICR is to accelerate improvements in the coverage, quality, and use of population-based cancer registries.

A key activity of the GICR during the biennium has been in knowledge translation. This has been enhanced through the launch of GICR*Net*, a train-the-trainer model whereby standardized teaching materials for cancer registries are developed jointly by IARC and local experts. To date, four networks have been formed to cover specific topic areas: CanReg5, coding and staging, data quality, and data analyses. A total of 61 designated IARC GICR Regional Trainers assist as faculty in courses, develop educational resources, and work with colleagues to provide tailored support. For example, in the area of data quality, Mr Francis Okongo organized a course in the United Republic of Tanzania (December 2018, 20 participants), and Dr Lamia Kara translated teaching materials into French and organized a 1-day course in Algeria (June 2019, 30 participants). Similar activities have taken place in the other IARC Regional Hubs, leading to an increase in the number of training courses. Work to develop self-learning e-modules is also under way, together with a GICR Mentorship Programme.

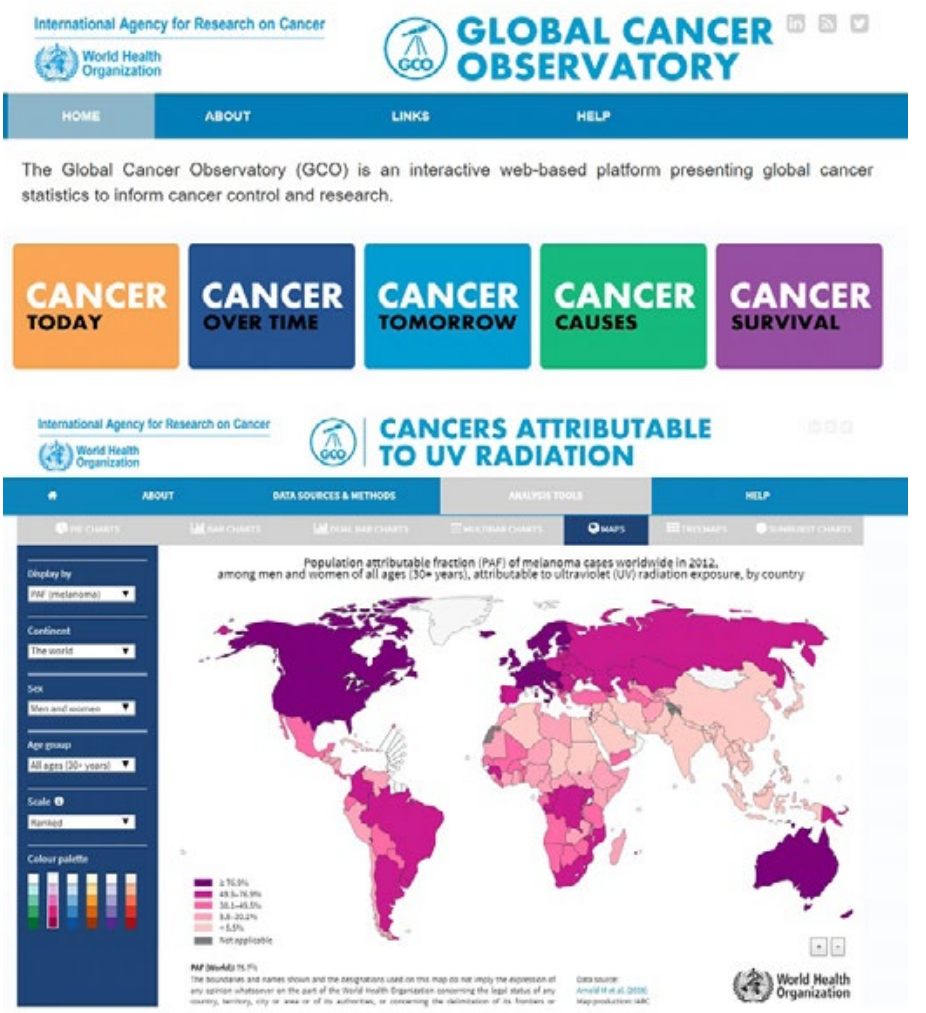
Expanding regional partnerships have led to seven new IARC GICR Collaborating Centres: one in Africa (Morocco), five in Asia (China, Islamic Republic of Iran, Japan, Republic of Korea, and Thailand), and one in the Caribbean (Martinique). Complementing those in Latin America, these Collaborating Centres work to fulfil the functions of the IARC Regional Hubs in the areas of training, support, research, and networks. The first regional IARC GICR Summer School was held in July 2019 through this model, funded and hosted by the National Cancer Center of the Republic of Korea as a founding Collaborating Centre in the region. CSU has contributed to several multiauthor papers discussing the challenges of and solutions to cancer control in specific regions and subpopulations, such as small island nations (Sarfati et al., 2019a), particularly in the Caribbean (Spence et al., 2019a, b) and the Pacific Islands (Sarfati et al., 2019b), and the actions required to measure cancer accurately and appropriately in Indigenous populations (Sarfati et al., 2018).

CSU's support to registries also includes linkages with the International Association of Cancer Registries (IACR, http://www.iacr.com.fr). In addition to the annual IACR scientific conference, which was held in Arequipa, Peru, in 2018 and in Vancouver, Canada, in 2019, there are continuing efforts to further enhance registry standards. For example, an IACR Working Group compiled a list of the required additions, changes, and revisions to the International Classification of Diseases for Oncology (ICD-O) from version 3.1 to version 3.2, recommending that these be implemented by registries from 2020. Similarly, to improve the availability and comparability of cancer staging, CSU developed the simplified staging system Essential TNM (Piñeros et al., 2019).

Global cancer indicators

With a focus on data visualization and interactivity, the Global Cancer Observatory aims to make available a broad set of relevant indicators developed through the Section's flagship projects and studies across five subsites (Figure 1). Cancer Today includes GLOBOCAN estimates of national incidence, mortality, and prevalence in 185 countries for 2018, derived using data from registries worldwide. As well an increased granularity of data – estimates are available for 36 separate cancer entities – corresponding

Figure 1. Screenshots of (upper) homepage of the Global Cancer Observatory and (lower) Cancer Causes, showing the population attributable fraction of melanoma cases worldwide attributable to exposure to ultraviolet radiation (http://gco.iarc.fr). © IARC.



uncertainty intervals have been developed to provide a semi-qualitative assessment of the validity of estimates based on an assessment of the quality, representativeness, and timeliness of the source information nationally. Studies reviewing the data sources and methods (Ferlay et al., 2019) and the international variations in the cancer magnitude and profiles across 20 world regions (Bray et al., 2018) were published during the biennium. Cancer Tomorrow uses these current estimates alongside demographic projections to 2040 to predict the future burden worldwide; realistic scenario-based longer-term projections are also under development. Cancer Causes provides estimates of population attributable fractions (PAFs) to quantify the potential of prevention; the cancer burdens attributable to obesity, infections, and exposure to ultraviolet radiation are currently available, and PAFs as a result of tobacco use and alcohol consumption are under development. Cancer Survival is the most recent addition, reflecting a major emphasis on developing comparable survival estimates across different income settings. Finally, Cancer Over Time is now under development; funds from the Danish Cancer Society to redevelop NORDCAN (Cancer statistics for the Nordic countries), in collaboration with the Association of Nordic Cancer Registries (http://ancr.nu), are supporting regional templates for detailed analyses of cancer incidence and mortality trends nationally.

Descriptive epidemiology of cancer

The Section's activities revolve around several major lines of research that use the databases held at CSU, including in-depth assessments of the international variations of specific cancer types, quantification of the major risk factors contributing to the current cancer burden, and an assessment of the long-term benefits of preventive interventions.

International geographical and temporal studies have been undertaken for cancers of the colorectum (Araghi et al., 2018, 2019a, b), lung (Miranda-Filho et al., 2019a), endometrium (Lortet-Tieulent et al., 2018), ovary, prostate, and testis (Gurney et al., 2019), and for haematological cancers (Miranda-Filho et al., 2018, 2019b). Time-trend studies increasingly incorporate future trends-based predictions to advocate for preventive actions for longer-term public health gains; for example, the studies on colorectal cancer highlight the increasing burden in recent generations (Figure 2) and the need to monitor and target interventions among young adults (Araghi et al., 2019a). Related to this, there is continuing work applying frailty models to estimate the proportion of individuals who are susceptible to age-related subtypes of testicular germ cell cancer, Hodgkin lymphoma, and nasopharyngeal carcinoma. CSU has also published several papers that have sought to highlight the increasing burden of cancer among older adults (Pilleron et al., 2019a, b, c).

The Section is increasingly engaged in a quantification of the potential impact of cancer prevention. CSU completed a comprehensive assessment of the established causes of cancer in France in 2018 (Arnold et al., 2018a, b; Cao et al., 2018; Kulhánová et al., 2018; Marant Micallef et al., 2018, 2019a; Menvielle et al., 2018; Shield et al., 2018a, b, c, d; Soerjomataram et al., 2018; Marant-

Figure 2. Trends in age-standardized or age-truncated incidence rates of (a) colon cancer and (b) rectal cancer in seven high-income countries. Reprinted from Araghi et al. (2019a), Copyright 2019, with permission from Elsevier.

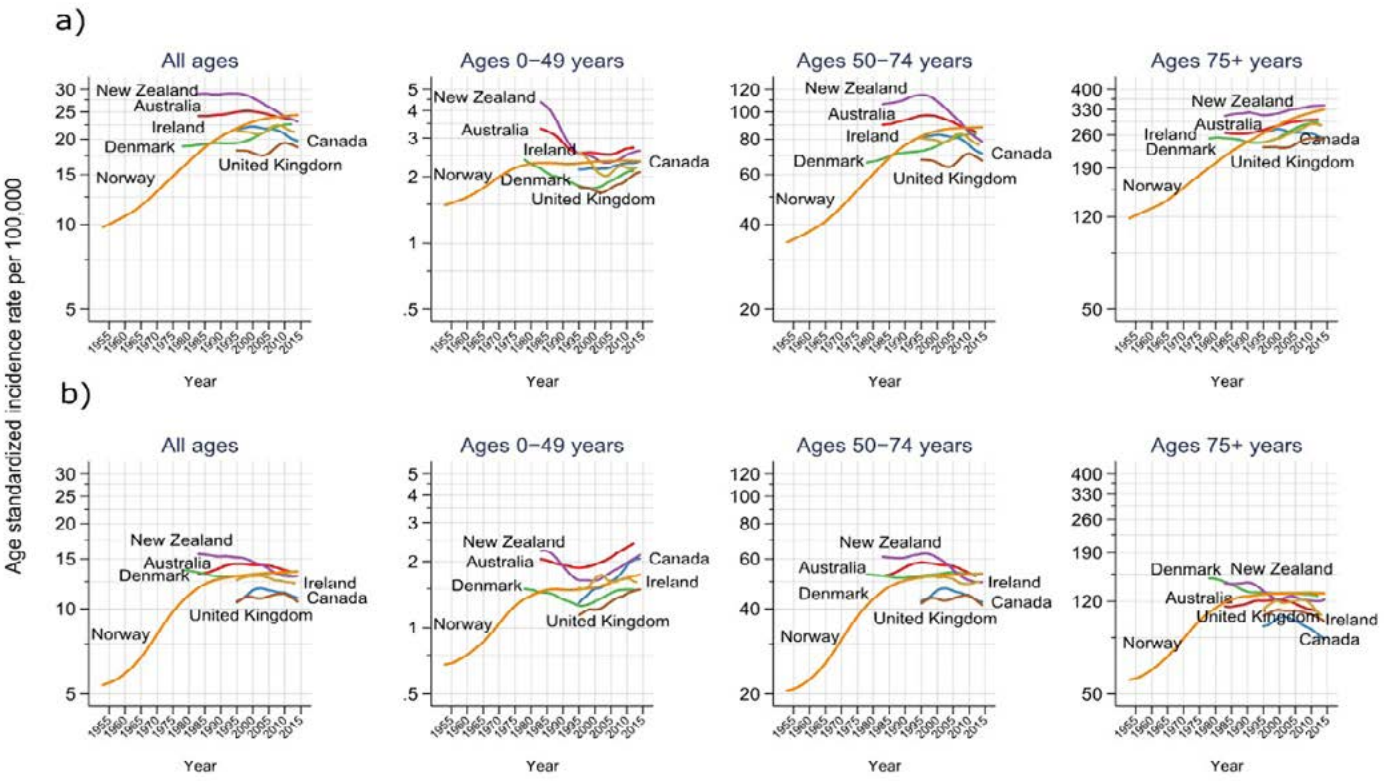
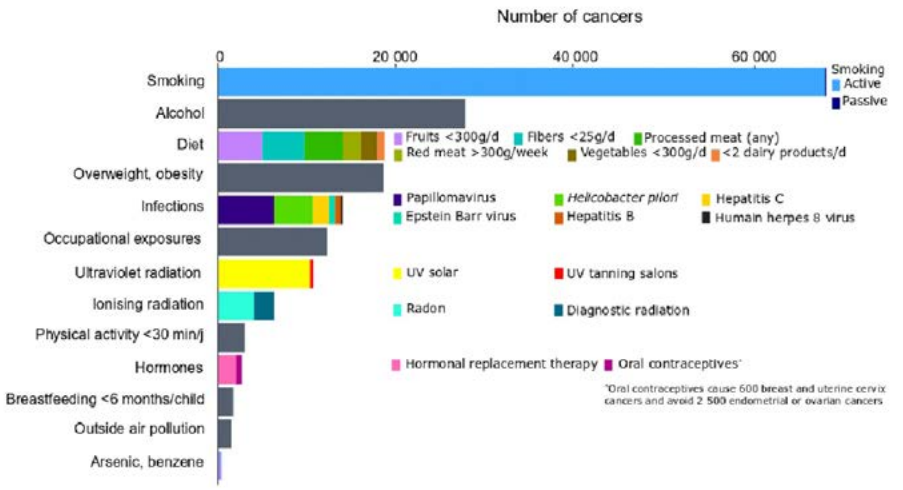


Figure 3. Number and proportion of cancer cases attributable to lifestyle and environmental factors in France in 2015, both sexes. Reprinted from Soerjomataram et al. (2018), Copyright 2018, with permission from Elsevier.



Micallef et al., 2019b; Touillaud et al., 2019), showing that 1 in 4 cancers are avoidable (Figure 3). Working across the relevant French authorities, the report (http://gco.iarc.fr/resources/paf-france_fr.php) serves as a basis for national prevention campaigns. CSU has also focused on specific risk factors globally, reporting on the burden related to exposure to ultraviolet radiation (Arnold et al., 2018c) and compiling the PAF estimates in Cancer Causes as part of the Global Cancer Observatory (Figure 1). A collaboration with colleagues from Cancer Council New South Wales, Australia, provided estimates of the cervical cancer burden until 2100 based on a scale-up of screening and human papillomavirus (HPV) vaccination programmes, driven by the ambitious Global Initiative for Cervical Cancer Elimination, led by the World Health Organization (WHO) (Simms et al., 2019); CSU also highlighted the importance of local population-based cancer registry data in achieving this goal (Baussano and Bray, 2019). Work is also continuing to estimate the impact of the implementation of effective tobacco control measures on the prevalence of tobacco use in Europe, based on measures of national adherence to the WHO Framework Convention on Tobacco Control.

A major component during this biennium has been the development of comparable population-based cancer survival estimates to assist planners in assessing the effectiveness of cancer services in different settings. Three international projects are under way: SURVMARK-2 (Cancer Survival in High-Income Countries), SURVCAN-3 (Cancer Survival in Countries in Transition), and SURVPOOL (A Consortium on Risk Factors and Cancer Survival). The first overview paper from SURVMARK-2 compared the survival of patients diagnosed with one of seven cancer types during 1995–2014 in seven countries (Figure 4), reporting marked progress in cancer control for several sites, while highlighting the extent to which international disparities persist (Arnold et al., 2019a). A recently published study that was part of SURVPOOL assessed the impact of lifestyle factors and demonstrated that duration and intensity of overweight were highly associated with poorer survival in women with breast and colorectal cancer (Arnold et al., 2019b). Further in-depth studies assessing the role of age, histology, and stage, among other factors, are in progress.

Childhood cancer

The Section's activities are fully aligned with the WHO Global Initiative for Childhood Cancer (GICC, https://www.who.int/cancer/childhood-cancer/en)

Figure 4. Age-standardized 5-year net survival by cancer site, country, and period of diagnosis, 1995–2014. Age-standardized net survival is for patients aged 15–99 years at diagnosis. The beginning of the arrow represents estimates for 1995–1999, and arrow heads from left to right refer to estimates for 2000–2004, 2005–2009, and 2010–2014. Australia includes New South Wales (1995–2012), Victoria, and Western Australia; Canada includes Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan; Ireland (1995–2013); the United Kingdom includes its four constituent countries: England, Scotland, Wales, and Northern Ireland; all other countries with national data (1995–2014). Reproduced from Arnold et al. (2019a). © 2019 World Health Organization; licensee Elsevier.

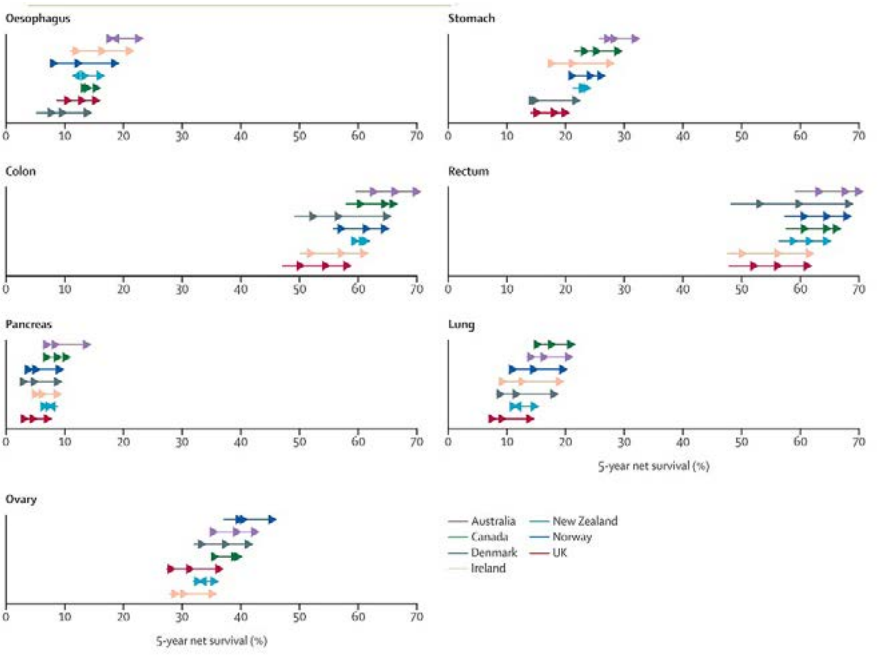
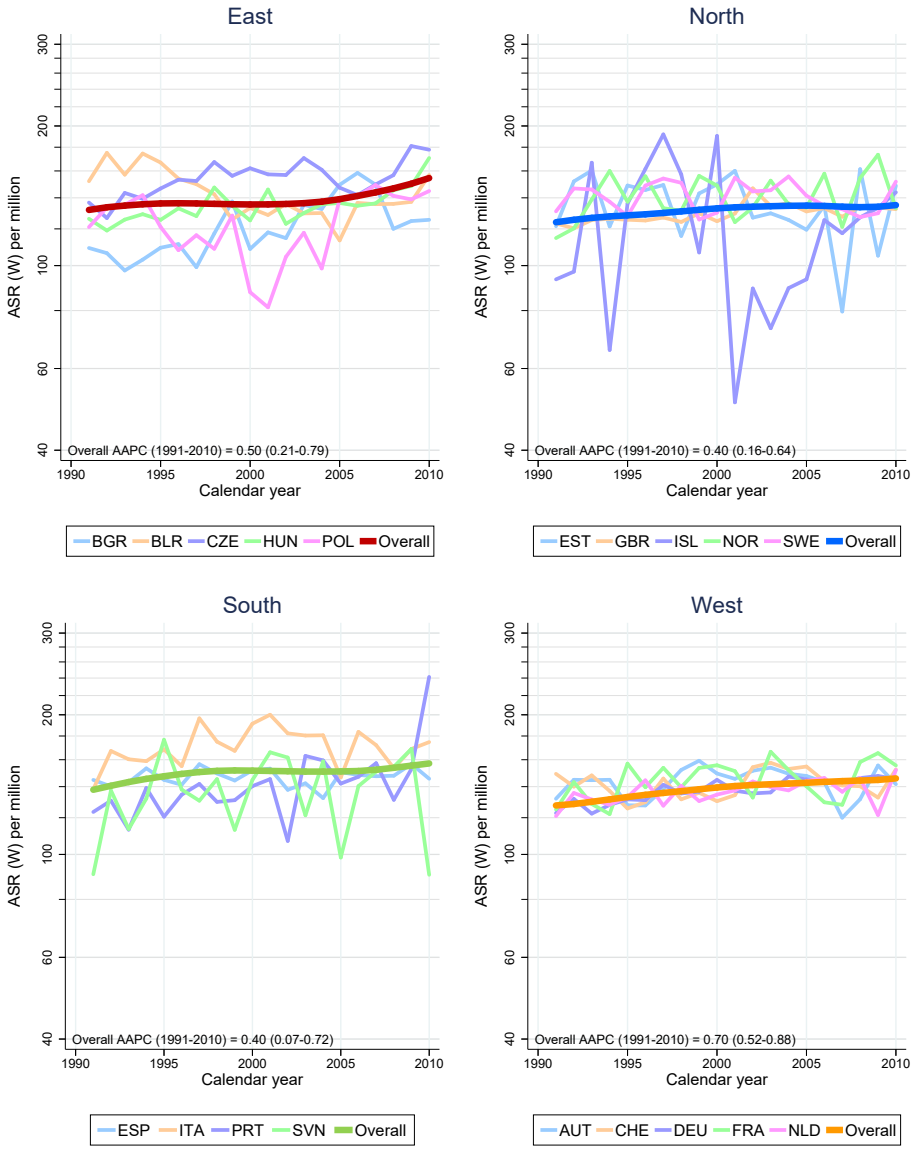


Figure 5. Trends in cancer incidence in children aged 0–14 years in Europe, 1991–2010. Thin lines are observed annual age-standardized (World) incidence rates (ASR) in countries; thick lines are the modelled incidence trends in each region of Europe. AAPC, average annual percentage change, with 95% confidence interval. Reprinted from Steliarova-Foucher et al. (2018), Copyright 2018, with permission from Elsevier.



and the unprecedented efforts to raise awareness of the impact of childhood cancer worldwide; specifically, there is an overwhelming need to reduce the marked disparities in childhood cancer survival observed between low- and high-income settings. Although cancer is relatively rare before the age of 20 years, recent research by CSU has shown that incidence rates of childhood cancer have been rising in the European Region (Steliarova-Foucher et al., 2018) (Figure 5). This highlights the need to continuously monitor the disease in every setting, particularly in LMICs, where underdiagnosis is an important determinant of poor survival (Steliarova-Foucher, 2019). The lack of population-based data in many LMICs impedes childhood cancer planning and treatment (Bhakta et al., 2019). Therefore, CSU, as a key partner of the GICC, is expanding the GICR programme to support the development of national childhood cancer registration in El Salvador, Ghana, Myanmar, Peru, the Philippines, Serbia, and Uzbekistan. A dedicated workshop with more than 100 participants from 50 countries was held at IARC in October 2019 and contributed multidisciplinary expertise to the development of a roadmap to improve the availability and quality of childhood cancer data globally.


IARC HANDBOOKS
COLORECTAL CANCER SCREENING
VOLUME 17
IARC HANDBOOKS OF CANCER PREVENTION
International Agency for Research on Cancer
World Health Organization
IARC MONOGRAPHS
STYRENE, STYRENE-7,8-OXIDE, AND QUINOLINE
VOLUME 121
IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS
International Agency for Research on Cancer
World Health Organization
WHO Classification of Tumours • 5th Edition
Digestive System Tumours
Edited by the WHO Classification of Tumours Editorial Board
World Health Organization

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Ms Helene Lorenzen-Augros (until June 2018)
Ms Lucy Shedden (until June 2019)

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Dr Kurt Straif (acting, until November 2018)

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WHO Classification of Tumours Group (WCT)

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Dr Laura Reguero Rodriguez de Liébana (until August 2019)

The Section of Evidence Synthesis and Classification (ESC), headed by Dr Ian Cree, comprises three Groups: the IARC Monographs Group (IMO), the IARC Handbooks Group (IHB), and the WHO Classification of Tumours Group (WCT).

The IARC Monographs Group (IMO), headed (acting) by Dr Mary Schubauer-Berigan, produces the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*, a series of systematic scientific reviews that identify environmental factors that may cause cancer in humans. IMO also organizes Advisory Groups and international scientific workshops on key issues pertaining to the assessment of carcinogens and their mechanisms.

The IARC Handbooks Group (IHB), headed by Dr Béatrice Lauby-Secretan, produces the *IARC Handbooks of Cancer Prevention*. This series of systematic scientific reviews identifies interventions and strategies that can reduce the risk of cancer or mortality from cancer.

The WHO Classification of Tumours Group (WCT), headed by Dr Ian Cree, produces the *WHO Classification of Tumours* series (also known as the WHO Blue Books). Now in its fifth edition as a series of 15 volumes, it provides the definitive and internationally accepted standards for the diagnosis of tumours.

For each volume of the *IARC Monographs*, the *IARC Handbooks*, and the *WHO Classification of Tumours*, IARC convenes international, interdisciplinary groups of expert scientists and physicians to systematically review the pertinent scientific literature and develop consensus evaluations and classifications. IARC selects these experts on the basis of their knowledge and experience as well as an absence of conflicting interests.

IARC Monographs Group (IMO)

The IARC Monographs Group (IMO) is responsible for producing the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*. The *IARC Monographs* are fundamental to the Agency's mission of identifying the preventable causes of human cancer. Since the inception of the *Monographs* programme in 1971, more than 1000 agents have been evaluated for carcinogenicity. This international, interdisciplinary endeavour provides an authoritative reference for researchers, health authorities, and the public. Health agencies worldwide rely on the *Monographs* for the scientific support of actions to control exposures and prevent cancer. In addition to producing this important resource, the scientific personnel of IMO contribute to the scientific literature on topics related to the methodology and contents of the *Monographs*.

Major accomplishments

IMO organized five Working Group meetings during the 2018–2019 biennium (Figure 1). The agents evaluated at the five Working Group meetings included

Figure 1. The Working Group meeting for IARC Monographs Volume 124, held in June 2019. © IARC.

Table 1. Summary of evaluations from the five *Monographs* meetings held in 2018–2019

Agent (Volume)	Evaluation[a]	Strength of evidence of cancer in humans (tumour type provided for *limited evidence*)	Strength of evidence of carcinogenicity in experimental animals	Key characteristics of carcinogens with strong evidence[b]
Styrene, Styrene-7,8-Oxide, and Quinoline (Volume 121)				
Styrene	Group 2A	*Limited* (lymphohaematopoietic malignancies)	*Sufficient*	Multiple (1, 2, 8, 10)
Styrene-7,8-oxide	Group 2A	*Inadequate*	*Sufficient*	Multiple (1, 2, 10)
Quinoline	Group 2B	*Inadequate*	*Sufficient*	2
Isobutyl Nitrite, β-Picoline, and Some Acrylates (Volume 122)				
Isobutyl nitrite	Group 2B	*Inadequate*	*Sufficient*	None
β-Picoline	Group 3	*Inadequate*	*Limited*	None
Methyl acrylate	Group 2B	*Inadequate*	*Sufficient*	None
Ethyl acrylate	Group 2B	*Inadequate*	*Sufficient*	Multiple (6, 10)
2-Ethylhexyl acrylate	Group 2B	*Inadequate*	*Sufficient*	None
Trimethylolpropane triacrylate	Group 2B	*Inadequate*	*Sufficient*	None
Some Nitrobenzenes and Other Industrial Chemicals (Volume 123)				
2-Chloronitrobenzene	Group 2B	*Inadequate*	*Sufficient*	None
4-Chloronitrobenzene	Group 2B	*Inadequate*	*Sufficient*	None
1,4-Dichloro-2-nitrobenzene	Group 2B	*Inadequate*	*Sufficient*	None
2,4-Dichloro-1-nitrobenzene	Group 2B	*Inadequate*	*Sufficient*	None
2-Amino-4-chlorophenol	Group 2B	*Inadequate*	*Sufficient*	None
ortho-Phenylenediamine and *ortho*-phenylenediamine dihydrochloride	Group 2B	*Inadequate*	*Sufficient*	2
para-Nitroanisole	Group 2B	*Inadequate*	*Sufficient*	None
N,*N*-Dimethylacetamide	Group 2B	*Inadequate*	*Sufficient*	None
Night Shift Work (Volume 124)				
Night shift work	Group 2A	*Limited* (breast, colorectum, prostate)	*Sufficient*	Multiple (6, 7, 10)
Some Industrial Chemical Intermediates and Solvents (Volume 125)				
Allyl chloride	Group 3	*Inadequate*	*Limited*	None
1-Bromo-3-chloropropane	Group 2B	*Inadequate*	*Sufficient*	10
1-Butyl glycidyl ether	Group 2B	*Inadequate*	*Sufficient*	10
4-Chlorobenzotrifluoride	Group 2B	*Inadequate*	*Sufficient*	None
Glycidyl methacrylate	Group 2A	*Inadequate*	*Sufficient*	Multiple (2[c], 10)[d]

[a] Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans.
[b] Numbers correspond to one or more of the 10 key characteristics of carcinogens, as identified by Smith et al. (2016; https://www.ncbi.nlm.nih.gov/pubmed/?term=26600562) and described in the Preamble to the *IARC Monographs* (https://monographs.iarc.fr/preamble-to-the-iarc-monographs/).
[c] In human primary cells.
[d] There is also strong evidence that glycidyl methacrylate belongs, based on mechanistic considerations, to a class of reactive agents (glycidyl epoxides) for which one member has been classified as probably carcinogenic to humans.

several that had been recommended as priorities for evaluation:

- Volume 121: Styrene, Styrene-7,8-Oxide, and Quinoline (20–27 March 2018)
- Volume 122: Isobutyl Nitrite, β-Picoline, and Some Acrylates (5–12 June 2018)
- Volume 123: Some Nitrobenzenes and Other Industrial Chemicals (9–16 October 2018)
- Volume 124: Night Shift Work (4–11 June 2019)
- Volume 125: Some Industrial Chemical Intermediates and Solvents (5–11 November 2019).

Table 1 presents the results of these meetings, highlighting the important contribution of the *Monographs* in evaluating the carcinogenicity of diverse agents. These agents range from chemicals tested only in animal bioassays to complex exposures that have been evaluated in epidemiological and mechanistic studies, such as night shift work.

The evaluations reached in these meetings included 24 classifications, comprising 14 agents never before evaluated by IARC and re-evaluations of 10 agents considered previously.

A concise summary of each evaluation with the classification, accompanying rationale, and key references is published in *The Lancet Oncology* within several weeks of each meeting. Full details and supporting data are provided in the complete *Monograph*, which is expected to be published about a year after a meeting. Both are available for free download from the *Monographs* website (https://monographs.iarc.fr/monographs-available/).

IMO also convened two Advisory Group meetings during the biennium:

- Advisory Group to Recommend an Update to the Preamble to the *IARC Monographs* (12–14 November 2018)
- Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 (25–27 March 2019).

The Advisory Group to Recommend an Update to the Preamble to the *IARC Monographs* comprised 21 experts from nine countries. Two invited specialists, seven representatives of national and international health agencies, three observers from interested organizations, and 16 members of the IARC/WHO secretariat also attended the meeting. This revision of the Preamble was a critical milestone for IARC, updating the rigorous criteria and procedures for the scientific review and evaluation of carcinogenic hazards by independent experts, free from vested interests (see https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf). An article describing the rationale for and new features of the revised Preamble was published in the *Journal of the National Cancer Institute*.

The Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024 comprised 29 scientists from 18 countries. The Advisory Group assessed the response to a public call for nominations and considered more than 170 unique candidate agents. A broad range of agents were recommended with high, medium, or low priority for evaluation, on the basis of evidence of human exposure and the extent of available evidence for evaluating carcinogenicity (see https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30246-3/fulltext and Tables 2 and 3). These recommendations will help to ensure that the *IARC Monographs* evaluations reflect the current state of scientific evidence relevant to carcinogenicity.

Publications

During the 2018–2019 biennium, the following *IARC Monographs* Volumes were published:

- Volume 122: Isobutyl Nitrite, β-Picoline, and Some Acrylates (2019)
- Volume 121: Styrene, Styrene-7,8-oxide, and Quinoline (2019)
- Volume 120: Benzene (2018)
- Volume 119: Some Chemicals That Cause Tumours of the Urinary Tract in Rodents (2019)
- Volume 118: Welding, Molybdenum Trioxide, and Indium Tin Oxide (2018)
- Volume 117: Pentachlorophenol and Some Related Compounds (2019)
- Volume 116: Drinking Coffee, Mate, and Very Hot Beverages (2018)
- Volume 115: Some Industrial Chemicals (2018)
- Volume 114: Red Meat and Processed Meat (2018)
- Volume 113: DDT, Lindane, and 2,4-D (2018).

IARC Scientific Publication No. 165 (Tumour Site Concordance and Mechanisms of Carcinogenesis) was also published during the biennium.

Table 2. Agents recommended for evaluation by *IARC Monographs* during 2020–2024 with high priority[a]

Agent name	Rationale
Agents not previously evaluated by IARC Monographs	
Haloacetic acids (and other disinfection by-products)	Relevant human cancer, bioassay, and mechanistic evidence
Metalworking fluids	Relevant human cancer and bioassay evidence
Cannabis smoking, fertility treatment, glucocorticoids, *Salmonella typhi*, sedentary behaviour[b], tetracyclines and other photosensitizing drugs	Relevant human cancer and mechanistic evidence
Cupferron, gasoline oxygenated additives, gentian violet, glycidamide, malachite green and leucomalachite green, oxymetholone, pentabromodiphenyl ethers, vinclozolin	Relevant bioassay and mechanistic evidence
Breast implants, dietary salt intake[b], neonatal phototherapy[b], poor oral hygiene[b]	Relevant human cancer evidence
Aspartame	Relevant bioassay evidence
Arecoline, carbon disulfide, electronic nicotine delivery systems and nicotine[b], human cytomegalovirus, parabens	Relevant mechanistic evidence
Agents previously evaluated by IARC Monographs[c]	
Automotive gasoline (leaded and unleaded), carbaryl, malaria	New human cancer, bioassay, and mechanistic evidence to warrant re-evaluation of the classification
Acrylamide[b], acrylonitrile, some anthracyclines, coal dust, combustion of biomass, domestic talc products, firefighting exposure, metallic nickel, some pyrethroids (i.e. permethrin, cypermethrin, deltamethrin)	New human cancer and mechanistic evidence to warrant re-evaluation of the classification
Aniline, acrolein, methyl eugenol and isoeugenol[b], multiwalled carbon nanotubes[b], non-ionizing radiation (radiofrequency)[b], some perfluorinated compounds (e.g. perfluorooctanoic acid)	New bioassay and mechanistic evidence to warrant re-evaluation of the classification
Estrogen:estradiol and estrogen–progestogens[d], hydrochlorothiazide, Merkel cell polyomavirus, perchloroethylene, very hot foods and beverages	New human cancer evidence to warrant re-evaluation of the classification
1,1,1-Trichloroethane, weapons-grade tungsten/nickel/cobalt alloy	New bioassay evidence to warrant re-evaluation of the classification
Acetaldehyde, bisphenol A[b], cobalt and cobalt compounds, crotonaldehyde, cyclopeptide cyanotoxins, fumonisin B_1, inorganic lead compounds, isoprene, *o*-anisidine	New mechanistic evidence to warrant re-evaluation of the classification

[a] Evidence of human exposure was identified for all agents.
[b] Advisory Group recommend an evaluation in the latter half of the 5-year period.
[c] See https://monographs.iarc.fr/list-of-classifications-volumes/ for list of current classifications.
[d] Group 1 carcinogen; new evidence of cancer in humans indicates possible causal association(s) for additional tumour site(s) (see Section 3 of Preamble to the *IARC Monographs*, https://monographs.iarc.fr/preamble-to-the-iarc-monographs/).

Table 3. Agents recommended for evaluation by *IARC Monographs* during 2020–2024 with medium and low priority[a]

Agent name	Previous evaluation status
Medium-priority agents	
2,3-Butanedione (diacetyl), alachlor, biphenyl, chlorinated paraffins, chlorpyrifos, C.I. Direct Blue 218, diphenylamine, hydrazobenzene, indole-3-carbinol, mancozeb, nanomaterials (e.g. titanium dioxide or nanosilica), nitrogen dioxide, *o*-benzyl-*p*-chlorophenol, ozone, pendimethalin, sleep, styrene-acrylonitrile trimer, terbufos, tris(chloropropyl)phosphate	Agents not previously evaluated by *IARC Monographs*
Aflatoxins[b], anthracene, antimony trioxide, atrazine, bromate compounds, dimethyl hydrogen phosphite, furan, *N*-methylolacrylamide, *p*-nitrotoluene, *Schistosoma mansoni*, tris(2-chloroethyl) phosphate, tobacco smoking (including second-hand)[b]	Agents previously evaluated by *IARC Monographs*[c]
Low-priority agents	
2-Hydroxy-4-methoxybenzophenone, aluminium, androstenedione, butyl methacrylate, cinidon ethyl, dysbiotic microbiota, fonofos, furmecyclox, isoflavones, isophorone, laboratory work and occupation as a chemist, methanol, *S*-ethyl-*N*,*N*-dipropylthiocarbamate, semiconductor manufacturing, sucralose	Agents not previously evaluated by *IARC Monographs*
1,1-Dimethylhydrazine, benzophenone-1, carbon black, catechol, chlordecone, cumene, dichloromethane, hepatitis D virus, human papillomavirus (beta (cutaneous) and some alpha (mucosal) types), *Opisthorchis felineus*, outdoor air pollution[b], pyrrolizidine alkaloids, selenium and selenium compounds	Agents previously evaluated by *IARC Monographs*[c]

[a] Evidence of human exposure was identified for all agents.
[b] Group 1 carcinogen; new evidence of cancer in humans indicates possible causal association(s) for additional tumour site(s) (see Section 3 of Preamble to the *IARC Monographs*, https://monographs.iarc.fr/preamble-to-the-iarc-monographs/).
[c] See https://monographs.iarc.fr/list-of-classifications-volumes/ for list of current classifications.

IARC Handbooks Group (IHB)

The IARC Handbooks Group (IHB) is responsible for producing the IARC *Handbooks of Cancer Prevention*. The objective of the *IARC Handbooks* is to publish critical reviews and evaluations of interventions and strategies that can reduce the burden of cancer. The principles of systematic review are applied to the identification, screening, synthesis, and evaluation of the evidence. Interventions or strategies are selected for evaluation on the basis of published scientific evidence of preventive effects and potential public health relevance. *Handbooks* evaluations have included chemopreventive agents, preventive actions, effectiveness of screening, and effectiveness of tobacco control. The *Handbooks* are used worldwide by public health representatives to set guidelines and recommendations for cancer prevention.

Major accomplishments

IHB organized three meetings during the biennium: the Working Group meeting for *IARC Handbooks* Volume 17 (Colorectal Cancer Screening), an Advisory Group meeting to Recommend an Update to the Preambles to the *IARC Handbooks* (previous referred to as the *IARC Handbooks* Working Procedures), and a scoping meeting for *IARC Handbooks* Volume 18 (Cervical Cancer Screening).

Volume 17: Colorectal Cancer Screening (14–21 November 2017)

The outcome of the meeting was published in *The New England Journal of Medicine* in March 2018 (Table 4). The full report is available for free download in PDF format from the IARC Publications website (http://publications.iarc.fr/573).

Table 4. *IARC Handbooks* Volume 17: Summary of the evaluations of the different colorectal cancer screening techniques

Screening technique	Strength of evidence		
	Reduction in CRC incidence	Reduction in CRC mortality	Benefit–harm ratio
Biennial screening with gFOBT without rehydration	*Evidence suggesting lack of effect*	*Sufficient*	*Sufficient*
Annual or biennial screening with gFOBT of higher sensitivity	*Limited*	*Sufficient*	*Sufficient*
Biennial screening with FIT	*Limited*	*Sufficient*	*Sufficient*
Single screening with sigmoidoscopy	*Sufficient*	*Sufficient*	*Sufficient*
Single screening with colonoscopy	*Sufficient*	*Sufficient*	*Sufficient*
Single screening with CTC	*Limited*	*Limited*	*Inadequate*

CRC, colorectal cancer; CTC, computed tomography colonography; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test.

Update to the Preambles (11–13 February 2019)

IARC convened an Advisory Group to Recommend an Update to the Preambles to the *IARC Handbooks* (previously referred to as the *IARC Handbooks* Working Procedures), to reflect on the scientific developments and procedural changes that have occurred in the fields of primary and secondary prevention. This was the first update of the procedures by an external Advisory Group since the launch of the *Handbooks* programme, in 1995, and represents a major milestone in the development of the programme. The Advisory Group made recommendations on several overarching issues, including the scope of the programme, future priorities, transparency of the systematic review process, and evaluation schemes. The Advisory Group also recommended that IARC continue to develop approaches to disseminate the findings of the *Handbooks*.

An internal Advisory Group Report explains the process followed and highlights the main updates. The Instructions for Authors, which constitute the documentation used for implementing the principles laid out in the Preambles, have been revised in line with the updated Preambles.

All documents listed are available on the *Handbooks* website (http://handbooks.iarc.fr/).

Volume 18: Cervical Cancer Screening (scoping meeting, 14–16 October 2019)

Cervical cancer screening will be re-evaluated at a meeting on 23–30 June 2020, at which new screening technologies, including human papillomavirus (HPV) testing, and the implementation of screening in the context of HPV vaccination will be considered. This *Handbook* is an integral part of the WHO Global Cervical Cancer Elimination Initiative, launched following the call by Dr Tedros Adhanom Ghebreyesus at the World Health Assembly in May 2018. This will be the first close collaboration between the *Handbooks* programme and WHO, and will allow the *Handbooks* evaluations to be considered during the WHO process to develop recommendations.

Publications

- Volume 16 of the *IARC Handbooks*, Absence of Excess Body Fatness, was published online in October 2018 and in print in July 2019.
- Volume 17 of the *IARC Handbooks*, Colorectal Cancer Screening, was published online in June 2019 and in print in October 2019.

WHO Classification of Tumours Group (WCT)

The WHO Classification of Tumours Group (WCT) was established in 2017 and took over the publication of the WHO Classification of Tumours series (also known as the WHO Blue Books). Previously published in its 12-volume fourth edition, the series was revised for its 15-volume fifth edition to encompass the formation of a formal *WHO Classification of Tumours* Editorial Board to advise IARC on content (Figure 2). The WHO Blue Books are of considerable importance in both cancer diagnosis and research, and provide the international criteria and standards against which tumours are diagnosed. The definitive diagnosis and classification of individual cancers in turn underpins research into cancer causation, prevention, diagnosis, and treatment.

During the 2018–2019 biennium, the following volumes were published:

- *WHO Classification of Skin Tumours*, fourth edition (2018)
- *WHO Classification of Tumours of the Eye*, fourth edition (2018)
- *Digestive System Tumours*, fifth edition (2019)
- *Breast Tumours*, fifth edition (2019).

Pathology is currently undergoing a more rapid transformation than at any time during the past 30 years, as a result of the introduction of new technologies. Whereas cancer classification has previously been based on consensus of histopathological opinion, the understanding of cancer at a molecular level is now at a point where it needs to be integrated into diagnosis. In addition, digital pathology and image analysis are producing new insights and providing quantitative justification of many existing diagnostic criteria, while challenging others. Finally, the pace of improvement in computer technology, including artificial intelligence, is already producing clinically applicable aids to diagnosis, and this trend is likely to accelerate. There is an urgent need to integrate these facets of diagnosis into cancer classification.

WCT provides a timely, definitive synthesis for tumour classification based on an expert consensus review of reproducible peer-reviewed published evidence. Dr Iciar Indave, appointed as systematic reviewer, ensures that the methods used by WCT to assess evidence are as robust as possible given the volume of information available and the timescale for updates.

The WHO Blue Books are available in multiple formats to meet the needs of users in low-, middle-, and high-income countries. The new website, launched

Figure 2. The first meeting of the WHO Classification of Tumours Editorial Board. © IARC.

in September 2019, provides a platform from which additional content can be added to the volumes, including whole slide images of histopathology and clinical images including radiology. WCT works in collaboration with other organizations to advance the practice of high-quality cancer pathology diagnostic practice and research globally. The WHO Blue Books provide an invaluable resource for both trainee junior pathologists and experienced pathologists.

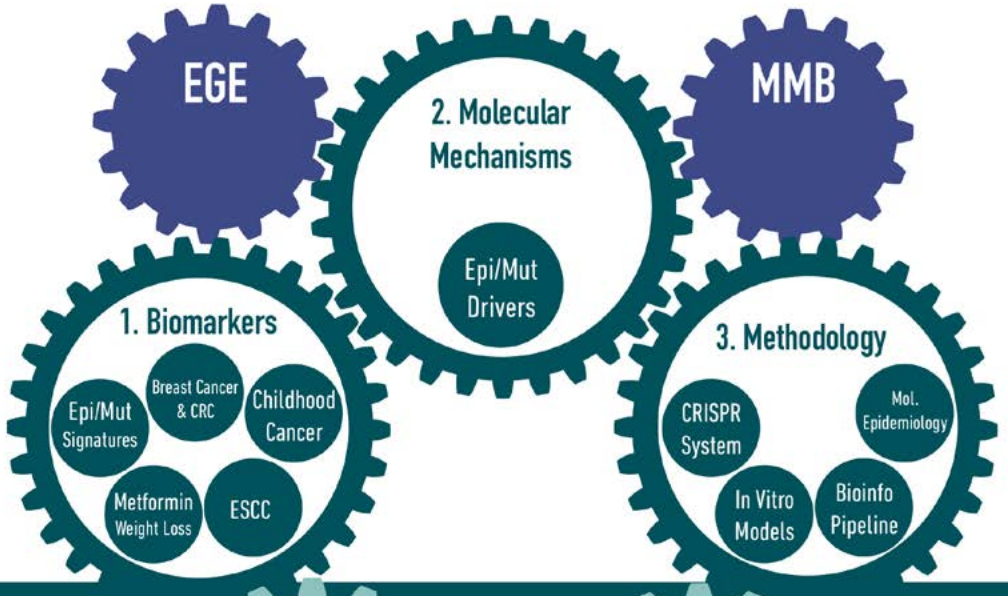
Finally, WCT collaborates with other researchers, particularly in computational pathology, molecular pathology, and evidence-based pathology evaluations (systematic reviews). WCT hosts the histology laboratory, run by a laboratory scientist and supervised by highly experienced pathologists, providing a centralized service for histopathology to IARC.

Themes & Projects

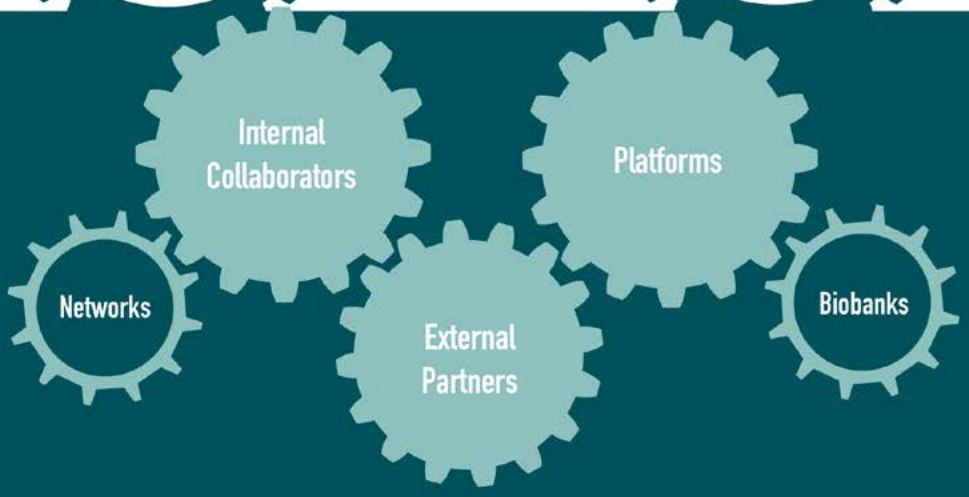
1. Identify (epi)genetic biomarkers of exposure and cancer risk to reinforce epidemiological associations

2. Investigate functional role of (epi)genetic changes and deregulated pathways induced by environmental exposures to provide biological plausibility

3. Develop (epi)genomic methodologies, profiling strategies, bioinformatics/ biostatistics tools and state-of-the-art in vitro models



Enabling Resources & Collaborators



Networks:
EpiMARK, MetBreCS, EXPOsOMICS, I4C, CLIC, EpiEARLY, PACE, CHARGE, ESCCAPE, Mutographs, PRECAMA, LYRICAN

Internal Collaborators:
BMA, ENV, GEP, GCS, ICB, IMO, NEP, NME, WCT, ITS

External Partners:
DKFZ-Heidelberg, CeMM, IGR-Paris, Univ. Oslo, Imperial College London, Duke-NUS/NCC Singapore, Univ-Minnesota, Univ-Maastricht, IEO-Milan, ISS-Rome, Mount Sinai NY, INCA-Rio, Korean Natl Cancer Institute, Sanger Inst, CRCL-Lyon, King's College London

Platforms:
NextSeq, MiSeq, Illumina BreadArray, Pyrosequencer, IP-Star Robot

Biobanks:
IARC, EPIC, I4C, DKFZ-Heidelberg, IGR-Paris, Univ-Oslo, Univ-Melbourne, Barretos, UCSD, IEO-Milan, ISS-Rome

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Ms Cedrine Milesi
Ms Lya Parres
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Ms Cleandra Silva
(until August 2018)
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The main objective of the Section of Mechanisms of Carcinogenesis (MCA) is to provide the evidence base for the study of cancer causation and prevention by elucidating the molecular mechanisms by which genetic and epigenetic alterations resulting from environmental exposures and lifestyle alter critical molecular pathways and promote cancer development. The primary aims of MCA's studies are: (i) to elucidate genetic and epigenetic changes and molecular pathways induced by environmental exposures in cancer causation; (ii) to identify specific molecular changes ("signatures" of exposure) to environmental risk factors and biomarkers of cancer risk; and (iii) to develop (epi)genomic methodologies, profiling strategies, and bioinformatics tools and resources that are applicable to biobanks associated with population-based studies coordinated by IARC and external collaborators. These aims are achieved by bringing together skills in laboratory sciences, molecular epidemiology, and bioinformatics, and capitalizing on existing and developing new, multidisciplinary projects that exploit recent conceptual and technological advances as well as the uniqueness and strengths of IARC. MCA also contributes to the development of translational studies, through the discovery of mechanism-based biomarkers of exposure and cancer risk, and to cancer research that is relevant to, although not exclusive to, low- and middle-income countries. New and original research topics developed by MCA take advantage of state-of-the-art, powerful molecular and/or cell biology and functional genomics tools, recent progress in understanding of the cancer (epi) genome, and the development of genomics databases and new bioinformatics tools. These advances have facilitated the development of a multifaceted research programme aimed at identifying molecular changes associated with exposure to risk factors and providing biological plausibility for the associations that are detected in epidemiological studies. These developments have also led to synergies among several programmes at IARC and have enhanced collaborations across different Groups and/or Sections and with external researchers, creating added value for IARC's scientific activities. The Section comprises two Groups – the Epigenetics Group (EGE) and the Molecular Mechanisms and Biomarkers Group (MMB) – that work in close collaboration to create synergies and better exploit and further expand unique research tools and expertise.

Epigenetics Group (EGE)

The overarching aim of the Epigenetics Group (EGE) is to advance the understanding of the role of epigenetic changes and pathways induced by environmental factors in cancer causation, underpinning studies of etiology, carcinogen evaluation, and prevention. EGE exploits new concepts in cancer epigenetics, the availability of unique population-based cohorts, and recent technological advances in epigenomics (Van Baak et al., 2018; Woo et al., 2018; Josipović et al., 2019; Küpers et al., 2019; Patil et al., 2019). 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 (Felix et al., 2018; Herceg et al., 2018; Alcala et al., 2019).

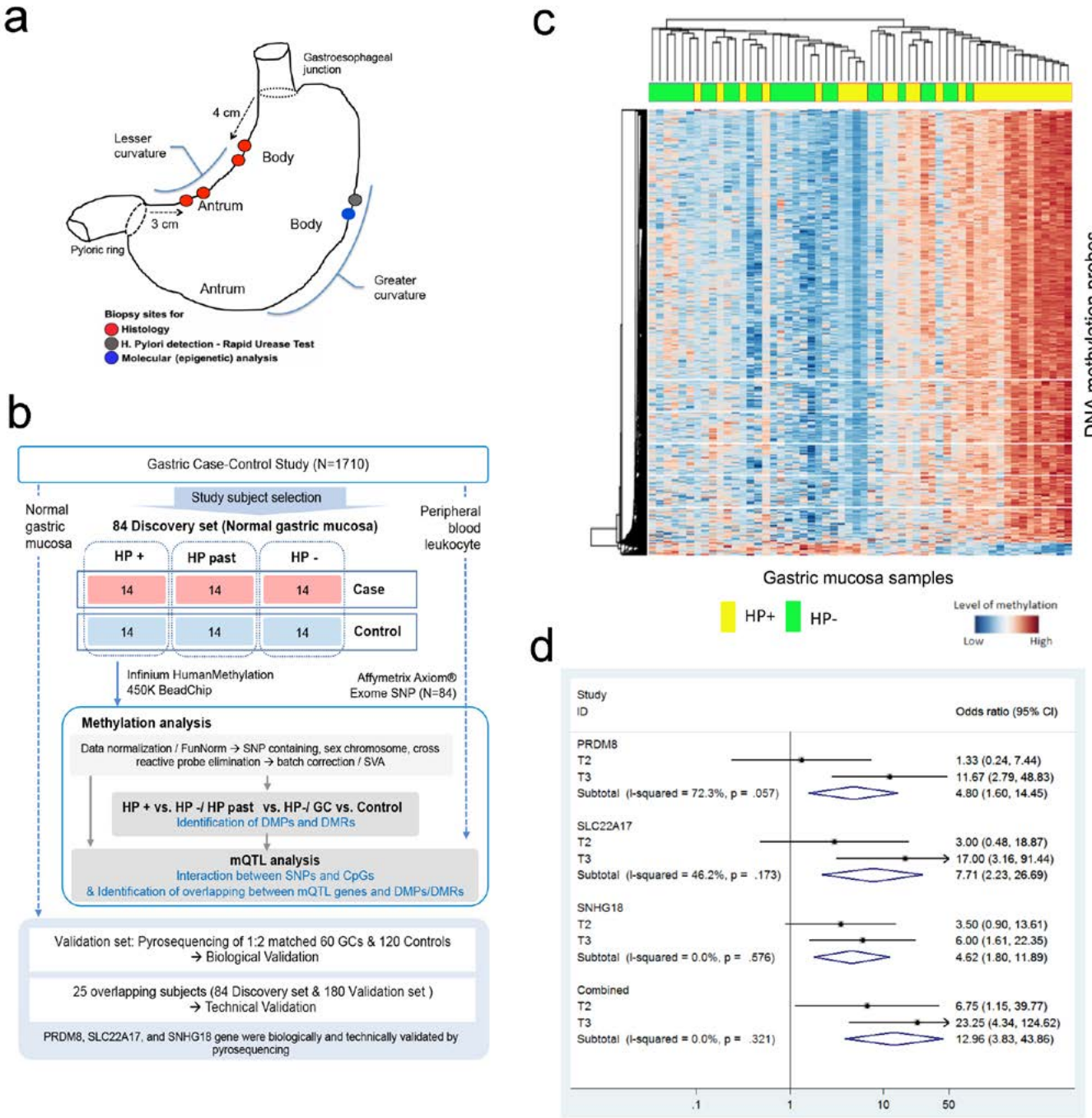
Genome-wide profiling of normal gastric mucosa to identify *Helicobacter pylori*-associated epigenetic changes associated with cancer risk

Infection with the bacterium *Helicobacter pylori* is thought to be the single most common cause of gastric cancer, which is the third most common cause of cancer-related deaths worldwide. EGE investigated the impact of both current *H. pylori* infection and epigenetic memory of past (eradicated) infection on aberrant epigenetic (DNA methylation) patterns. In collaboration with the National Cancer Center of the Republic of Korea, EGE analysed a series of normal gastric mucosa from cases and controls representing various *H. pylori* and gastric cancer statuses using genome- and epigenome-wide approaches (Woo et al., 2018). A total of 438 differentially methylated regions (DMRs) were associated with *H. pylori* infection, most of which showed marked reversibility, albeit selective stability of specific DMRs ("epigenetic memory"), after *H. pylori* clearance. Interestingly, 152 DMRs were associated with cancer risk independent of *H. pylori* status in normal gastric mucosa (Figure 1). The comprehensively characterized methylome changes associated with *H. pylori* infection and gastric cancer risk in this study may serve as potential biomarkers for early cancer progression in tumour-free gastric mucosa.

Pan-cancer genome and transcriptome analysis and orthogonal experimental assessment of epigenetic driver genes and their link to environmental carcinogens

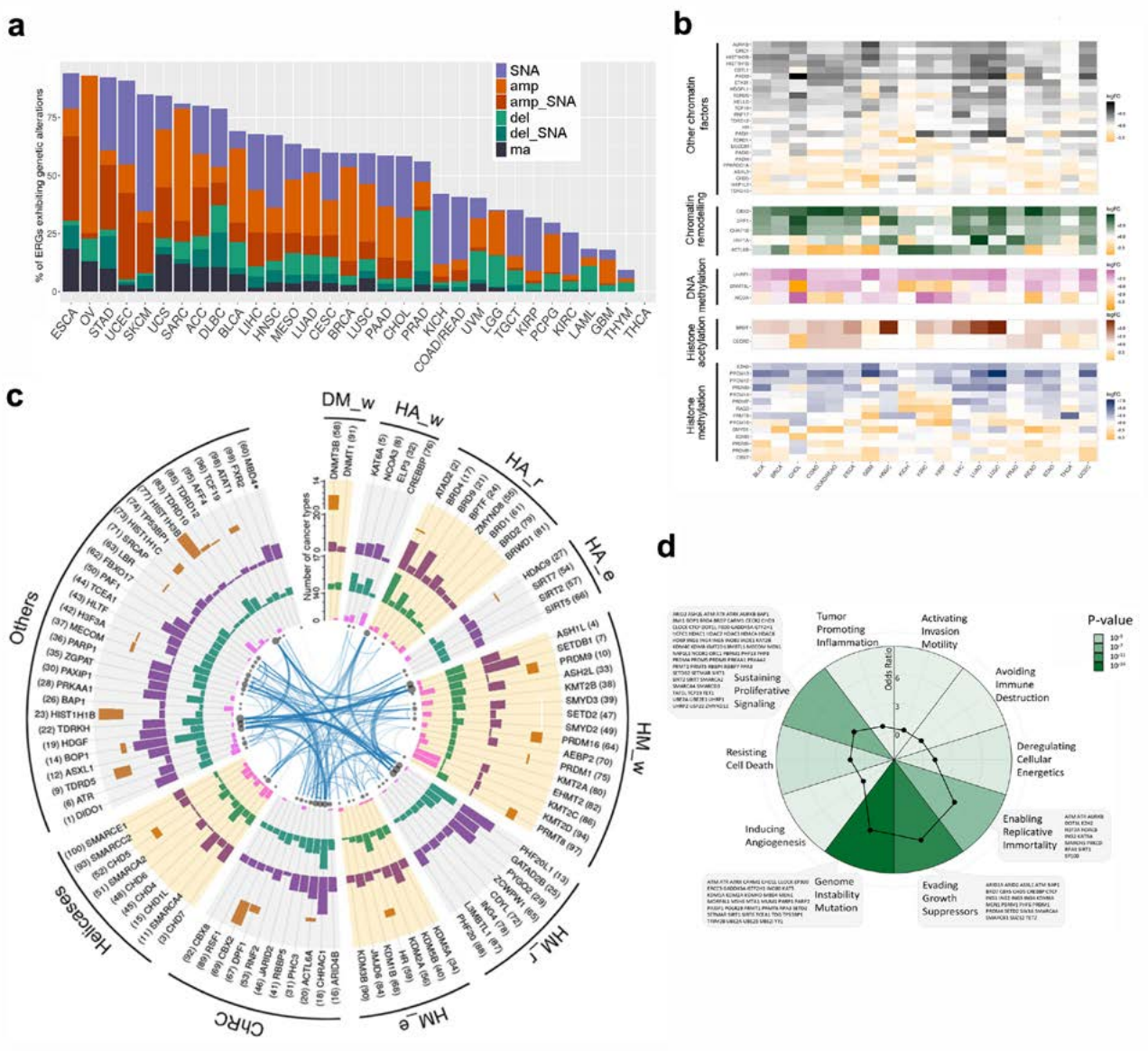
The recent discovery of numerous genetic alterations in the genes that directly regulate the epigenome (referred to here as epigenetic regulator genes [ERGs]) in human cancers sparked a debate on whether these genes potentially act as drivers of tumorigenesis and on the mechanisms that fuel epigenome changes that are rampant in human malignancies. EGE developed and tested a conceptual framework for experimental identification and functional characterization of the mechanistically important epidrivers that reshape the epigenome and contribute to cancer phenotypes (see text box). First, the Group conducted a pan-cancer and integrative analysis of global genetics- and transcriptome-based disruption of a curated list of 426 ERGs in 33 cancer types on the basis of sequencing information from 10 845 tumour samples and 730 normal tissues (see text box). A high rate of alterations in ERGs was

Figure 1. DNA methylome profiling of normal gastric mucosa by *Helicobacter pylori* infection status. (a) Gastric mucosa biopsy samples for molecular (epigenetic) analysis were obtained from the greater curvature of the gastric body (blue circle). (b) Flow chart illustrating the overall design of the study. Subjects were stratified by *H. pylori* infection status (current [HP+], negative [HP−], or past [HP past]) and cancer status (case or control), and were matched for age, sex, and Laurén classification (for cases). (c) Cluster heat map analysis of differentially methylated positions (DMPs) with delta β ≥ 20%. The rows represent probes for the 1924 DMPs, and the columns represent individual HP+ and HP− samples. The cells are coloured according to the level of methylation. Among these DMPs, 52 CpG sites (2.7%) were hypomethylated and 1872 (97.3%) were hypermethylated. (d) Putative biomarker genes for gastric cancer incidence and their combined methylation score. Odds ratios and 95% confidence intervals (CIs) of gastric cancer by tertile (T) of methylation levels for three putative biomarker genes. DMR, differentially methylated region; mQTL, methylation quantitative trait loci; SNP, single-nucleotide polymorphism. Figure adapted from Woo et al. (2018). © 2018 IARC/WHO; licensed by UICC.



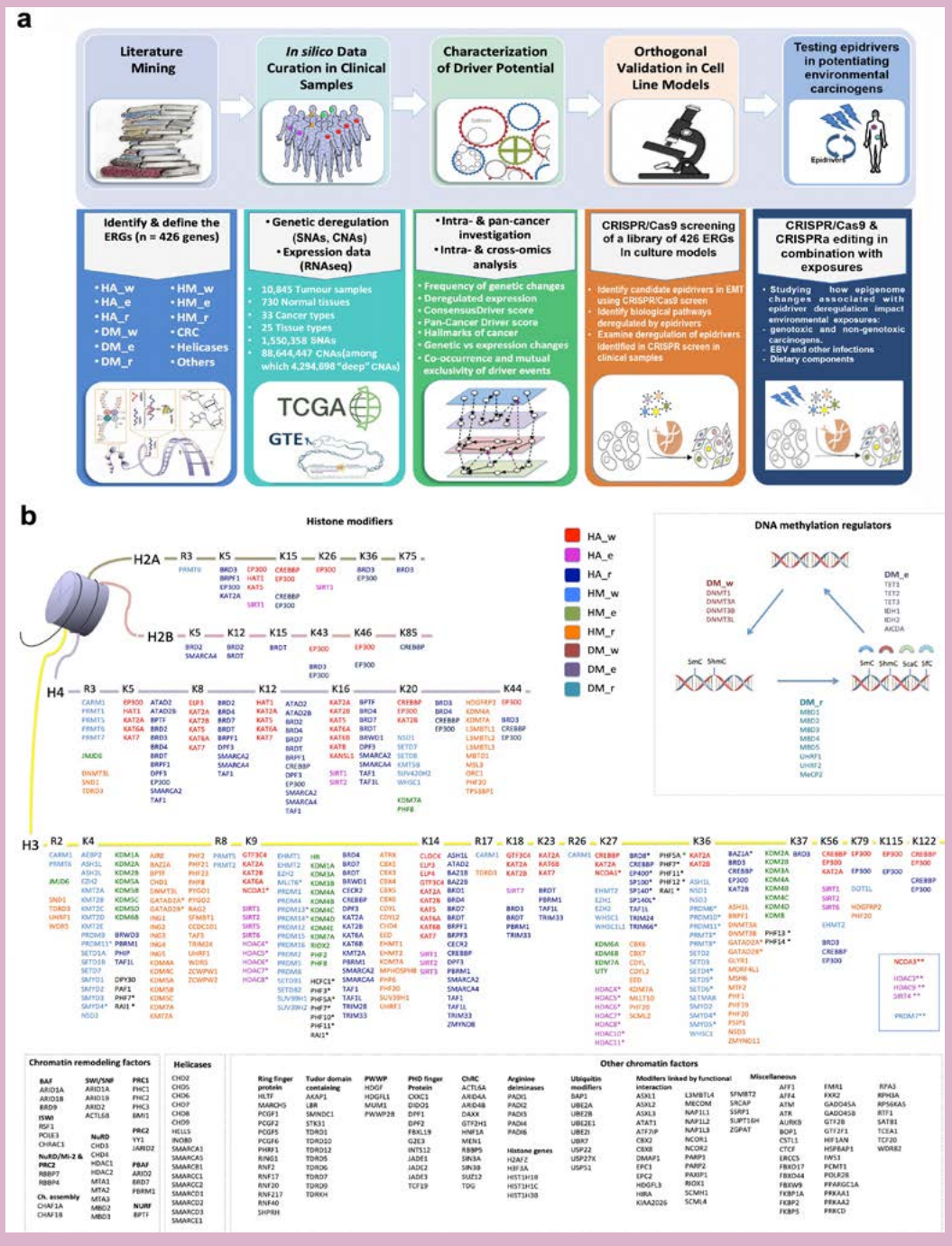
identified for most cancer types, with recurrent pan-cancer mutations and copy number alterations (CNAs) in specific ERGs or classes of ERGs, which were tightly linked to changes in gene expression (Figure 2). Further, EGE applied a novel bioinformatics approach (Pan-Cancer Driver) that integrates the strengths of various driver prediction algorithms and accounts for multiple –omics layers, to reveal ERGs with driver potential in cancer (Figure 2). Finally, the

Figure 2. Pan-cancer genome discovery of epigenetic driver genes. (a) Pan-cancer analysis of genetic alterations across epigenetic regulator gene (ERG) categories and classes. The bar plot shows the percentage of ERGs exhibiting different types of genetic deregulation by cancer type. Genetic alterations: single-nucleotide alteration (SNA), deep copy number amplification (amp), deep amplification co-occurring with SNA (amp_SNA), deep copy number deletion (del), deep deletion co-occurring with SNA (del_SNA), and multiple alterations (ma). ERGs are considered altered (deep amplification, deep deletion, or SNA) if at least 1% of samples harbour these alterations. (b) The heat maps show the most differentially expressed ERGs comparing tumour samples with adjacent normal tissues among cancer types. Only the top differently expressed ERGs with |log fold change (FC)| > 3 and false discovery rate (FDR) < 0.05 are annotated. (c) Characterization of the driver potential of ERGs. Top 100 ERGs by pan-cancer driver score using SNA (5% of samples), copy number alteration (CNA) (5% of samples), and expression data (15% of samples with significant z-score or FDR < 0.05 with $\log_2$ FC > 1). Results are presented as bar plots counting the number of cancers in which a given gene has a particular genomic or expression alteration. From inner to outer track: pink, SNAs; green, CNAs; purple, z-score; orange, log2 FC. Genes are aggregated by their functional features. (d) The spider pie chart shows enrichment of the 426 ERGs in pathways affecting the 10 hallmarks of cancer; the corresponding *P* values are illustrated by green gradients and the odds ratios by black spots. The names of ERGs overlapping with the four significantly enriched hallmarks are indicated. Figure based on EGE work (unpublished). © IARC.



Group developed and applied epigenome-wide functional screens (based on the CRISPR/Cas9 system) targeting all 426 ERGs in vitro and identified candidate ERGs with a driver role conferring on cancer cells the traits associated with the hallmarks of cancer. This is the largest and most comprehensive analysis to date of the cancer-associated disruption of ERGs and is the first experimental effort to specifically identify epidrivers in oncogenic processes, providing crucial insights into the deregulation of ERGs and their functional impact in cancer (Halaburkova et al., 2019). Current and future studies (in collaboration with MMB and external partners) are aimed at examining how epidriver events synergize with environmental carcinogens in cancer causation.

General pan-cancer genomic and experimental strategy for identifying and characterizing epigenetic driver genes and their environmental determinants. (a) A five-stage approach adopted to identify and assess epigenetic regulator genes (ERGs) with driver potential includes: (1) comprehensive literature mining, (2) in silico data curation in clinical samples, (3) modelling the driver potential of candidate genes, (4) CRISPR/Cas9 screen for orthogonal in vitro assessment of driver potential, and (5) characterizing the synergy between epidrivers and environmental exposures. (b) A compendium of ERGs included in the study, comprising 426 ERGs categorized as histone modifiers, chromatin remodellers, or DNA methylation regulators. Histone acetylation, histone methylation, and DNA methylation modifiers are further stratified as "writers" (w), "editors" (e), or "readers" (r). The remaining ERGs are categorized as chromatin remodelling factors (ChRC), helicases, or other chromatin modifiers (some of which are further divided into subgroups on the basis of function or their presence in molecular complexes). An asterisk (*) denotes the histone-modifying genes whose functions are not well characterized and which are therefore assigned based on Encyclopedia of DNA Elements (ENCODE) chromatin immunoprecipitation (ChIP) sequencing data; two asterisks (**) denote the histone-modifying genes without assignment of residues in the histone tails. CNA, copy number alteration; EBV, Epstein–Barr virus; EMT, epithelial-to-mesenchymal transition; GTEx, Genotype-Tissue Expression database; SNA, single-nucleotide alteration; TCGA, The Cancer Genome Atlas.



Epigenetic regulation of the mitochondrial genome in cancer

In a recent study, EGE examined epigenetic modification in the genome of mitochondria, the powerhouses of cells, and revealed the first reported evidence of DNA methylation patterns of the mitochondrial genome at high resolution. Notable differences were seen between the methylation patterns in normal cells and in cancer cells (Figure 3). The study examines the technical considerations that have so far impeded the study of mitochondrial epigenetics, and addresses the potential functional consequences of methylation of mitochondrial DNA in cancer (Patil et al., 2019). Cancer cells have a greater need for energy compared with normal cells, and mitochondrial dysfunction plays an important role in tumorigenesis. These findings could lead to new methods of identifying novel cancer biomarkers or targeting the energy metabolism of cancer cells.

Identifying epigenetic changes induced by in utero and adult-life exposures and their causal relationship with cancer

EGE leads a multidisciplinary study investigating the causal relationship between in utero and later-life exposures and an increased risk of cancer in childhood and adulthood. Building on a unique epigenetic epidemiology framework at IARC and several major international consortia, the Group has made major advances in identifying epigenetic signatures of in utero (Alfano et al., 2018; Gruzieva et al., 2019; Küpers et al., 2019) and later-life (Woo et al., 2018; Johansson et al., 2019a; Perrier et al., 2019) exposures and in deciphering their effects on phenotypic outcomes, with a primary focus on childhood cancer and selected adult cancer types (Table 1).

Figure 3. Mapping epigenetic modifications of the mitochondrial genome in normal and cancer cells. Schematic representation of (a) mitochondrion and (b) mitochondrial genome. (c) Baseline patterns of the mitochondrial DNA (mtDNA) methylation methylome in normal and cancer breast cells sequenced on the next-generation sequencing platform using the protocol established by EGE. The circular plot represents genomic position (1–16 kb) of all methylated cytosines with respect to sequence order. Each segment of the circle represents a separate functionally relevant region, transfer RNA (tRNA), ribosomal RNA (rRNA), gene, or displacement loop (D-loop). The *y*-axis indicating methylation level is represented on the left side of the D-loop segment. The large outer ring displays methylation at each cytosine within the heavy strand (H-strand), whereas the large inner ring displays methylation at each cytosine on the light strand (L-strand). Thin inner bands indicate the genomic position of all cytosines within the H-strand or L-strand sequence. Note that global mtDNA methylation patterns differ between cancer and normal cells. (d) Summary statistics of the frequency of mitochondrial mCpN context in liver cells. (e) Methylation index (MI) across tRNA-encoding regions in breast cancer versus normal cells. Each horizontal segment compares the MI within tRNAs that have been grouped according to the amino acid they carry (acidic, basic, aromatic, or hydrophobic). The left panel indicates MI across the H-strand, and the right panel indicates MI across the L-strand. (f) Comparative box plot indicating significant ($P < 0.001$) difference of mean methylation across gene-encoding regions of normal versus cancer cells in each strand. (g) Density plot of the distribution of methylation values along the D-loop region. Figure adapted from Patil et al. (2019). © Patil V, Cuenin C, by permission of Oxford University Press.

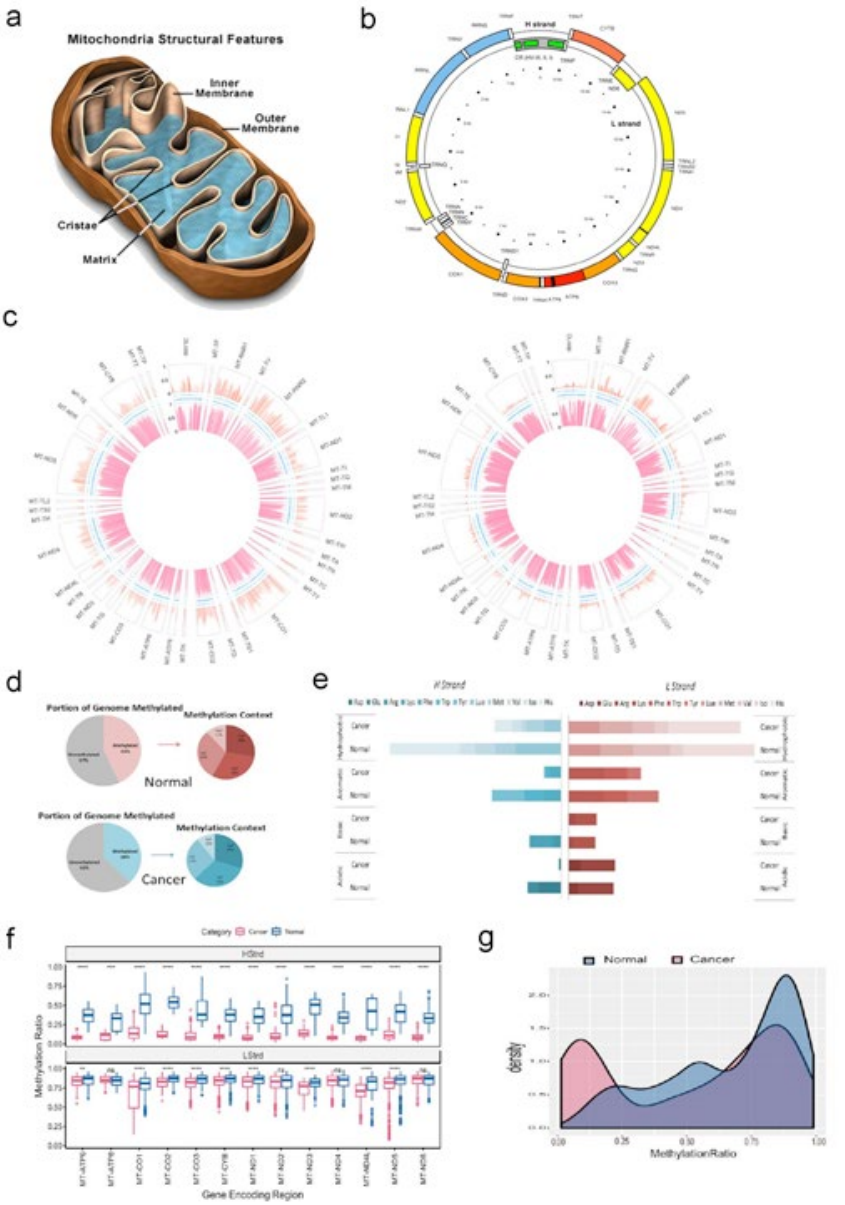


Table 1. Summary of epigenetic signatures of exposures, phenotypes, and cancer risk identified to date

Exposure/cancer risk	Study (sample size)	Number of significant CpGs[a]	Major finding	Reference
Exposures during pregnancy				
Paternal pre-pregnancy BMI	9340 (19 cohorts)	0 [0]	Little evidence of association was seen between paternal pre-pregnancy BMI and offspring methylation, including at imprinted regions	In preparation
Gestational diabetes	3677 (7 cohorts)	3 [2]	Little evidence of association was seen between gestational diabetes and offspring methylation	Submitted
Season of conception or birth	120 (1 cohort); expansion into other cohorts is in under way	Only DMRs reported	Dry vs rainy season in rural Gambia (hence maternal nutrition) altered the methylation of the tumour suppressor metastable epiallele, *VTRNA2–1*, and exhibited the hallmarks of metabolic imprinting	In progress
Socioeconomic status	914 (1 cohort); expansion into other cohorts is in under way	4 [1]	Among four major socioeconomic indicators (maternal and paternal education and occupation), only maternal education was associated with methylation levels at birth	Alfano et al. (2019); in progress
Maternal infection	In progress	In progress	NA	In progress
Intermediate phenotypes				
Birth weight	8825 (24 cohorts)	8170 [914]	Birth weight was largely associated with epigenomic variations in newborns, with a difference in birth weight ranging from −183 g to 178 g per 10% increase in methylation. Ten CpGs remained nominally associated with birth weight later in childhood (age 2–13 years), adolescence (age 16–18 years), and adulthood (age 30–45 years).	Küpers et al. (2019)
Gestational age	3648 (17 cohorts)	NR [8899]	Gestational age was largely associated with the newborn's epigenome. For most CpGs, the effect of gestational age on methylation diminished over time and stabilized after school age.	Submitted
Early-life end-points				
Childhood leukaemia/ CNS tumours	In progress	In progress	In progress	In progress
Adult or life-course exposure				
Alcohol/folate	EPIC cohort	24 DMRs (folate), 90 DMRs (alcohol)	Weak association with DMPs, but the DMR analysis revealed a total of 24 and 90 regions associated with dietary folate and alcohol, respectively	Perrier et al. (2019)
Estrogen (lifetime exposure)	EPIC-Italy (*n* = 216)	694 CpG sites	The EWAS identified 694 CpG sites associated with an estimated lifetime estrogen exposure model; in vitro follow-up study	Johansson et al. (2019a)
Oral contraceptive use	EPIC cohort	Large number of DMPs	Strong association with DMPs; replication using an independent cohort in progress	In preparation
Helicobacter pylori	National Cancer Center of the Republic of Korea study	1924 DMPs and 438 DMRs	1924 DMPs and 438 DMRs were found to be associated with *H. pylori* infection, most of which were hypermethylated	Woo et al. (2018)
Cancer risk				
Breast cancer risk	Meta-analysis, 4 cohorts (1663 cases and 1885 controls)	None	Methylation measured at individual CpGs (using 450K arrays) was not associated with risk of breast cancer	Bodelon et al. (2019)

BMI, body mass index; CNS, central nervous system; DMP, differentially methylated position; DMR, differentially methylated region; EPIC, European Prospective Investigation into Cancer and Nutrition; EWAS, epigenome-wide association study; FDR, false discovery rate; NA, not applicable; NR, not reported; vs, versus.
[a] Number of statistically significant CpGs (FDR < 0.05) identified. The number of Bonferroni-significant CpGs is shown in square brackets.

Molecular Mechanisms and Biomarkers Group (MMB)

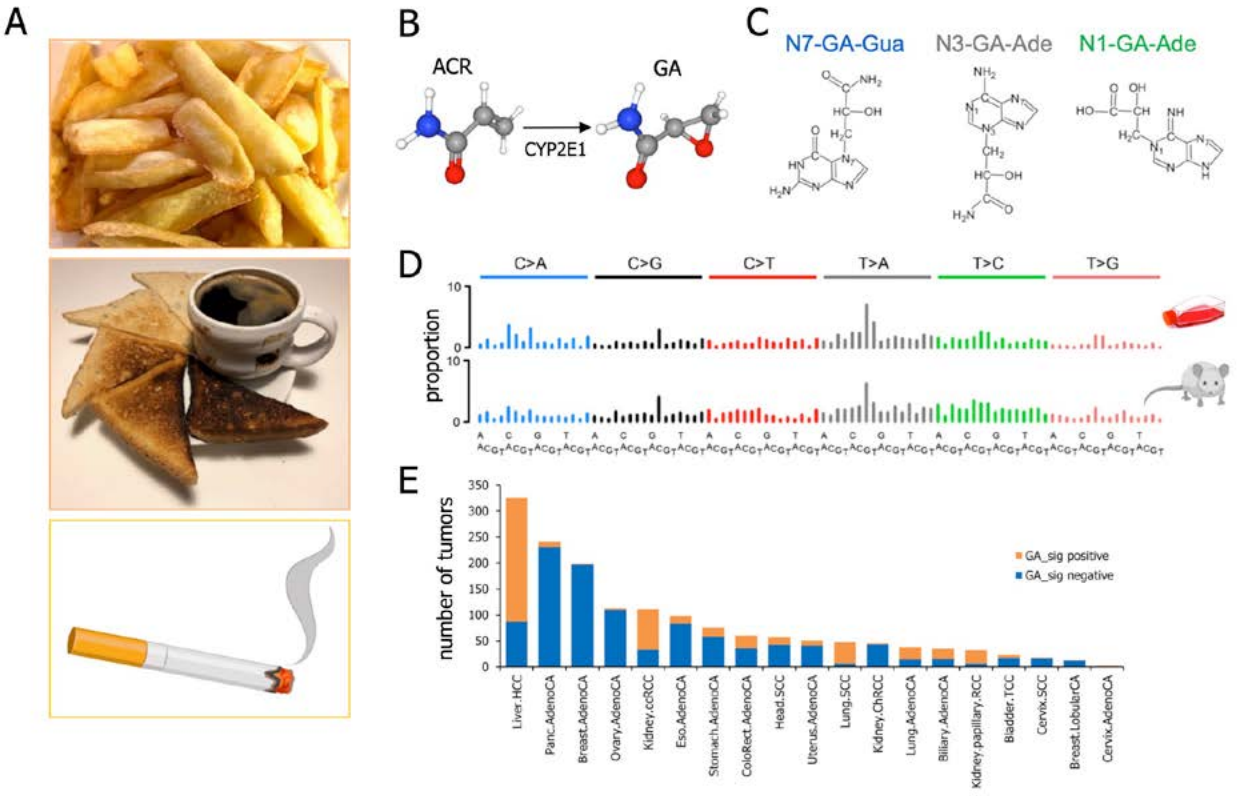
Molecular Mechanisms and Biomarkers Group (MMB)

The overarching goal of the Molecular Mechanisms and Biomarkers Group (MMB) is to develop and coordinate international collaborations aiming to determine molecular processes and markers of carcinogenesis associated with specific environmental, iatrogenic, and lifestyle risk agents. The impact of cancer risk agents on the genome is studied in experimental systems and in human and animal tissues. Furthermore, MMB devises experimental and bioinformatic methods (Marques et al., 2019) applicable to experimental and molecular cancer epidemiological studies. Taken together, the activities of MMB support cancer prevention strategies, including evidence-based carcinogen evaluation and classification (Samet et al., 2019).

Mutational signature of glycidamide (a metabolite of acrylamide) is widespread in human cancers

Acrylamide is carcinogenic in rodents and is classified by the IARC Monographs programme as probably carcinogenic to humans (Group 2A). It is present in common foods processed at a high temperature, for example, potato chips, French fries, crackers, bread, cookies, breakfast cereals, coffee, canned black olives, and prune juice. Tobacco smoke is another major source of acrylamide exposure in humans. To date, epidemiological studies have yielded rather inconclusive evidence as to the association between exposure to acrylamide and cancer, except for weak positive trends for cancers of the kidney, endometrium, and ovary in never-smokers. The mutagenicity of acrylamide is attributed to glycidamide, its reactive metabolite. By using genome-wide DNA sequencing of cell clones and of mouse lung tumours arising from glycidamide exposure, MMB identified a novel mutational signature of glycidamide. The signature is remarkably stable across the experimental models (Figure 4), and its composition corresponds to known pre-mutagenic DNA adducts. Using innovative targeted computational screens and mutation spectra modelling in synthetic genomes, the glycidamide

Figure 4. The mutational signature of glycidamide, a metabolite of acrylamide, is widespread in human cancers. (A) Some common sources of human exposure to acrylamide. (B) Metabolic activation of acrylamide (ACR) to a reactive epoxide glycidamide (GA) by CYP2E1 enzymatic activity (source: PubChem). (C) Major DNA adduct species identified in mouse tissues and cells upon exposure to ACR or GA. (D) The mutational signature of GA observed in vitro (upper panel) and in vivo (lower panel). (E) Total tumour counts versus human tumour types (total, 19) characterized by subsets harbouring the mutational signature of GA (labelled in orange). © IARC.



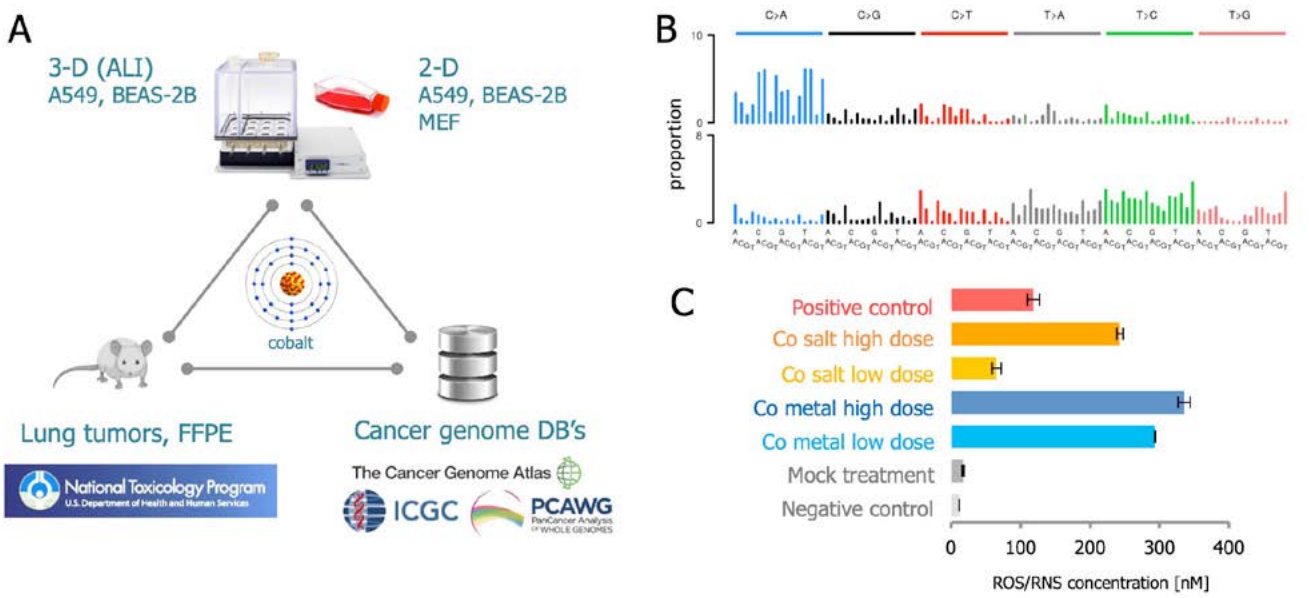
signature was identified in 34% of 1584 tumour genomes from the Pan-Cancer Analysis of Whole Genomes (PCAWG) of the International Cancer Genome Consortium. The tumours positive for the glycidamide signature comprised 19 human tumour types from 14 anatomical organs, and the signature was most enriched in cancers of the lung, kidney, liver, bile duct, head and neck, stomach, uterus, and oesophagus, and was present to a lesser extent in other cancer sites. These results (Zhivagui et al., 2019) reveal an unexpectedly widespread contribution of acrylamide-associated mutagenesis to human cancers. Acrylamide and glycidamide have recently been assigned a high priority for evaluation by the IARC Monographs Priorities Group (Marques et al., 2019), and new molecular cancer epidemiology studies are addressing the potential causal effects of acrylamide in human carcinogenesis.

Toxicity and genomic DNA damage by cobalt metal and cobalt salt

Various occupational, environmental, and clinical settings can lead to human exposure to cobalt and cobalt compounds, which are known to be carcinogenic in rodents and are possibly carcinogenic to humans (IARC Group 2B). Despite some evidence for in vivo and in vitro toxicity, the exact mechanisms underlying cobalt-associated tissue and DNA damage are not well understood. MMB aims to determine the damaging effects of cobalt on DNA by conducting integrated toxicogenomic analyses in exposed human lung cell lines propagated in two-dimensional cultures or under three-dimensional air–liquid interface conditions, in mouse primary fibroblasts, and in mouse lung tumours arising from chronic treatment with cobalt (Figure 5A). Treatment-specific genotoxic and oxidative damage effects were observed across the model systems. Furthermore, whole-genome sequencing of cell clones and mouse lung tumours yielded mutation spectra specific to cobalt exposure, indicating a genome-wide mutational signature of oxidative DNA damage; this observation was then validated by biochemical analysis (Figure 5B, C). These results provide a basis for future molecular epidemiology studies exploring the link between cobalt exposure and human cancers, further justified because cobalt and cobalt compounds have been assigned a high priority for evaluation by the IARC Monographs Priorities Group (Marques et al., 2019).

The EVAMOVAIRE2 project, conducted in collaboration with Centre Léon Bérard and the Lyon Sud Hospital Center, aims to elucidate the patterns of genomic damage in ovarian tumours as a result of exposure to asbestos. The INVITROMICS project, conducted in collaboration with EGE, aims to identify novel molecular markers of early tumorigenesis in experimental models of cell transformation. The OROQAT project, conducted in collaboration with the Section of Environment and Radiation, aims to investigate the cancer driver mutations in oral and oropharyngeal cancers of qat users from Ethiopia, to define markers of qat-chewing-specific mutagenesis and carcinogenesis. In the PUVARCC project, the genome-wide effects of 8-methoxypsoralen, a component of the treatment of skin diseases by psoralens and ultraviolet radiation class A (PUVA therapy), are being investigated for potential contributions to the development of renal cancer.

Figure 5. Toxicity and genomic DNA damage induced by cobalt metal and cobalt salt. (A) The study design integrating two-dimensional (2-D) and three-dimensional (3-D) mouse and human cell culture exposure systems (mouse lung tumours induced by chronic inhalation of cobalt metal particulate aerosol) (source: United States National Toxicology Program) and mining of public pan-cancer genome data. (B) The main mutational signatures identified in cells and mice; top panel: the accumulation of C > A mutations suggests oxidative-stress-related damage of guanines. (C) Significantly increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) identified in mouse fibroblast cells treated with cobalt metal and cobalt salt, 24 hours after exposure. ALI, air–liquid interface; Co, cobalt; DB, database; FFPE, formalin-fixed, paraffin-embedded tissue; ICGC, International Cancer Genome Consortium; MEF, mouse embryonic fibroblast; PCAWG, Pan-Cancer Analysis of Whole Genomes. © IARC.



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The Section of Infections (INF) has two groups: the Infections and Cancer Biology Group (ICB) and the Infections and Cancer Epidemiology Group (ICE). The research activities of both Groups aim to evaluate the role of infectious agents in human cancers through biological and epidemiological studies.

Using in vitro and in vivo experimental models, ICB is focused on (i) the characterization of the transforming properties of well-established and novel potential oncogenic viruses; and (ii) the evaluation of possible cooperation between viruses and other environmental risk factors, such as ultraviolet (UV) radiation, in promoting cancer development (Viarisio et al., 2018). In addition, ICB collaborates intensively with epidemiologists at IARC and worldwide, offering many laboratory assays for biomarker detection to evaluate the role of infections in human cancer (Donà et al., 2019; Hampras et al., 2019).

The overall strategy of ICE is to improve the epidemiological evidence base with respect to prevention of infection-attributable cancer. This strategy relies on obtaining both high-quality data and biological samples from populations that have been well characterized epidemiologically. Although the strategy of ICE is global, work is naturally focused on low- and middle-income countries (LMICs), which have a disproportionate burden of infection-attributable cancers, and particularly on countries in Africa and Asia. There are currently 11 infectious agents that are classified as carcinogenic by the IARC Monographs, and they are at different stages along the pathway from discovery to public health intervention. Correspondingly, ICE research includes a wide portfolio of study designs that are tailored to specific infectious agents across a spectrum of epidemiological research, from etiology or natural history through global burden assessment to evaluation and modelling of the impact of interventions and/or policy.

ICB and ICE are also participating in several collaborative studies to assess the impact of human papillomavirus (HPV) vaccine in LMICs (see text box) and characterize the role of mucosal high-risk (HR) HPV infection in the etiology of head and neck cancer.

Infections and Cancer Biology Group (ICB)

Role of beta HPV types in the development of cutaneous squamous cell carcinoma

A large number of HPV types have been isolated and fully characterized so far (Rollison et al., 2019a). They are subdivided into genera and species in the HPV phylogenetic tree according to the DNA sequence of the late gene L1. Genera alpha, beta, and gamma comprise the majority of the known HPV types. A subgroup of genus alpha, referred to as mucosal HR HPV types, infect the epithelia of the anogenital tract as well as the upper respiratory tract; these HR HPV types have been clearly associated with a broad spectrum of human cancers, including cervical and oropharyngeal cancers. In addition to the HR HPV types, cutaneous beta HPV types also appear to be implicated in carcinogenesis, although by different mechanisms. Epidemiological and biological studies support the model of synergistic cooperation between cutaneous beta HPV types and UV radiation in the development of cutaneous squamous cell carcinoma (cSCC) (Rollison et al., 2019a). Many findings indicate that beta HPV infection plays a role in an initial phase of skin carcinogenesis, but it is not essential for the viability of the tumour cells once they have become malignant (Rollison et al., 2019a; Tommasino, 2019). Using a beta HPV transgenic (Tg) mouse model, in which E6 and E7 genes can be conditionally silenced via the use of the Cre/Lox system, ICB has recently obtained additional lines of evidence that support this beta HPV-mediated model of skin carcinogenesis (Viarisio et al., 2018). This mouse model has a high susceptibility to UV-induced skin carcinogenesis. Indeed, long-term UV irradiation of keratin 14 (K14) HPV38 E6/E7 Tg mice induced cSCC, although wild-type animals subjected to identical treatments did not develop any type of skin lesions. Accordingly, K14 HPV38 E6/E7 Tg mice accumulate a large number of UV-induced DNA mutations, which increase proportionally with the severity of the skin lesions (Viarisio et al., 2018). In contrast, no mutations were detected in the skin of wild-type animals exposed to the same doses of UV radiation. The mutation pattern detected in the Tg skin lesions closely resembles that detected in human cSCC, with the highest mutation rate in p53 and Notch genes (Figure 1)

Figure 1. Several genes mutated in human skin lesions are also mutated in the ultraviolet (UV) radiation-induced skin lesions of cutaneous squamous cell carcinoma (cSCC) of keratin 14 (K14) HPV38 E6/E7 transgenic (Tg) mice. Heatmap of mutations in genes in normal skin, pre-malignant lesions, and cSCC from different mice (M1–3) reported as significantly mutated in human cSCC. SNV, single-nucleotide variant. Reproduced from Viarisio et al. (2018).

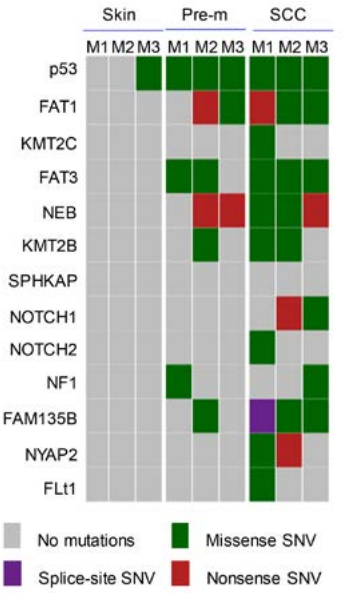
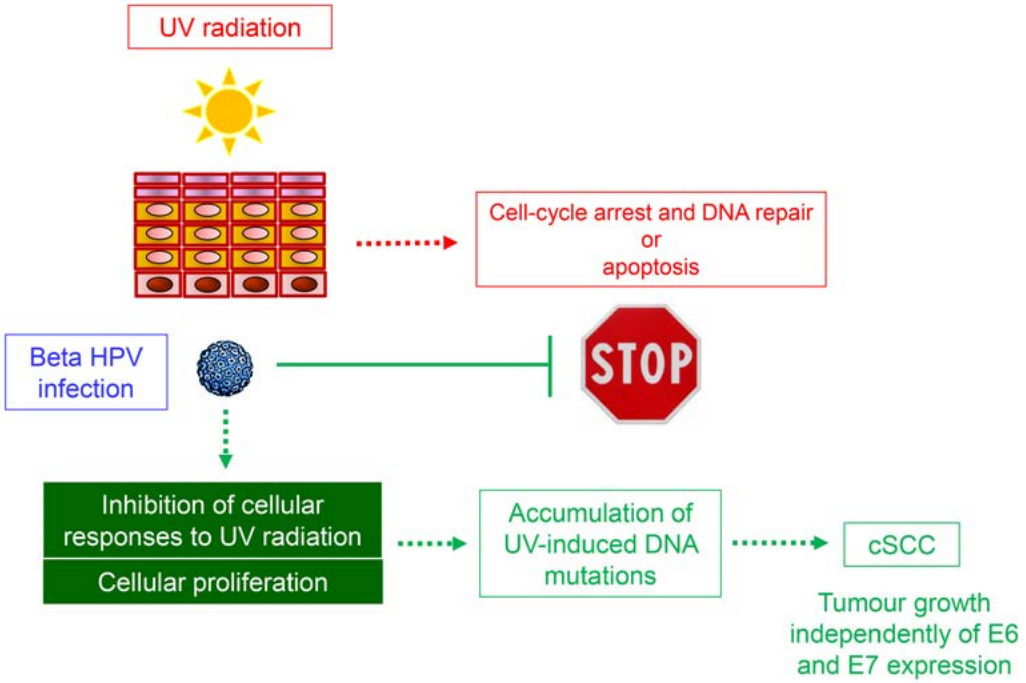


Figure 2. Working model for cooperation between beta human papillomavirus (HPV) types and ultraviolet (UV) radiation in promoting cutaneous squamous cell carcinoma (cSCC). Under normal conditions, UV irradiation of the skin induces DNA mutations in keratinocytes in the basal layer, with consequent (i) cell-cycle arrest and repair of DNA mutations, or (ii) apoptosis, if the DNA damage is unrepairable. Upon beta HPV infection, E6 and E7 expression inhibits the cellular response to UV radiation-induced stress. As a consequence, DNA-damaged cells continue to proliferate, with a high risk of evolving into cancer cells. After inactivation of tumour suppressor genes or activation of cellular oncogenes by DNA mutations, the expression of the viral genes becomes dispensable. Reprinted from Tommasino (2019), Copyright 2019, with permission from Elsevier.



(Viarisio et al., 2018). Silencing the expression of HPV38 E6 and E7 before the long-term UV irradiation prevented the development of any type of skin lesions. In contrast, their loss after the development of UV-induced skin lesions did not have any impact on cancer cell growth.

Together, these findings support the model in which beta HPV E6 and E7 proteins act as facilitators of DNA mutations induced by HPV and UV radiation by targeting key cellular pathways. A plausible hypothesis is that beta HPV types, to efficiently complete their life-cycle in the skin, have developed strategies to maintain infected cells in a proliferative status, even if they have been damaged by UV radiation. By doing so, they strongly increase the probability of infected cells progressing towards malignancy. Because of the irreversible UV-induced DNA damage, the expression of the viral genes may become dispensable for the maintenance of cSCC (Figure 2).

Infections and Cancer Epidemiology Group (ICE)

Modelling cervical cancer control in high-income and low- and middle-income countries

A combination of infectious and chronic disease modelling techniques is helpful to gain insight into HPV infection transmission dynamics and the natural history of cervical cancer, and to design and evaluate prevention programmes (Baussano and Bray, 2019). ICE has developed mathematical models to support the introduction of HPV vaccination and the implementation of HPV DNA-based cervical cancer screening in both high-income countries and LMICs. The findings show that international variations in HPV prevalence, mostly a result of differences in sexual behaviour, have a direct effect on the levels of herd protection and affect the impact of vaccination programmes (Baussano et al., 2018). Overall, HPV vaccination programmes are expected

to be more efficient in populations with sexual behaviour based on traditional norms and lower HPV prevalence (Figure 3). Model-based findings, in combination with empirical data, also demonstrate that the coverage and cross-protection of HPV vaccines required to reduce or eliminate infection vary by individual HR HPV type; HPV 16 infection and the corresponding cancers are the most difficult to eliminate (Lehtinen et al., 2018a, 2019). Finally, on the basis of available data from European HPV DNA-based cervical cancer screening trials, ICE has used the cervical cancer screening model to assess the expected effectiveness of selected vaccination and screening scenarios in different populations (Berkhof, 2018).

HPV genomics

The reasons why only a small minority of HR HPV-infected women progress to cervical cancer remain largely unknown. Furthermore, the 13 established HR HPV types vary enormously in their cancer risk: HPV 16 is uniquely carcinogenic, but the closely genetically related types are much less carcinogenic. These intriguing observations, for which explanations must lie partly in the relatively small (8 kb) HPV genomes, have motivated studies of HPV genomics in the ICE biobank. Indeed, ICE has coordinated a wide variety of epidemiological studies on HPV and cervical cancer around the world, and the resulting biobank is a uniquely ethnically and geographically diverse resource with which to study the genetic determinants of HPV carcinogenesis. A high-throughput HPV 16 whole-genome sequencing platform developed at the United States National Cancer Institute was used to wholly sequence 7116 global HPV 16-positive cervical samples (including 2076 controls, 1878 squamous cell carcinomas, and 186 adenocarcinomas). The resulting global description of HPV 16 genomics (Figure 4) resulted in novel HPV 16 sublineage identification and an evolutionary model for HPV and human co-evolution, including HPV transmission from Neanderthals to modern humans (Chen et al., 2018a). HPV 16 genetic variation was shown to influence risk of cervical cancer: increased cancer risks were seen for the A3, A4, and D (sub) lineages in worldwide regions where they were common (Clifford et al., 2019) (Figure 4).

HPV 16 and risk of anal cancer

The incidence of anal cancer, which is caused by HPV, is increasing at a population level and is elevated in groups with increased anal HPV exposure and/or immunosuppression, particularly HIV-positive men who have sex with men. Compared with HPV and cervical

Figure 3. (a) Relative reduction in HPV 16 prevalence and (b) achievable post-vaccination HPV 16 prevalence among women aged 15–34 years after vaccination of girls aged 11 years in a population with gender-equal sexual behaviour, by coverage and pre-vaccination prevalence. (c) Relative reduction in HPV 16 prevalence and (d) achievable post-vaccination HPV 16 prevalence, among women aged 15–34 years after vaccination of girls aged 11 years in a population with traditional sexual behaviour, by coverage and pre-vaccination HPV 16 prevalence. Reproduced from Baussano et al. (2018). © 2018 IARC/WHO; licensed by UICC.

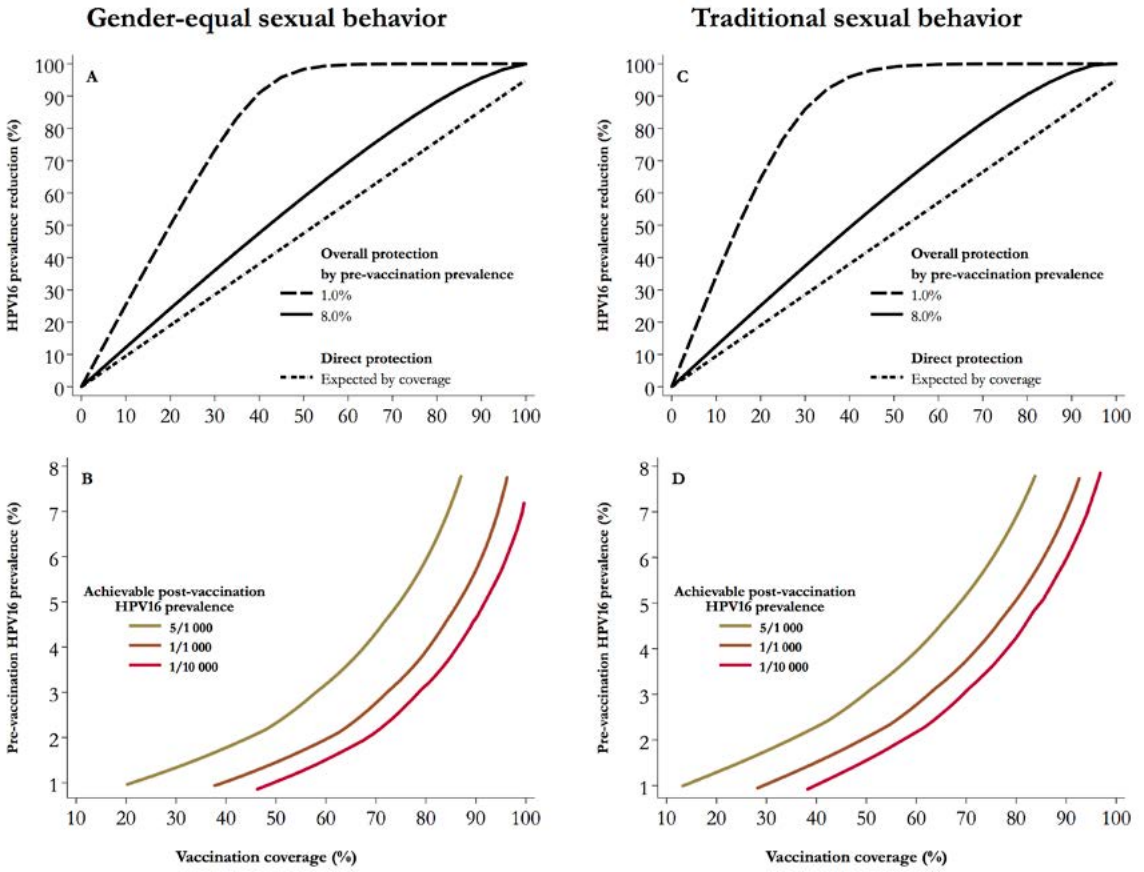
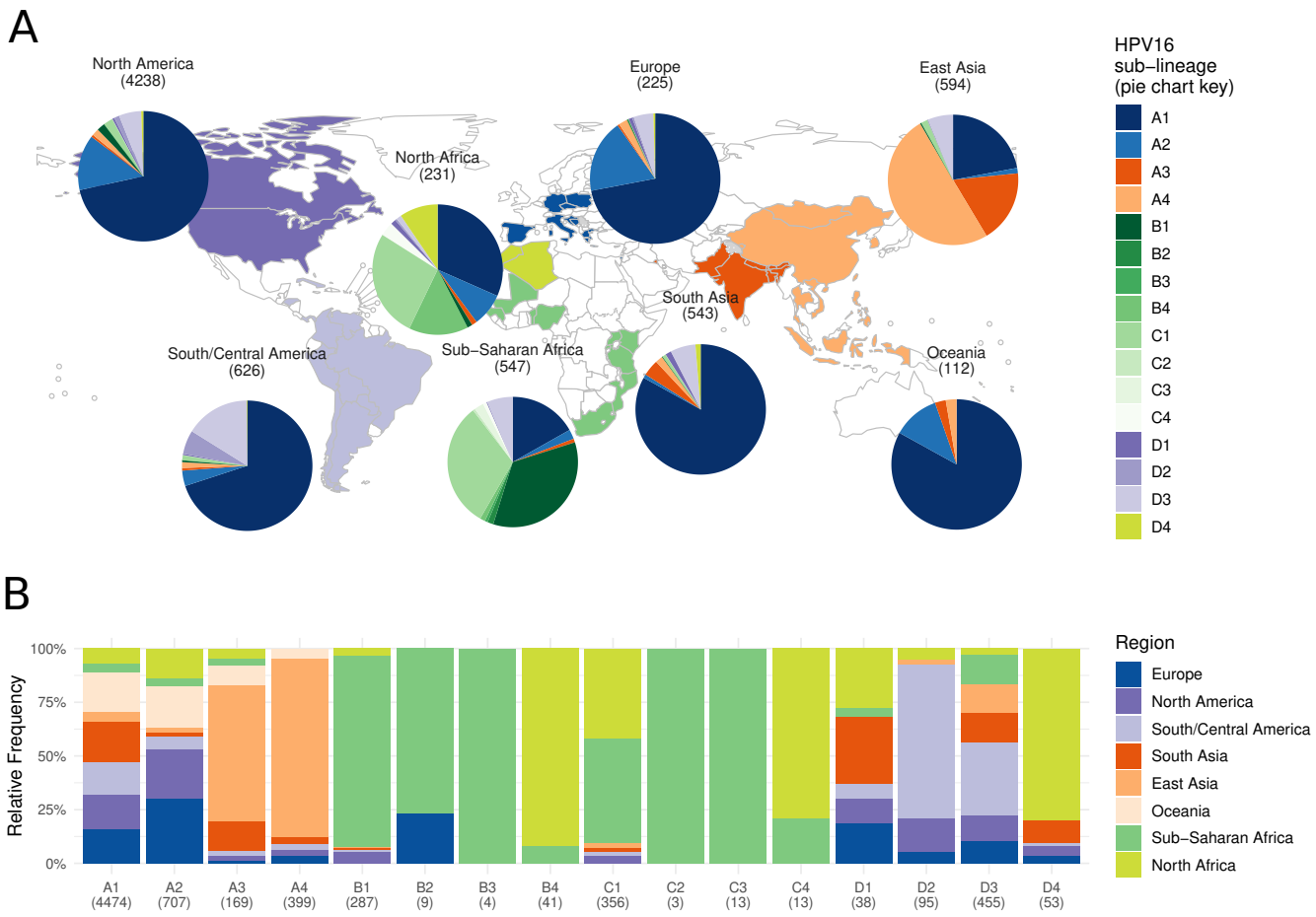


Figure 4. Distribution of sublineages in 7116 HPV 16-positive samples, by geographical region. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. Reprinted from Clifford et al. (2019), Copyright 2019, with permission from Elsevier.



cancer, much less is known about anal cancer natural history, which is key to informing appropriate prevention approaches. ICE undertook several relevant studies in this regard. First, a meta-analysis across the full disease spectrum from anal HPV infection to cancer confirmed the unique importance of HPV 16 in anal carcinogenesis: HPV 16 predominated over other HPV types in anal cancer, irrespective of HIV status (Lin et al., 2018a) (Table 1). In follow-up meta-analyses or pooled-analyses, notable determinants of anal HPV 16 infection were sexual preference and HIV infection for men (Marra et al., 2019) and cervical HPV 16 positivity for women (Lin et al., 2019), suggesting that HPV-based cervical screening may contribute to anal cancer prevention (Lin et al., 2019). In the APACHES study of the natural history of anal HPV in 500 HIV-positive men who have sex with men in France, anal HPV

Table 1. Number and prevalence (%) of single and multiple infections of human papillomavirus (HPV) types in HPV-positive anal cancer by HIV status. Reprinted from Lin et al. (2018), Copyright 2018, with permission from Elsevier.

HPV type	HIV-negative or unknown	HIV-positive
HPV 16	1333/1554 (86%)	96/144 (67%)
HPV 18	66/1554 (4%)	21/144 (15%)
HPV 33	44/1369 (3%)	12/130 (9%)
HPV 6	54/1415 (4%)	8/124 (6%)
HPV 58	23/1198 (2%)	1/123 (1%)
HPV 35	12/1332 (1%)	0/123 (0%)
HPV 31	19/1338 (1%)	6/129 (5%)
HPV 52	21/1198 (2%)	12/123 (10%)
HPV 11	37/1415 (3%)	10/124 (8%)
HPV 45	10/1329 (1%)	8/125 (6%)
HPV 56	6/1190 (1%)	1/123 (1%)
HPV 39	7/1190 (1%)	8/123 (7%)
HPV 68	4/1190 (< 1%)	10/123 (8%)
HPV 59	2/1190 (< 1%)	5/123 (4%)
HPV 51	11/1190 (1%)	8/123 (7%)
Any HPV	1424/1430 (> 99%)	128/130 (98%)
HPV 16/18	552/629 (88%)	87/118 (74%)
HPV 6/11/16/18	579/629 (92%)	91/118 (92%)
HPV 6/11/16/18/31/33/45/52/58	618/629 (98%)	109/118 (92%)

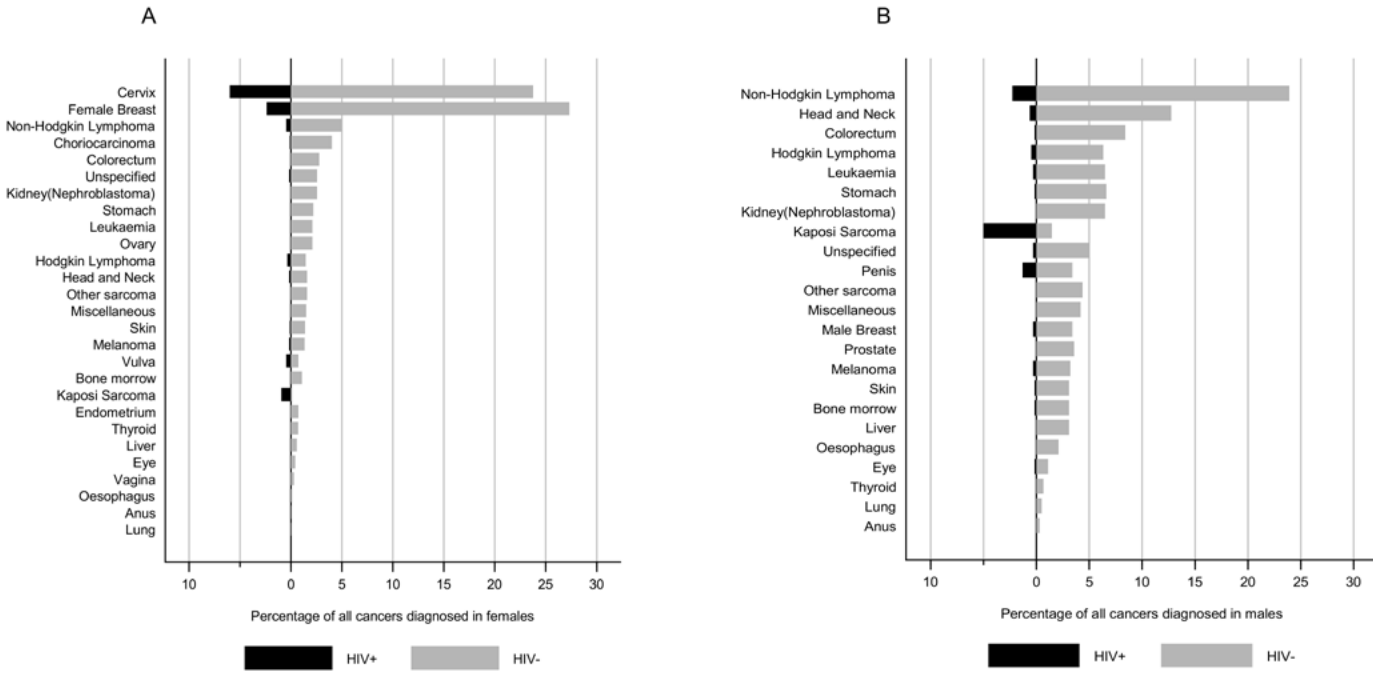
Data are *n*/*N* (%) for overall prevalence.

16 infection was also shown to be the strongest predictor of anal precancerous lesions (Clifford et al., 2018; Combes et al., 2018a).

HIV and cancer risk

HIV-related immunosuppression can worsen oncogenic viral infections, increasing the risk of infection-related cancer. ICE studied the link between HIV infection and a broad spectrum of cancers diagnosed in the era of combination antiretroviral therapy (cART) in Rwanda. People seeking cancer care at Butaro Cancer Center of Excellence were routinely screened for HIV before being confirmed with or without cancer (2656 cases and 1196 controls, respectively). HIV was shown to be significantly associated with diagnoses of Kaposi sarcoma, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL), as well as cancers of the cervix, vulva, penis, and eye (Figure 5). Associations varied by subtype of NHL or HL, with the association for NHL being limited to diffuse large B-cell lymphoma, particularly plasmablastic lymphoma. No significant associations with HIV were seen with other commonly diagnosed cancer types such as breast, prostate, or colorectal cancer. Overall, 6% of all cancer cases diagnosed at this national referral hospital were estimated to be attributable to HIV infection. In a separate collaboration involving a worldwide consortium of cohort studies, important variations in NHL incidence among HIV-positive people were observed according to geographical region, probably driven by differences in prevalence of oncogenic viruses and/or access to cART (AIDS-defining Cancer Project Working Group of IeDEA and COHERE in EuroCoord, 2018).

Figure 5. Proportion of individual cancer types among all cancers diagnosed at Butaro Cancer Center of Excellence, Rwanda, 2012–2016, by HIV status: (a) women and (b) men. Reproduced from Mpunga T, Chantal Umulisa M, Tenet V, Rugwizangoga B, Milner DA Jr, Munyanshongore C, et al. (2019). Human papillomavirus genotypes in cervical and other HPV-related anogenital cancer in Rwanda, according to HIV status. Int J Cancer. ijc.32491. https://doi.org/10.1002/ijc.32491 PMID:31173641. © 2019 IARC/WHO; licensed by UICC.



Assessing HPV vaccine impact through urine surveys

ICE is engaged in assessing the impact of national human papillomavirus (HPV) vaccination in several low- and middle- income countries (LMICs), such as Armenia, Bhutan, Rwanda, and Uganda. Working in close collaboration with local public health authorities, ICE is conducting a series of baseline and repeat urine surveys, targeting young women before and after the introduction of HPV vaccination, respectively, to follow up type- and age-specific HPV prevalence trends. Data from Rwanda and Bhutan, the first two LMICs to implement national HPV vaccination, show that the prevalence of vaccine-targeted HPV types has decreased significantly as a result of a high-coverage school-based national vaccination programme.

Assessing HPV vaccine impact through urine surveys, Rwanda. © IARC.

Urine collection is a very powerful alternative to standard methods for HPV testing because it is a well-accepted non-invasive procedure, facilitates sample storage and processing, and displays good concordance with cervicovaginal cells for HPV positivity in women. ICE has designed and optimized transferable procedures and skills for designing and conducting repeat urine-based surveys, which may be used by public health authorities in other LMICs to monitor the impact of their vaccination programmes and optimize the allocation of the resources devoted to cervical cancer control.

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The overall objectives of the Section of Environment and Radiation (ENV) are to investigate environmental, occupational, and lifestyle- and radiation-related causes of cancer and death from cancer in human populations. With this wide remit, ENV focuses its endeavours on three main areas: (i) research in settings where levels of exposure to putative or established carcinogens are high, and research is thus warranted; (ii) studies of common cancer types and of specific exposures that occur in under-researched settings, particularly but not exclusively in low- and middle-income countries (LMICs); and (iii) studies evaluating the role of broader social as well as biological factors throughout the course of the disease. The objectives of ENV are achieved through the conduct of collaborative international epidemiological studies, including co-ordination of international consortia or through the initiation of targeted individual analytical epidemiological studies. In selecting projects, an effort is made to ensure that the involvement of the Agency makes a specific and substantial difference, by facilitating international collaboration, by overcoming political barriers, by assisting local collaborators in targeted studies with expertise and with increased local visibility and trust in their work, and by using the general expertise, international network, and special function of the Agency as part of the World Health Organization.

With a strong focus on environmental (including occupational and radiation-related) and lifestyle risk factors, ENV fills a major research gap to further understand the cancer burden attributed to these factors. ENV has steered its research focus to LMICs in particular, a direction that is warranted because in these settings, levels of environmental pollution are often higher. Capacity-building, as well as establishing research platforms, is another vision of IARC to which ENV contributes. Selected examples of ENV projects are described here.

Oesophageal cancer in East Africa: the ESCCAPE studies

The incidence of oesophageal cancer, particularly of the histological type oesophageal squamous cell carcinoma (ESCC), has a peculiar spatial distribution worldwide. Similar to the Asian ESCC belt, East Africa has a

high-incidence corridor stretching from Ethiopia to Malawi; in this corridor, ESCC is among the most common cancer types and is a leading cause of cancer death, but its etiology is understudied. ENV initiated the Oesophageal Squamous Cell Carcinoma African Prevention Research (ESCCAPE) study 5 years ago after conducting an extensive review of priority factors requiring investigation in this setting. ESCC case–control studies are continuing in Kenya, Malawi, and the United Republic of Tanzania and represent the largest multi-country African ESCC study, with 1200 cases and 1200 controls. Investment in biobanking for future molecular studies has been a priority throughout. In a collaboration with Moi University, Kenya, the first results from this country are already providing important clues to the underlying multifactorial etiology. The clear role of alcohol consumption, particularly of traditional brews and distillations, is present and contributes to ESCC incidence more in men than in women (Menya et al., 2019a). Another modifiable risk factor is drinking of very hot tea (Middleton et al., 2019a). ENV has also observed increased risks of ESCC associated with various indicators of oral health and hygiene, including the first-ever findings for an indicator unique to this setting: dental fluorosis (Menya et al., 2019b). Indoor air pollution from cooking and heating is another concern, and measuring indoor air pollution is the focus of a recently started study extension (Figure 1). Research is continuing into the pathways driving these associations, to inform effective primary prevention avenues. The ESCCAPE studies have opened doors to, and benefited from, capacity-building opportunities for all partners (see text box).

Fostering collaborations and capacity-building in cancer research

At the heart of the cancer studies of ENV is an extensive network of collaborators across countries, institutions, and disciplines, making research possible and ensuring high-quality scientific insights. Such collaborations are sustained and enriched through capacity-building. The photograph taken at the Oesophageal Squamous Cell Carcinoma African Prevention Research (ESCCAPE) project annual meeting held in October 2018 in Eldoret, Kenya, represents a snapshot of such collaborations.

Left to right, first row: Odipo Osano, Fatma Some, Stephen Kararu Maina, Margaret Oduor, Winnie Chepkomoi, Betsy Chelangat, and Zdenko Herceg; second row: Charles Dzamalala, Blandina Mmbaga, Jiri Zavadil, Caroline Kibosia, Joachim Schüz, Diana Menya, Valerie McCormack, and Ian Simel; and third row: Esilaba Maina, Steady Chasimpha, Bongani Kaimila, Gissela Maro, Daniel Middleton, Ghislaine Scelo, and Robert Parker. Also present (but not in photograph): Nicholas Kigen.

At this meeting were the ESCCAPE country principal investigators, Dr Diana Menya of Moi University (Kenya), Dr Charles Dzamalala of the College of Medicine (Malawi), and Dr Blandina Mmbaga of the Kilimanjaro Clinical Research Institute (United Republic of Tanzania), and collaborators from Tenwek Hospital (Kenya), the National Cancer Institute (USA), and the University of North Carolina (USA). Researchers from the Section of Mechanisms of Carcinogenesis and the Genetic Epidemiology Group attended the meeting and presented results from mutation and methylation studies. Meeting attendees represented expertise in epidemiology, genetics, surgery, veterinary science, dentistry, endoscopy, and pathology.

The ESCCAPE team benefited from the IARC Summer School in Cancer Epidemiology (seven attendees); two UICC-IARC Development Fellowships (in collaboration with the Union for International Cancer Control), including to Mr Stephen Kararu Maina (Kenya); biobanking support; and pathology training provided by IARC's Dr Behnoush Abedi-Ardekani (Genetic Cancer Susceptibility Group). ESCCAPE has also been the basis of one IARC postdoctoral fellowship and three PhDs. The face-to-face interactions within this collaborative group were rewarding and motivational for all.

Figure 1. Indoor air pollution from biomass burning on a traditional cooking stove, Iten, Rift Valley, Kenya, October 2018. © IARC/Jiri Zavadil.

Recommendations on long-term thyroid health monitoring after nuclear accidents

The increasing public awareness and fears about the radiation-related risks of thyroid cancer and the issues related to overdiagnosis revealed the need for the development of guidelines about whether and how to conduct thyroid health monitoring after nuclear accidents. In 2017, ENV convened an international, multidisciplinary Expert Group to develop respective recommendations on long-term strategies for thyroid health monitoring, on the basis of the scientific evidence and previous experiences (Figure 2). The Expert Group recommended against population thyroid screening after a nuclear accident and that consideration be given to offering a long-term thyroid monitoring programme for higher-risk individuals (defined as those exposed in utero or during childhood or adolescence with a thyroid dose of 100–500 mGy or more) after a nuclear accident. A thyroid monitoring programme is defined as including education to improve health literacy, registration of participants, centralized data collection from thyroid examinations, and clinical management. It is an elective activity offered to higher-risk individuals, who may choose how and whether to undergo thyroid examinations and follow-ups. The choice of a thyroid dose range of 100–500 mGy for an actionable level reflects the option to be more inclusive (lower actionable levels) or to be more efficient (higher actionable levels) in identifying and monitoring radiation-related thyroid disease in higher-risk individuals. The decision should be made in the broader context of nuclear emergency preparedness and response, such as dosimetry monitoring, protective actions, risk communication, and health monitoring infrastructure, as well as the health-care resources and social values of the affected population. This work was published as IARC Technical Publication No. 46, and a summary was published as a commentary in *The Lancet Oncology* (Togawa et al., 2018).

Epidemiological studies on cancer risk after paediatric computed tomography

EPI-CT is a retrospective European cohort study of almost 1 million children and young adults who underwent at least one computed tomography (CT) examination in the radiology departments of 276 participating hospitals in Belgium, Denmark, France, Germany,

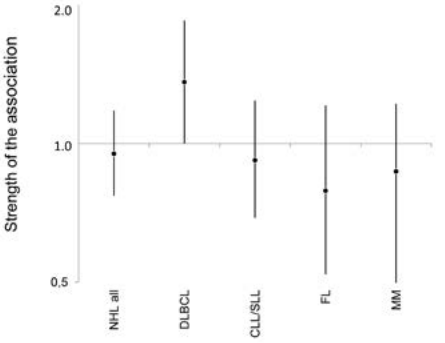
Figure 2. Expert Group on Thyroid Health Monitoring after Nuclear Accidents with colleagues from Japan, second and final meeting in Lyon, 21–23 February 2018. Left to right, first and second rows: Enora Clero, Catherine Sauvaget, Evgenia Ostroumova, Louise Davies, Ausrele Kesminiene, Geraldine Thomas, Christoph Reiners, Kayo Togawa, and Hiroki Shimura; back row: Salvatore Vaccarella, André Ilbawi, Anssi Auvinen, Mykola Tronko, Dominique Laurier, Sergey Shinkarev, Furio Pacini, Joachim Schüz, Catherine Chassin, and Andrew J. Bauer. © IARC.

The Netherlands, Norway, Spain, Sweden, and the United Kingdom in 1977–2014 and who were followed up for cancer diagnosis. The absorbed dose to organs of interest was individually calculated using the National Cancer Institute dosimetry system for Computed Tomography (NCICT) software for each CT scan. Mean cumulative doses for various organs ranged from 2.5 mGy to 47.4 mGy. A total of 948 174 participants were identified through the Radiology Information System and were alive and cancer-free before and 1 year after the first CT scan (Bernier et al., 2019). Of those, 658 424 were alive and cancer-free 5 years after their first CT scan and were included in the analyses for brain cancers and other solid cancers. During an average of 7 years of follow-up, 203 brain cancers occurred as well as 1561 other solid cancers at the sites that met the criterion (at least 50 cases overall), chosen to limit bias. A dose–response relationship was observed for cancers of the brain, breast, kidney, and remaining solid cancers in the torso; the excess relative risk at 100 mGy was 2.39 (95% confidence interval [CI], 1.24–4.51), 1.61 (95% CI, 0.35–3.45), 3.47 (95% CI, 0.98–7.61), and 1.37 (95% CI, 0.72–2.21), respectively. These results confirm the importance of the basic principles of radiological protection in the medical setting, namely that the choice of a medical imaging modality with ionizing radiation is justified and that doses to the patient are as low as reasonably possible.

Other recent findings

In a pooled analysis from the AGRICOH consortium of three large cohorts of agricultural workers totalling more than 300 000 farmers, ENV investigated the relationship of ever-use of 14 selected pesticide chemical groups and 33 individual active chemical ingredients with non-Hodgkin lymphoma malignancies overall or by major subtypes. An association was seen with terbufos, whereas the broader groups of organochlorine insecticides and phenoxy herbicides showed inverse associations. Deltamethrin and glyphosate were associated with non-Hodgkin lymphoma subtypes but not overall (Figure 3). No associations were seen for most of the pesticides investigated (Leon et al., 2019a). From the same three prospective

Figure 3. Association between occupational use of glyphosate and risk of non-Hodgkin lymphoma (NHL) observed in the AGRICOH pooled study of agricultural cohort studies from France, Norway, and the USA. CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma.© IARC.

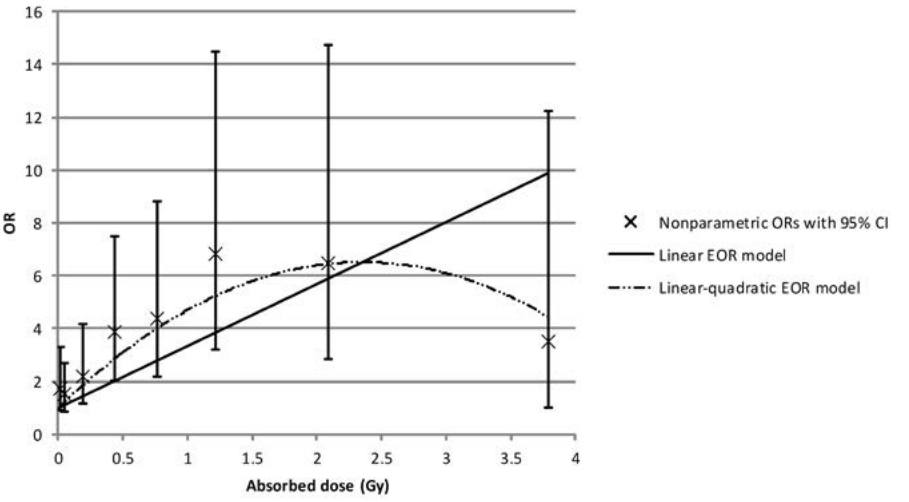


agricultural cohorts, no association was observed between animal farming and risk of lymphohaematopoietic cancer, but a few associations between specific animal species and subtypes of lymphohaematopoietic cancer were observed (El-Zaemey et al., 2019).

To identify host and environmental factors that modify radiation-related risk of thyroid cancers after childhood exposure to iodine-131 (^{131}I), ENV studied 298 post-Chernobyl thyroid cancer cases and 1934 matched controls from the most contaminated regions of Belarus and the Russian Federation using advanced dose methodology. The study reconfirmed a significant dose–effect association between exposure and thyroid cancer within thyroid doses of up to 2 Gy and 5 Gy (Figure 4). Stable iodine supplementation in the years after the accident could lower ^{131}I-related risk of thyroid cancer (Zupunski et al., 2019). In female populations of the most radioactively contaminated areas of Belarus (1978–2010) and Ukraine (1990–2010), no statistically significant increases in risk of breast cancer were observed in association with raion-average accumulated breast dose after adjustment for age, time, and urbanicity (a raion is an administrative region). Because of the limitations of the ecological study design, a detailed analytical study on breast cancer is warranted.

In the ASTRO-RF project, survival among patients with glioma in Denmark, Finland, and Sweden in relation to their mobile phone use at the time of diagnosis was studied. Marginal survival benefits were observed in the mobile phone users among patients; this is likely to be an artificial association explained by prodromal symptoms in cases, resulting in patients not starting to use mobile phones, if it also coincides with poorer survival (Olsson et al., 2019). Not observing any reduction in survival is concordant with the results found in the parallel study in experimental animals of radiofrequency electromagnetic fields (Ouadah et al., 2018).

Figure 4. Association between ^{131}I thyroid dose and thyroid cancer risk adjusted for self-reported personal history of benign nodules in the study subjects with 131I thyroid absorbed doses of < 5 Gy. CI, confidence interval; EOR, excess odds ratio; OR, odds ratio. © IARC.



The increased risks of developing vestibular schwannoma (also referred to as acoustic neuroma) with noise exposure related to work and leisure activities were observed in case–control studies conducted in 13 countries. For occupational exposures, duration, time since start of exposure, and a metric combining lifetime duration and weekly exposure showed significant trends of increasing risk with increasing exposure; however, relative risk estimates did not differ markedly by source or other characteristics of noise. Recall bias remains a concern; although a complementary validation study in 111 cases and 217 controls comparing self-reported noise exposure with expert assessments of workplaces showed relatively accurate reporting by study participants, the impact of reporting uncertainties on the risk estimation was non-negligible (Deltour et al., 2019a).

Updates on continuing studies

The African Breast Cancer – Disparities in Outcomes (ABC-DO) study is an ENV-led hospital-based cohort of 2200 women diagnosed with breast cancer across five countries in sub-Saharan Africa, examining multidimensional barriers to improving breast cancer survival. In 3-year survival analyses, lagging survival was found for the cohort as a whole, but with large between-setting differences. ENV also observed within-setting survival deficits associated with late stage, lower education level, undertreatment, and being HIV-positive. High proportions of women who remained untreated within 1 year of diagnosis (up to one third in some settings), particularly women in groups with lower socioeconomic status, were documented (Foerster et al., 2019).

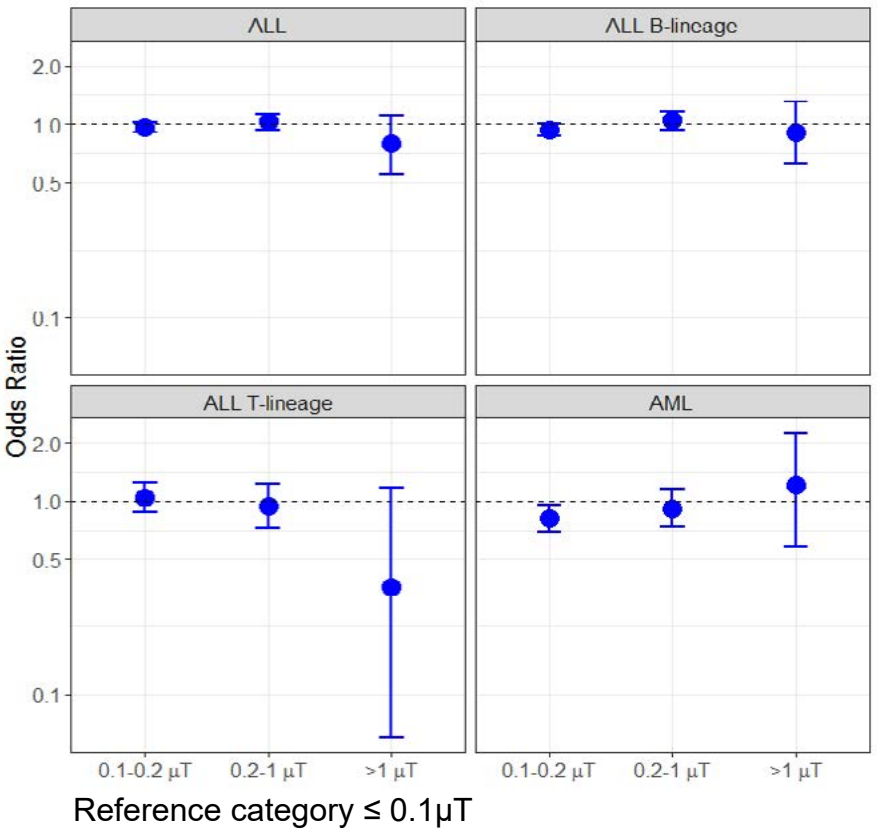
ENV reached a milestone in its occupational cohort study of workers exposed to chrysotile in mines and processing facilities in Asbest, Russian Federation (Asbest Chrysotile Cohort), carried out in collaboration with the Federal State Budgetary Scientific Institution Izmerov Research Institute of Occupational Health in Moscow. The cohort includes 35 837 individuals, 37% of whom are women. Exposure was estimated from more than 90 000 measurements of airborne dust concentrations made since the 1950s across the mines and processing mills. The cohort was followed up for mortality from 1975 to 2015 with vital status obtained from original death certificates and official records of the Sverdlovsk oblast, which included information on migration from the oblast. Risk analysis began in autumn 2019.

ENV hosts the Data Coordination Center of the Childhood Leukemia International Consortium of more than 20 case–control studies around the world, from which data are pooled to obtain further insight into the etiology of childhood leukaemia. In an ENV-led project, no association was seen between parents' exposure to extremely low-frequency electric and magnetic fields at their workplace before conception or during pregnancy and the risk of leukaemia in their offspring (Talibov et al., 2019a) (Figure 5). However, a modestly increased risk of acute myeloid leukaemia was seen in children whose mothers consumed more than 1 cup of coffee per day (Karalexi et al., 2019). Advanced parental age was positively associated with the risk of lymphoblastic leukaemia (Petridou et al., 2018), but results were inconsistent for acute myeloid leukaemia (Panagopoulou et al., 2019).

The Cohort Study of Mobile Phone Use and Health (COSMOS) is a prospective cohort of mobile phone users addressing the open question of whether radiofrequency electromagnetic fields emitted during the use of mobile phones or other wireless technologies have adverse health effects. ENV completed the major recruitment of the French branch of COSMOS, in collaboration with the large French cohort Constances, in early 2019, enrolling approximately 18 000 participants.

In the large-scale collaboration between ENV and the Cancer and Environment Unit of Centre Léon Bérard, Lyon, on the

Figure 5. Association between paternal occupational exposure to extremely low-frequency magnetic fields (ELF-MF) in the months before conception and the subsequent risk of leukaemia in the offspring; results displayed for all leukaemia combined and major subtypes acute lymphoblastic leukaemia (ALL) of B-lineage or T-lineage and acute myeloid leukaemia (AML). Courtesy of Madar Talibov.



causes of testicular cancer (TESTIS), including components to better measure and predict people's occupational and domestic exposure to pesticides, the fieldwork of the core case–control study has been completed, and analysis is under way. From the methodological ancillary studies, it was found that domestic use and the persistence of banned pesticides may contribute substantially to indoor pesticide contamination in France (Béranger et al., 2019).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The Section of Nutrition and Metabolism (NME) comprises three highly integrated groups: the Biomarkers Group (BMA), the Nutritional Epidemiology Group (NEP), and the Nutritional Methodology and Biostatistics Group (NMB). The Section combines large-scale population-based studies with laboratory and biostatistical expertise to identify causal links between nutrition, metabolic factors, and cancer. The goal of the Section is to provide robust evidence on the role of nutrition in cancer development that can be translated to clinical interventions and public health policy. NME aims to go beyond what may be considered as the traditional domains of nutrition in cancer research and to fully exploit methodological advances in –omics and molecular profiling techniques to implement an integrated, multidisciplinary programme of research. The overall strategic vision of NME is based on three major research themes: (i) understanding the role of obesity and metabolic dysfunction in cancer development; (ii) identification of biomarkers of diet and nutrition and their application within studies of cancer; and (iii) multimorbidity and biological pathways common to cancer, diabetes, and cardiovascular disease. Within these themes, NME focuses on a core set of cancer sites, primarily gastrointestinal cancers, as well as hormone-related cancers, such as breast cancer and endometrial cancer. A particular emphasis is placed on cancer types that have clear links to nutrition and metabolic abnormalities and for which much remains to be discovered about disease etiology.

Biomarkers Group (BMA)

Metabolic profiles and breast cancer risk

To identify novel pathways of breast cancer development, targeted metabolomics was applied to samples from incident breast cancer cases and matched controls from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. In women not using exogenous hormone therapy at baseline (n = 2248), concentrations of arginine, asparagine, and phosphatidylcholines were inversely associated with breast cancer risk, and the concentration of acylcarnitine C2 was positively associated (Figure 1) (His et al., 2019). These findings point to potentially novel pathways that involve dysregulated amino acid, lipid, and energy metabolism in breast cancer development.

Inflammation biomarkers and thyroid cancer

Inflammation has been hypothesized to represent an etiological pathway for thyroid cancer development, but epidemiological data are limited. In a case–control study nested within EPIC, which included 475 first primary incident thyroid cancer cases and 1016 matched controls, adiponectin levels were inversely associated with risk of thyroid cancer in women but not in men. Interleukin-10 levels were positively associated with risk of thyroid cancer in women only (Dossus et al., 2018).

Coffee biomarkers and risk of liver cancer

Coffee drinking is associated with a lower risk of liver cancer, but the biological basis of this relationship is not understood. To advance knowledge in this area, 11 coffee metabolites were identified in blood from 451 subjects from the EPIC cohort (Rothwell et al., 2019a). In collaboration with the United States National Cancer Institute, BMA identified novel associations between coffee-related metabolites and liver cancer in two case–

Figure 1. Odds ratios (ORs) and permutation-based stepdown minP adjusted *P* values for associations between metabolites and risk of breast cancer in hormone non-users (1124 cases and 1124 controls). ORs are estimated per standard deviation (SD) increase in log-transformed metabolite concentrations, from logistic regression conditioned on matching variables. Adjusted *P* values greater than 0.05 (dashed line) were considered to be statistically significant after correction for multiple tests. PC, phosphatidylcholine; SM, sphingomyelin. Reproduced from His et al. (2019). CC BY 3.0 IGO.

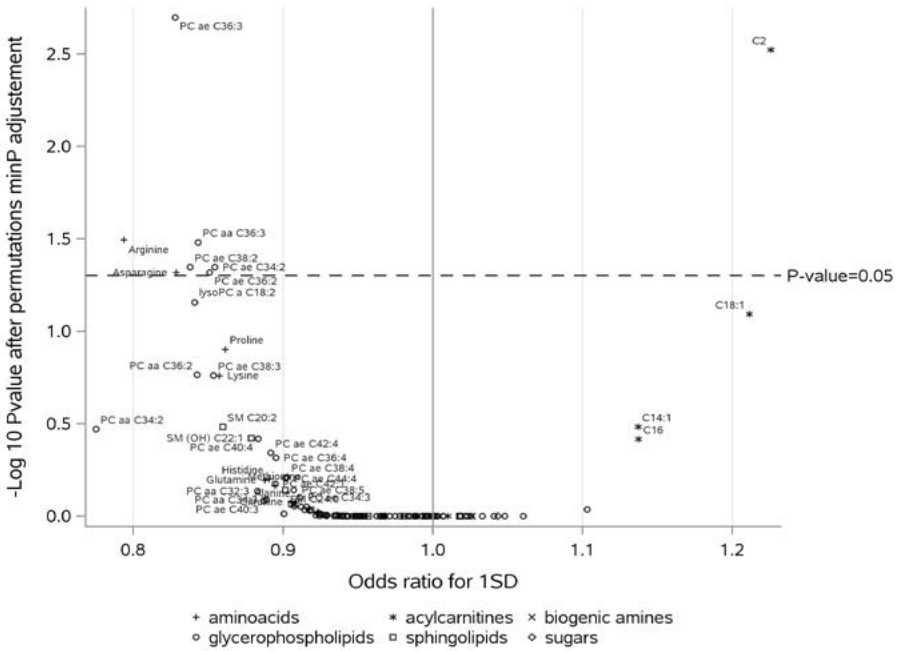
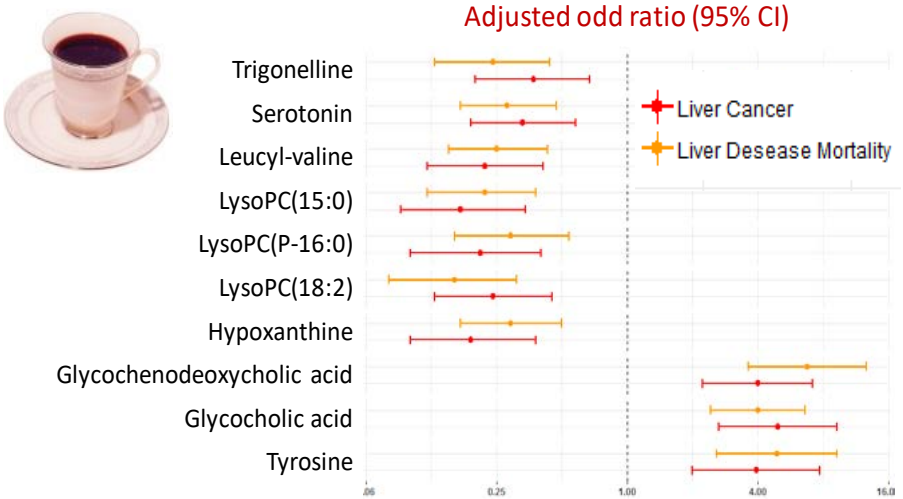


Figure 2. Odds ratios and 95% confidence intervals (CIs) for incident liver cancer and liver disease death comparing men in the 90th and 10th percentiles in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort, for 10 metabolites associated with coffee intake. Compiled from Loftfield E, Rothwell JA, Sinha R, Keski-Rahkonen P, Robinot N, Albanes D, et al. (2019). Prospective investigation of serum metabolites, coffee drinking, liver cancer incidence, and liver disease mortality. J Natl Cancer Inst. djz122. https://doi.org/10.1093/jnci/djz122 PMID:31168595.



control studies nested within the EPIC and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohorts, indicating common mechanisms that may explain the lower risk of liver cancer in coffee drinkers (Figure 2).

Wholegrain intake and intestinal serotonin production

Wholegrain intake is associated with a decreased risk of colorectal cancer, but the underlying mechanisms are not well understood. A BMA study aimed to characterize the metabolic effects of wholegrain intake by performing untargeted metabolomic analyses in a clinical dietary intervention. Among various metabolic changes, decreased plasma concentrations of serotonin were identified after consumption of wholegrain rye, compared with controls. In agreement with these results, a decrease was observed in serotonin concentrations in the colonic mucosa of mice fed a meal supplemented with rye bran or wheat fibres (Figure 3). These results suggest that decreased peripheral serotonin production may represent a link between the effects of wholegrain consumption and the risk of colorectal cancer (Keski-Rahkonen et al., 2019).

Polyphenols and risk of colon cancer

Polyphenols are major antioxidants in the diet, known for their antimutagenic and anticarcinogenic properties. A novel and highly sensitive assay based on mass spectrometry was developed to measure 37 polyphenols in blood samples (Achaintre et al., 2018). The assay was applied in a nested case–control study in the EPIC cohort to evaluate the relationship between pre-diagnostic plasma levels of polyphenols and risk of colon cancer (Murphy et al., 2018a). Two polyphenols were significantly associated with risk of colon cancer, including equol, a metabolite that is formed from soy isoflavones by the gut microbiota and is known for its estrogenic properties (Figure 4).

Figure 3. (A) Serotonin in fasting plasma after two 4-week intervention periods in crossover design. (B) Tissue serotonin in the intestines of mice fed similar high-fat diets containing different sources of dietary fibre for 9 weeks: powdered cellulose (*n* = 14), rye bran flour (*n* = 11), or wheat aleurone (*n* = 9) with matched calorie density, macronutrient, and dietary fibre content. (A) © IARC (B) © Keski-Rahkonen et al. (2019), by permission of Oxford University Press.

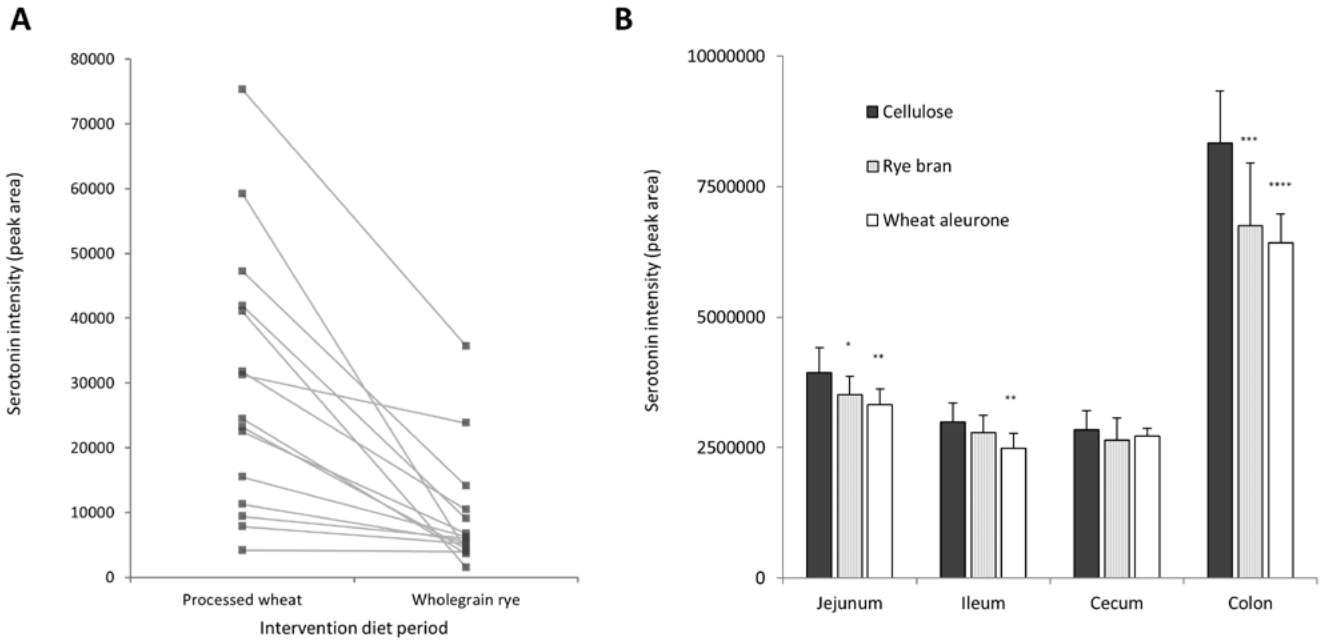
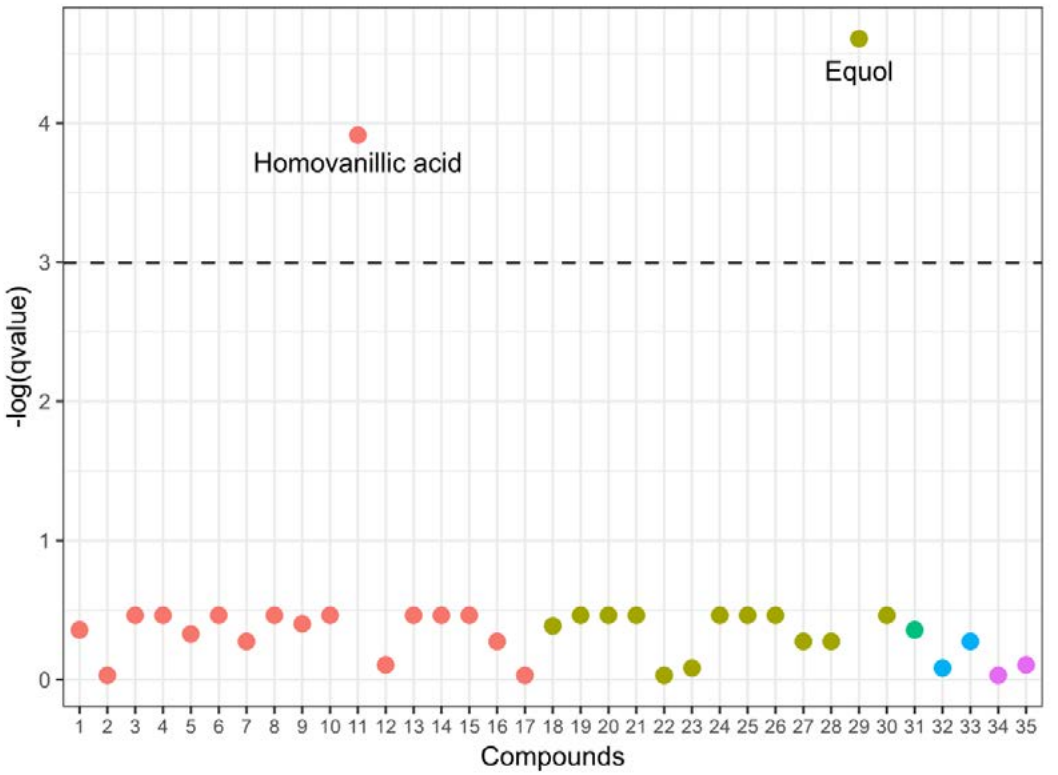


Figure 4. Associations between log2-transformed polyphenol concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Compiled from Murphy et al. (2018a).



Studies of breast cancer in low- and middle-income countries

NME is coordinating three new studies on breast cancer in low- and middle-income countries, specifically in Morocco (Determinants of Breast Cancer in Morocco, EDSMAR), South Africa (South Africa Breast Cancer, SABC), and Latin America (Molecular Subtypes of Premenopausal Breast Cancer in Latin American Women, PRECAMA).

Patients attending the breast unit at Chris Hani Baragwanath Hospital, Johannesburg, South Africa. © IARC.

Preliminary analyses from PRECAMA showed that reproductive factors are differentially associated with breast cancer subtypes in young Latin American women: an older age at first full-term pregnancy and at last pregnancy were associated with an increased risk of estrogen receptor-positive (ER+) tumours; pregnancy, number of childbirths, and history of breastfeeding were inversely associated with the risk of ER+ tumours; and older age at menarche and longer duration of breastfeeding were inversely associated with risk of estrogen receptor-negative (ER−) tumours.

Results from the SABC study showed that 91% of the study population had at least one metabolic condition (e.g. adiposity, hypertension, or impaired glucose) or another comorbidity (e.g. depression or HIV), highlighting the need to address the chronic noncommunicable disease epidemic in South Africa and to coordinate multidisciplinary care.

Analyses of food intake suggested that consumption of fresh fruit was associated with a lower risk of breast cancer in premenopausal women, whereas consumption of savoury food was associated with a higher risk in postmenopausal women (Romieu et al., 2018; Ayeni et al., 2019; Jacobs et al., 2019).

Nutritional Epidemiology Group (NEP)

Fish, long-chain fatty acids, and colorectal cancer

The link between fish and marine n-3 long-chain polyunsaturated fatty acid (LC-PUFA) intake and colorectal cancer is uncertain. NEP has examined how fish consumption and dietary and circulating levels of n-3 LC-PUFA are associated with colorectal cancer risk in the EPIC cohort. Compared with individuals consuming very little fish, those eating the highest levels had a 12% lower risk of colorectal cancer over a 16-year follow-up period. Similarly, those in the highest category of intake of n-3 LC-PUFA had a 14% lower risk of colorectal cancer compared with individuals with the lowest intakes. Regular consumption of fish may lower the risk of colorectal cancer, possibly through exposure to n-3 LC-PUFA. Following international recommendations for fish and n-3 LC-PUFA intake may reduce an individual's risk of colorectal cancer (Aglago et al., 2019).

Energy balance, metabolic health, and liver cancer

NEP has previously shown that an increased risk of hepatocellular carcinoma is associated, in part, with unhealthy lifestyle patterns, such as being physically inactive (Baumeister et al., 2019). Unhealthy lifestyle factors may act collectively to weaken the protective barrier functionality of the gut, hence increasing the exposure of the liver to environmental carcinogens, or may

cause perturbations in the metabolism of bile acids, further exposing the liver to carcinogenic compounds. Poor dietary habits may also lead to lower blood levels of micronutrients, such as selenium and zinc, both of which have been shown to be associated with a higher risk of hepatocellular cancer. Overall, numerous clear metabolic differences have been observed between cases of hepatocellular cancer and controls, assessed using high-resolution liquid chromatography–mass spectrometry metabolomic methods in collaboration with BMA.

Consumption of soft drinks and mortality

The association between total, sugar-sweetened, and artificially sweetened soft drinks consumption and subsequent total and cause-specific mortality was evaluated in 451 743 individuals from the EPIC cohort. Compared with those consuming less than 1 glass per month, individuals drinking 2 or more glasses per day of total soft drinks had a 17% higher risk of all-cause mortality. For consumers of sugar-sweetened soft drinks, the risk of premature death was elevated by 8%; for artificially sweetened soft drinks, the risk was increased by 26%. These results support public health campaigns aimed at limiting the consumption of soft drinks.

Physical activity and breast and colorectal cancer: genetic studies

Epidemiological studies have consistently observed inverse relationships between physical activity and risks of breast cancer and colorectal cancer, but they have generally relied on self-reported measures of physical activity, which may be prone to bias. NEP examined the associations between genetic variants associated with physical activity and risk of breast cancer (122 977 breast cancer cases and 105 974 controls) and of colorectal cancer (58 221 colorectal cancer cases and 67 694 controls). An increment of one standard deviation in genetically predicted average physical activity was associated with a 41% lower risk of breast cancer and a 34% lower risk of colorectal cancer. These results support a potentially causal relationship between higher physical activity levels and lower risks of breast cancer and colorectal cancer.

Nutritional Methodology and Biostatistics Group (NMB)

Alcohol and cancer

The association between alcohol consumption and cancer risk is still ambiguous for certain cancer sites, and the underlying biological pathways are not understood. Within the EPIC study, alcohol intake was associated with risk of pancreatic cancer (Naudin et al., 2018). Using novel statistical methodology to examine potential mechanisms, NMB found that concentrations of specific sex hormones did not have a major role in the relationship between alcohol intake and risk of breast cancer. The application of –omics to understand the link between alcohol consumption and cancer is also a promising area of study within the Group. With metabolomics data from EPIC participants, alcohol consumption was significantly associated with several lipid metabolites, and with specific acylcarnitines and amino acids (van Roekel et al., 2018). With epigenetic data, dietary folate and alcohol intake were associated with genomic regions with tumour suppressor activity, such as the *GSDMD* and *HOXA5* genes, supporting the hypothesis that epigenetic mechanisms may have a role in folate and alcohol metabolism and their relation to cancer (Perrier et al., 2019). These results may prove useful in future research aiming to elucidate the mechanisms of the effects of alcohol consumption in relation to several cancer sites (van Roekel et al., 2018).

Health indicators and cancer

A healthy lifestyle indicator (HLI) – a function of baseline body mass index (BMI), smoking status, alcohol intake, level of physical activity, and adherence to a healthy diet – was found to be strongly inversely associated with risk of pancreatic cancer in the EPIC cohort. Also within the EPIC cohort, HLI was inversely related to the risk of developing more than one chronic condition among cancer, cardiovascular disease, and type 2 diabetes. These findings emphasize the need for primary and tertiary prevention with guidelines targeting several lifestyle/nutritional behaviours at once. With molecular data, metabolic signatures of the HLI were strongly inversely related to the risk of hepatocellular carcinoma (Assi et al., 2018a). Circulating levels and genetic predictors of bilirubin, a metabolite with antioxidant properties, were positively associated with risk of colorectal cancer in men; an inverse association was observed in women. Nut consumption may play a role in reducing the risk of individual cancer types, specifically colorectal cancer, possibly through weight control during adulthood (Freisling et al., 2018).

Statistical methodology

Modern cancer epidemiology increasingly requires the development of ad hoc methodology to comprehensively address the challenges raised by sets of complex data. The predictive ability of established risk factors for breast cancer was evaluated in risk prediction models for ER+ and ER− tumours in the Women's Health Initiative and EPIC cohorts (Li et al., 2018a). Causal mediation analysis, used to investigate biological processes underlying the carcinogenic effect of specific risk factors, showed that sex hormones partly mediated the association between obesity and breast cancer.

Specific signatures of metabolomics data were observed to mediate, in part, the association between alcohol intake, obesity, and hepatocellular carcinoma (Assi et al., 2018b). Statistical methods for the normalization of –omics data were evaluated (Perrier et al., 2018, 2019) using tools for the pre-processing and analysis of large-dimension data previously developed within NMB (the principal component partial R-square technique). Penalized approaches can yield more accurate estimates by properly accounting for specific structures of large-dimension data, and were shown to be particularly useful in identifying and evaluating heterogeneity in subgroup analyses, under graphical models (Ballout and Viallon, 2019), or under conditional and multinomial logistic regression models.

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The Section of Genetics (GEN) includes the Genetic Epidemiology Group (GEP) and the Genetic Cancer Susceptibility Group (GCS). The work of the Section combines large population-based studies as well as laboratory and bioinformatics expertise to identify specific genes and genetic profiles that contribute to the development of cancer and elucidate how they exert their effect along with environmental factors. GEN also tries to identify individuals who are at high enough risk that they are likely to benefit from potential screening strategies.

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

Genetic Epidemiology Group (GEP)

The overall goal of the Genetic Epidemiology Group (GEP) is to contribute to understanding the causes of cancer through the study of genetic susceptibility variants of various cancer sites, and also patterns of genetic mutations that are observed in tumours. Additional goals include identifying genetic predictors of outcome, as well as developing accurate risk prediction models that take both demographic information (e.g. age and sex) and biomarkers (genetic and non-genetic) into account. The work of GEP includes studies of cancers related to tobacco use and alcohol consumption (lung and aerodigestive tract cancers) and cancers related to obesity (such as kidney, pancreatic, and colorectal cancers). GEP devotes substantial resources to extensive fieldwork, with the goal of recruiting large series of cases and controls, comprising extensive questionnaire information and biological samples. Genetic analyses of inherited susceptibility usually comprise a genome-wide approach initially, with subsequent large-scale coordinated replication studies in diverse populations. This latter aspect is aided by the development of international consortia in which GEP takes a leading role. Confirmed susceptibility loci are investigated in more detail with a variety of techniques, including in silico, expression, and sequencing studies, which are often conducted in collaboration with other IARC Groups. Analysis of these large genome-wide studies also includes a Mendelian randomization approach that aims to understand how lifestyle factors influence cancer onset.

GEP is also undertaking a large international study of the causes of cancer by analysis of mutation patterns (or mutational signatures) in cancer genomes. Most of the Group's efforts in this domain are included in the Mutographs project, which aims to understand the causes of five different cancer types across five continents.

In addition to studies of genetic factors, GEP is conducting a wide range of studies involving non-genetic factors, including evaluations of circulating biomarkers such as human papillomavirus (HPV) antibodies for head and neck cancers, and a wide range of protein and other biomarkers for lung cancer. The overall goal of these studies is to identify individuals at sufficiently high risk to justify screening and early detection.

Some prominent examples of the Group's work over the 2018–2019 biennium are described here.

Elucidating the etiological role of obesity and related risk factors in multiple cancers – a Mendelian randomization approach

Elevated body mass index (BMI) and obesity-related risk factors have been associated with multiple cancer types studied by GEP. Because these risk factors are inherently interrelated, traditional epidemiological studies have not been able to untangle which specific factors exert a causal influence and which are merely correlated with the underlying causal factor.

By leveraging data from genome-wide association studies of tens of thousands of cancer cases and controls that GEP has led or contributed to, the Group has conducted a series of studies in which the causal relevance has been interrogated for several obesity-related risk factors for various cancers. Because these analyses were based on genetic instruments, they are not influenced by reverse causation and are less sensitive to confounding than those using direct exposure measures. The results have been illuminating for a wide variety of cancer types, including colorectal, ovarian, and endometrial cancers, and extend the Group's earlier work on kidney and pancreatic cancers (Mariosa et al.,

2019). In particular, the results provide compelling evidence that earlier studies of obesity based on epidemiological data have underestimated the impact of this important risk factor. GEP's analysis also suggests a potentially important role for obesity in lung cancer, which is likely to be driven by the association between BMI and smoking status (Carreras-Torres et al., 2018).

Progress in the Mutographs study

A major initiative of the Section, Understanding of the Causes of Cancer through Studies of Mutational Signatures – Mutographs, launched in May 2017, is an effort to understand the causes of cancer by generating mutational signature profiles based on whole-genome sequence data. The study results from a major Cancer Research UK (CRUK) Grand Challenge grant – one of the world's most ambitious cancer research awards – and is co-led by Dr Paul Brennan together with overall principal investigator (PI) Professor Sir Mike Stratton from the Sanger Institute (Cambridge, United Kingdom) and four other co-PIs.

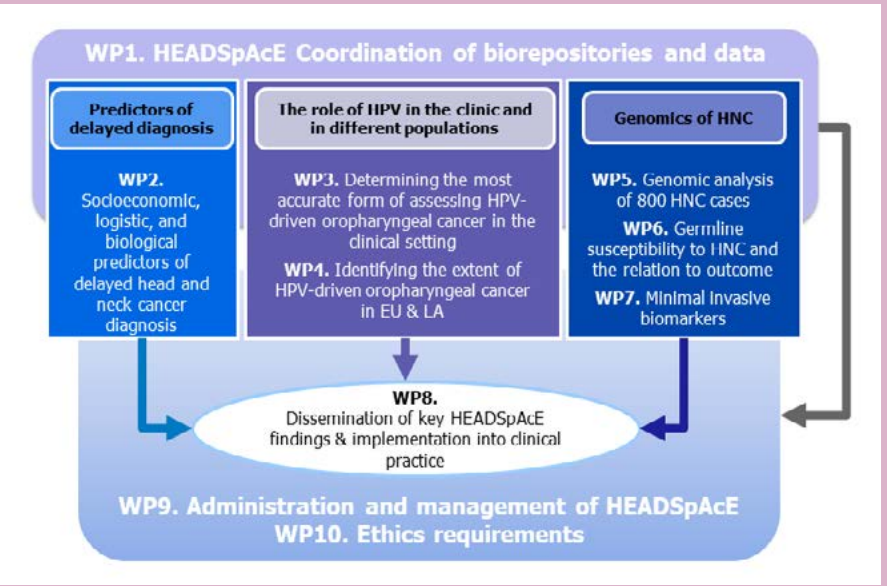
Within the Mutographs initiative, GEP is coordinating the recruitment of 5000 individuals with cancer (colorectal cancer, renal cancer, pancreatic cancer, oesophageal adenocarcinoma, or oesophageal squamous cancer) across five continents to explore whether different mutational signatures explain the marked variation in incidence. Through an international network of collaborators, biological materials are collected, along with demographic, histological, clinical, and questionnaire data. Whole-genome sequences of tumour–germline DNA pairs are generated at the Sanger Institute. Extracted somatic mutational signatures are then correlated with data on risk factors. By September 2019, 39% of the cases had been recruited and the biological samples received at IARC, with full-genome sequencing completed on 28% of those.

HEADSpAcE project

The large-scale initiative Translational Studies of Head and Neck Cancer in South America and Europe (HEADSpAcE) was recently launched to address the high mortality rate of head and neck cancer in South America and Europe. This work is funded by the European Commission as part of the Horizon 2020 European Union Research and Innovation Programme and is coordinated by GEP across 15 sites across two continents.

Head and neck cancer is the sixth most common cancer in both South America and Europe. A major reason for the high mortality rate of this cancer is the late stage of diagnosis for many patients. Accurate assessment of the prognosis of head and neck cancer cases enables appropriate treatment decisions. For this project, GEP brings together a consortium of 15 partners to understand reasons for late diagnosis and reduce the proportion of head and neck cancers that are diagnosed at a very late stage. Through the international network of collaborators, biological materials are collected, along with demographic, histological, clinical, and questionnaire data. Genomic evidence of strong predictors of prognosis that will have the potential to improve care and reduce treatment-related morbidity will be developed, along with guidelines for implementation in clinical care.

Overview of comprehensive approach (Work Packages 1–10) to assessing high mortality from head and neck cancer: the HEADSpAcE project. EU, European Union; HNC, head and neck cancer; HPV, human papillomavirus; LA, Latin America; WP, Work Package. © IARC



Genetic Cancer Susceptibility Group (GCS)

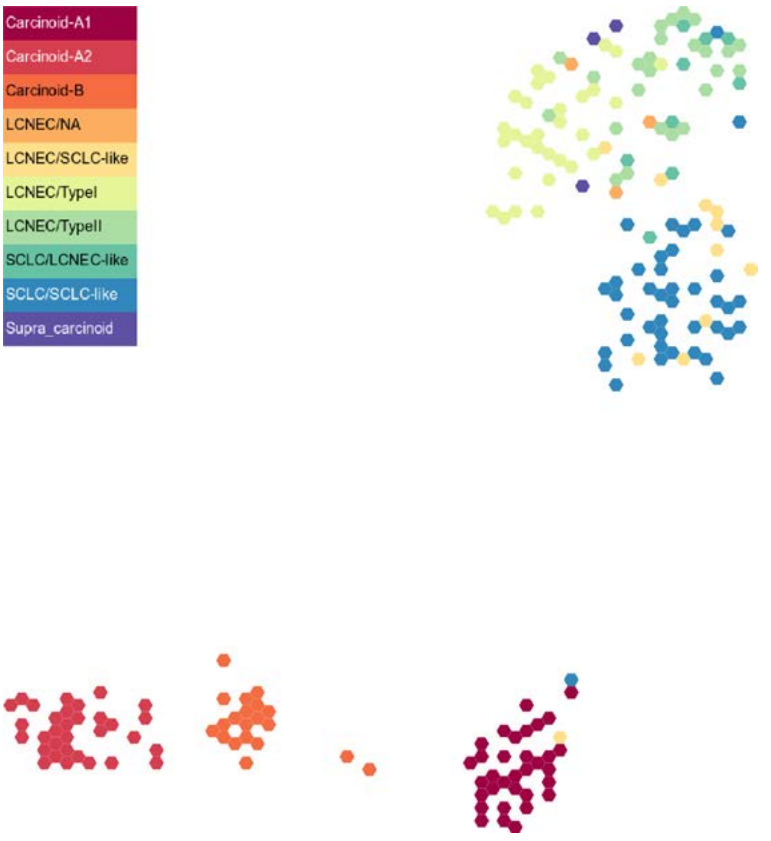
The Genetic Cancer Susceptibility Group (GCS) contains a multidisciplinary scientific team, covering genetics, genomics, bioinformatics, and pathology. These combined skills are used to undertake genetic and genomic research to identify cancer-related genes, explore their mechanisms of action, and determine how tumours are classified and detected. Working within international consortia, GCS is able to assemble the appropriate sample sizes required for informative genetic and genomic studies. GCS's multifaceted genomic analysis and multidisciplinary team provide additional depth to these consortia-based studies.

The general focus of GCS has been on four areas during the 2018–2019 biennium: the genomic characterization of lung neuroendocrine neoplasms and malignant pleural mesothelioma, the exploration of *TERT* mutations as early detection biomarkers in urothelial cancer, the Group's traditional area of understanding germline genetic susceptibility, and facilitating genetic and genomics research at IARC and within the wider community.

In the context of the Rare Cancers Genomics project (http://rarecancersgenomics.com), which is aimed at the molecular characterization of rare cancers, including lung neuroendocrine neoplasms (lungNENomics) and malignant pleural mesothelioma (MESOMICS), GCS collaborated with researchers from 20 centres in 10 countries to assemble an important collection of these rare cancers. Using this resource, GCS has (i) provided an integrative genomic profiling of large-cell neuroendocrine carcinomas, revealing distinct subtypes of high-grade neuroendocrine lung tumours (George et al., 2018), which appear to be predictive of clinical response (Derks et al., 2018a); (ii) unveiled the existence of new molecular subtypes of pulmonary carcinoids, including, of particular interest, a group named supracarcinoids (Alcala et al., 2019a); (iii) redefined malignant pleural mesothelioma types as a continuum, uncovering immune–vascular interactions, which have clinical implications (Alcala et al., 2019b); (iv) contributed to recommendations for the classification of both malignant mesothelioma and neuroendocrine neoplasms (Rindi et al., 2018); and (v) created the first molecular maps (https://tumormap.ucsc.edu) (Figure 1) for malignant mesothelioma and lung neuroendocrine neoplasms, which will assist and increase the translational impact of molecular studies in these rare cancer types.

In the context of biomarkers, GCS has explored the possibility that highly recurrent telomerase reverse transcriptase (*TERT*) gene promoter mutations (C228T and C250T) detected from tumour cells shed in the urine of patients might be potential biomarkers for urothelial cancer (Figure 2). Drawing on the Group's laboratory and bioinformatics skills, GCS developed a singleplex assay (UroMuTERT) that detects *TERT* promoter mutations, even at low abundance, and tested it using a series of cases and controls from France (blood, urine samples, and, for the cases, tumours) and Portugal (urinary exfoliated

Figure 1. Integrative molecular map of lung neuroendocrine neoplasms (LNEN) based on transcriptome data from the LungNENomics project. Uniform Manifold Approximation and Projection (UMAP) representation of 208 LNEN samples (small-cell lung cancer [SCLC]; large-cell neuroendocrine carcinomas [LCNEC]; typical and atypical carcinoids) based on the expression of the most variable genes (6398 genes explaining 50% of the total variance). The layout was created on the University of California Santa Cruz TumorMap (https://tumormap.ucsc.edu) using a hexagonal grid; point colours correspond to molecular clusters previously identified in each study individually (George et al., 2018; Alcala et al., 2019a). © IARC.

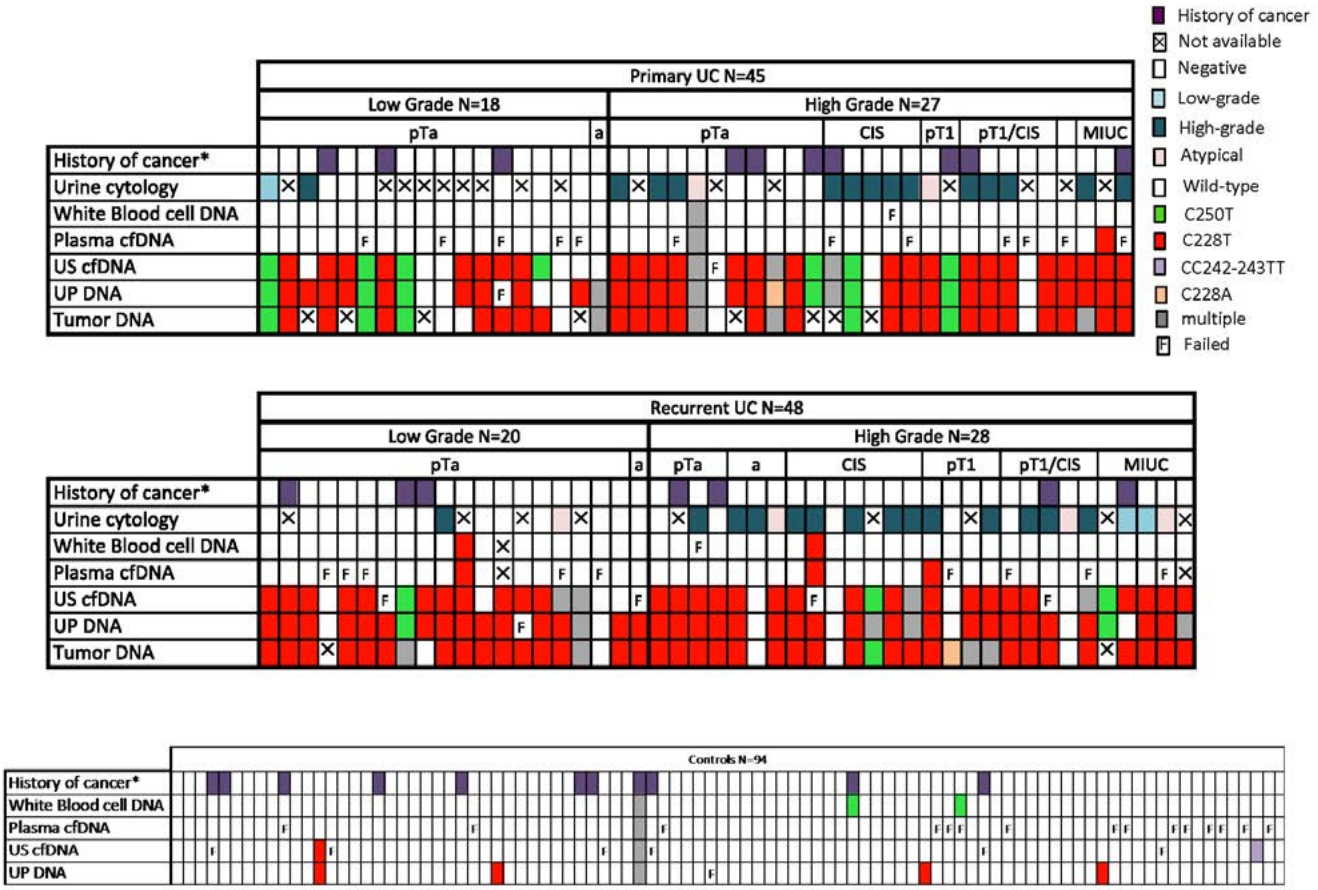


cell samples). In detecting *TERT* promoter mutations in urinary DNA, UroMuTERT showed excellent sensitivity and specificity for detection of urothelial cancer, especially for low-grade and/or early-stage cancers, and considerably outperformed urine cytology (Avogbe et al., 2019). The Group is now investigating the viability of these mutations as early detection biomarkers for bladder cancer in pre-diagnostic samples collected within a prospective population-based cohort in the Islamic Republic of Iran (the Golestan Cohort).

In the context of germline susceptibility, GCS continues to play an important role in coordinating genetic studies within the large international consortia, particularly the International Lung Cancer Case–Control Consortium (ILCCO) and the International Lymphoma Epidemiology Consortium (InterLymph). GCS aims to introduce aspects of genomics into the germline genetic studies carried out by these consortia. An example of the integrative approach of GCS in these studies is the Group's identification of *DIS3* as a multiple myeloma (MM) susceptibility gene, with important genetic effects (Pertesi et al., 2019). This study included analysis of germline material from patients with familial and sporadic MM, transcriptomics of normal blood samples, and mutation and transcriptomics of MM tumours. Although each branch of research in isolation was only suggestive, the evidence that *DIS3* is a MM susceptibility gene is more compelling when accumulated across the different areas of complementary molecular analysis.

Finally, GCS still plays an active role in the development of genomics capabilities at IARC and elsewhere. GCS has led the pathology workflow for the Mutographs project (see above), a large-scale international study that aims to unveil the carcinogenic role of environmental exposures by analysing the mutational signatures through whole-genome sequencing of 5000 cancers collected from 40 recruiting centres in five continents (https://www.mutographs.org/). Cancers of the oesophagus, pancreas, colorectum, and kidney are collected and shipped to IARC. GCS then leads the processing of samples and microscopic analysis of frozen tissues through the application of digital pathology and the contribution of a panel of expert external pathologists. With important contributions from other Groups, GCS has continued to build links within the genomics community at IARC, as well as provide access to the laboratory techniques, pathology expertise, electronic record-keeping, and computational resources for genomics-related activities at IARC. The Group is also active in ensuring the accessibility of developments and advances in knowledge within the Agency to the wider scientific community, for example, via the Group's GitHub website (https://github.com/IARCbioinfo/).

Figure 2. Overview of the detection of *TERT* promoter mutations by the UroMuTERT assay applied to body fluids and tumours, from the DIAGURO cohort, of primary and recurrent urothelial carcinoma cases and body fluids of controls. *, cancer other than urothelial; a, pTa/CIS; CIS, carcinoma in situ; MIUC, muscle-invasive urothelial carcinoma; UC, urothelial carcinoma; UP DNA, urine pellet DNA; US cfDNA, urine supernatant cell-free DNA. Reprinted from Avogbe et al. (2019), Copyright 2019, with permission from Elsevier.




LIFE PROJECT

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The Section of Early Detection and Prevention (EDP) conducts research on the efficacy, safety, and cost–effectiveness of cancer prevention and early detection interventions to guide rational cancer control policies, with a particular emphasis on low- and middle-income countries (LMICs). One of the principles that guide the work is the search for simplified, affordable technology adaptable to the available resources of LMICs. EDP provides technical support to current and planned population-based prevention and screening programmes in LMICs in the context of cancer control, conducts clinical and screening trials, and conducts implementation and health economics research. In addition, the Section develops educational materials and conducts training activities for cancer control.

One of the main topics has been the evaluation of alternative administration schedules of human papillomavirus (HPV) vaccines, including the reduction in the number of doses for more affordable and logistically feasible programmes. The gastric cancer research programme includes two large randomized clinical trials to evaluate the impact of *Helicobacter pylori* eradication and other interventions on the incidence of and mortality from gastric cancer. In secondary prevention, EDP projects include several large research and

implementation studies on early detection and screening of major cancer types, including cancers of the cervix, stomach, breast, colorectum, and oral cavity.

In general, the studies are multicentre and multidisciplinary, and EDP has established extensive networks involving highly capable clinicians, epidemiologists, and other staff. The networks facilitate the transfer of research technology to local researchers and often their students, who actively participate in the design and conduct of studies and the analysis of data. Finally, an important part of the work of EDP is the dissemination of the available scientific evidence base and the provision of technical assistance to governments and policy-makers in countries that are developing cancer control programmes.

Prevention and Implementation Group (PRI)

Cervical cancer vaccination and screening

The Prevention and Implementation Group (PRI) demonstrated the durable immunogenicity and protection of one-dose HPV vaccination in previous studies (Kreimer et al., 2018a; Safaeian et al., 2018). Given the public health potential, in collaboration with the United States National Cancer Institute, PRI is conducting a large randomized trial (the ESCUDDO study) of the non-inferiority of one versus two doses of the bivalent and nonavalent vaccines in 20 000 adolescent girls aged 12–16 years in Costa Rica (Sampson et al., 2018). In addition, 4000 women aged 17–20 years are being recruited as controls to estimate the efficacy of the vaccination schedules. Recruitment is currently at 16 000 women and will be completed in early 2020, with a 4-year follow-up.

Figure 1. Prevalence of cervical precancerous lesions and cancer in women aged 30–64 years in the ESTAMPA study of human papillomavirus (HPV) screening and triage. CIN, cervical intraepithelial neoplasia. © IARC.

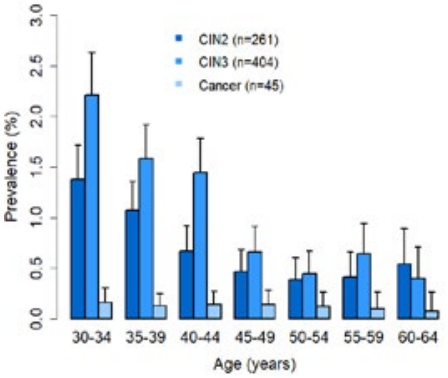


Table 1. Performance of the HPV 16/18 E6 oncoprotein for the detection of high-grade squamous intraepithelial lesion (HSIL) precancer (< HSIL) and/or cancer (≥ HSIL). Reproduced from Ferrera et al. (2019), with permission by John Wiley and Sons.

Cases	Disease status (n)		Sensitivity (%) (95% CI)[a]	Specificity (%) (95% CI)[a]
	< HSIL	≥ HSIL		
All cases included				
E6 16/18−	155	24	56.4 (43.3–68.6)	97.5 (93.7–99.0)
E6 16/18+	4	31		
Associated with HPV 16/18[b]				
E6 16/18−	155	1	96.8 (83.8–99.8)	97.5 (93.7–99.0)
E6 16/18+	4	30		
Associated only with HPV 16[b]				
E6 16−	157	0	100.0 (85.1–100.0)	98.7 (95.5–99.7)
E6 16+	2	22		
Associated only with HPV 18[b]				
E6 18−	157	1	87.5 (52.9–99.4)	98.7 (95.5–99.7)
E6 18+	2	7		

CI, confidence interval; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion.

[a] Confidence intervals for binomial probabilities. As part of assessing the performance of the E6 protein, we also estimated the sensitivity for cancer detection: 61.3% (95% CI: 43.8–76.3%) for all cases included and 100% (95% CI: 51–100%) for the other groups.

[b] Cases with ≥ HSIL not associated with HPV 16/18, HPV 16, or HPV 18 excluded. Genotyping based on GP5/GP6.

The ESTAMPA study, which is under way in 12 centres, is currently investigating emerging cervical cancer screening and triage techniques in Latin America in 50 000 women aged 30–64 years (recruitment is currently at about 36 000 women). HPV-positive women receive a colposcopy, biopsy, and treatment as needed, and a second screening after 18 months. The main outcome is advanced cancer precursors. The global prevalence of high-risk HPV infection is currently 14.2% (95% confidence interval: 13.8–14.6%), decreasing from 21% in those aged 30–34 years to 11% in those older than 60 years, with a similar age pattern for the prevalence of cervical cancer precursors (Figure 1). An evaluation of the performance of the E6 oncoprotein for the detection of cervical lesions demonstrated high sensitivity and specificity (Ferrera et al., 2019) (Table 1).

The study also enables the investigation of risk factors for HPV infection and precursors at the participating sites (Kasamatsu et al., 2019).

The CESTA study is investigating cervical cancer screening algorithms and treatment modalities in Africa, with an emphasis on HIV-positive women (Figure 2).

PRI continues to provide support to cervical cancer screening programmes in Belarus, Mongolia, Myanmar, Romania, and several countries in Latin America (Arrossi et al., 2019). In addition, PRI actively participates in the Cervical Cancer Elimination Initiative recently launched by the World Health Organization (WHO), and coordinates the Working Group on research within that initiative.

Figure 2. Site visit for the CESTA study, Dakar, Senegal, August 2019. © IARC.

Epidemiology and prevention of *H. pylori* infection and gastric cancer

In collaboration with the National Cancer Center of the Republic of Korea, PRI is conducting a randomized controlled trial of *H. pylori* eradication for gastric cancer prevention (the HELPER study), recruiting 11 000 subjects aged 40–65 years to attend endoscopic screening (completion in 2019). *H. pylori*-positive subjects are randomized to quadruple eradication therapy or placebo. All participants are followed up with endoscopic screening every 2 years within the country's National Cancer Screening Program for 10 years.

Another large randomized clinical trial (GISTAR), in collaboration with the University of Latvia, aims to determine whether combined *H. pylori* and pepsinogen screening, followed by *H. pylori* eradication in positive subjects and endoscopic follow-up of those with serologic atrophic gastritis, compared with routine care, reduces gastric cancer mortality. Recruitment for GISTAR continues in Latvia, where 8000 participants are included to date; the aim is to expand the study to eastern European countries, where the burden of gastric cancer remains high (Figure 3).

Figure 3. International Gastric Cancer Prevention Research Forum, introduction to the GISTAR study, Riga, Latvia, February 2018. © IARC.

PRI continues to investigate the prevalence of *H. pylori* and gastric lesions in low- and high-risk areas for gastric cancer around the world (the ENIGMA study), in an attempt to explain regional differences and generate etiological hypotheses (Figure 4).

Gambia Hepatitis Intervention Study

The Gambia Hepatitis Intervention Study (GHIS) was started in 1986. During 1986–1990, the vaccination of babies against hepatitis B virus was implemented in The Gambia with a "stepped-wedge" trial design. At the time, palm prints and footprints were collected from every baby in the study. In 2011, the third phase of the study started, aiming to evaluate the long-term efficacy of childhood hepatitis B virus vaccination in the prevention of liver cancer in adulthood.

Dr Ramou Njie, a hepatologist, was appointed as the head of the GHIS Group, based in The Gambia, to set up a liver disease clinic to ensure the identification of cases of liver cancer and to strengthen the national cancer registry, led by Mr Lamin Bojang. Cancer registrars based at the main hospitals around the country were also appointed to support the identification of cases of liver cancer as well as the registration of all cancer cases presenting at the hospitals.

About 100 cases of liver cancer have been identified in subjects born in 1984–1992, and three of them have been correctly matched to children's files with the help of Interpol in Lyon, where the linkage of palm prints and footprints of children and adult cases is carried out. This third phase of the GHIS will end in December 2019, but efforts in matching – both by improved data linkage through different methods and by matching prints – will continue. Potential collaborations are under considerations, including with engineering schools with expertise in the use of artificial intelligence to characterize images, in order to improve the rate of print matching.

Figure 4. ENIGMA study coordination meeting in the Islamic Republic of Iran, June 2019: (left) endoscopy clinic of ENIGMA study, Ardabil; and (right) collaborators of the ENIGMA study. © IARC.

Application of economics to cancer

Descriptive studies on the economics of cancer provide important insights into the economic burden (costs) of cancer, both for individuals and their households and for society as a whole. In collaboration with the Section of Cancer Surveillance (CSU) and other partners, PRI seeks to document the financial and economic costs of cancer, including studies on global productivity losses as a result of premature mortality from cancer (Pearce et al., 2018), a systematic review of the level of (catastrophic) out-of-pocket expenditures, and an invited chapter on the role of health systems in addressing inequalities in access to cancer control that was included in an IARC Scientific Publication.

Priority setting in cancer prevention and control seeks to achieve health system goals of health maximization, equity, and efficiency by providing guidance to countries on cancer control interventions that are cost-effective, affordable, and feasible to implement. Collaborating with WHO, PRI is developing: (i) an interactive platform to model the impact and costs associated with priority cancer control interventions; and (ii) an investment case for cancer prevention and control, to assist national policy-makers in obtaining the best value for money by identifying priority interventions.

Screening Group (SCR)

Cervical cancer vaccination and screening

In a multicentre cohort study involving 17 064 females vaccinated at age 10–18 years with one, two, or three doses of quadrivalent HPV vaccine, the Screening Group (SCR) demonstrated that two doses were adequate to protect girls aged 15–18 years (the current recommendation is three doses) against persistent HPV 16/18 infection (Basu et al., 2019b). The L1-binding antibody titres at 7 months against vaccine-targeted HPV types (HPV 16/18/6/11) in 15–18-year-old two-dose recipients were non-inferior compared with those in 15–18-year-old three-dose recipients or 10–14-year-old two-dose recipients (Bhatla et al., 2018a). Persistent infection was significantly lower in vaccinated participants, irrespective of age at vaccination and number of doses. A single dose of quadrivalent vaccine was as protective as two or three doses against persistent HPV 16/18 infections (Sankaranarayanan et al., 2018). The study outcomes were shared with the WHO Strategic Advisory Group of Experts.

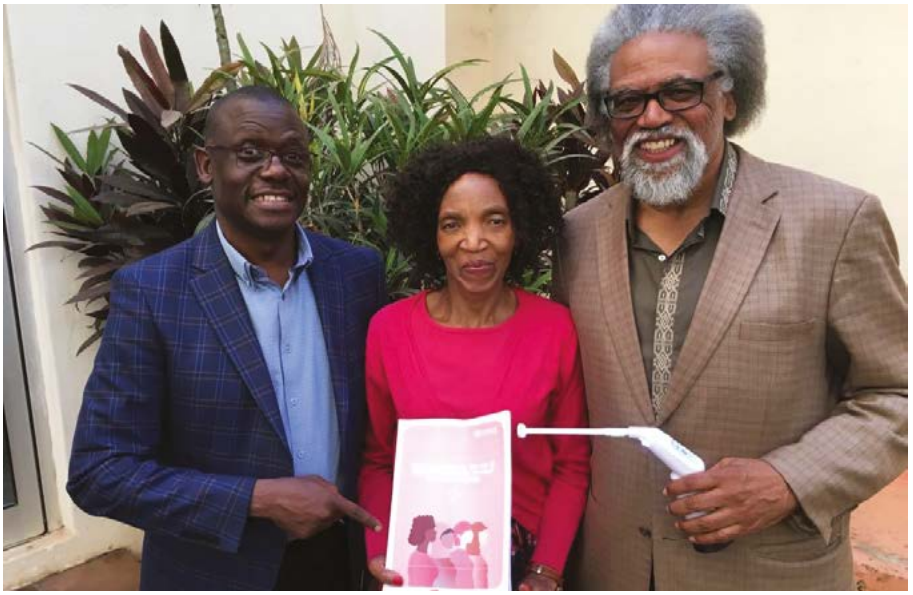
In a publication that had a high impact on public health, SCR described the rising cervical cancer incidence and mortality in young Japanese women over the past 25 years (Subramanian and Sauvaget, 2018; Utada et al., 2019) as a result of altered risk factors (sexual behaviour, smoking, and HPV prevalence) as well as limited screening coverage (only 34% in 2016). Another SCR study in Japan demonstrated that detection rates of high-grade precancer and cancer were significantly lower in HPV-vaccinated women (2.6 per 1000) compared with unvaccinated women (7.1 per 1000) at screening at age 25–29 years (Konno et al., 2018).

The collaborative project between SCR and the National Cancer Institute of Thailand showed that HPV messenger RNA (mRNA) and HPV DNA tests had similar performance characteristics (Sangrajrang et al., 2019). The sensitivity, specificity, and positive predictive value of the mRNA test to detect high-grade lesions were 73.1%, 97.8%, and 16.3%, respectively; for the DNA test, the values were 67.4%, 97.1%, and 12.1%, respectively. Triaging of HPV-positive women with cytology alone or HPV 16/18 genotyping and cytology in combination yielded comparable test accuracies. The study outcomes facilitated the drafting of the screening and triaging

protocol for HPV-based cervical screening in Thailand.

SCR supported the development and evaluation of a new battery-powered portable thermal ablator to treat cervical precancers (Figure 5). The success rate of treating cervical precancers with the new device in a screen-and-treat setting in Zambia was similar to that of standard cryotherapy (64.1% vs 60.0%) (Table 2). This new device avoids many of the practical disadvantages of cryotherapy, is preferred by health-care providers, and produces minimal complications or discomfort. A recent meta-analysis by SCR also demonstrated the high efficacy of thermal ablation in the treatment of high-grade cervical precancers (success, 93.8%) (Randall et al., 2019a). The SCR studies informed the recent drafting of thermal ablation guidelines by WHO.

Figure 5. The new battery-powered portable thermal ablator was developed with funding support from the National Institutes of Health, USA. SCR collaborator Professor Groesbeck Parham demonstrating the device. Courtesy of Dr Nothema Simelela.



Evaluation of national cancer screening programmes

SCR evaluated the cancer screening programme in Morocco through a project supported by the Ministry of Health and the Lalla Salma Foundation for the Prevention and Treatment of Cancers (Basu et al., 2018a; Selmouni et al., 2019). Breast and cervical cancer screening initiated in 2010 by the Ministry of Health in Morocco was high-volume opportunistic. Nurses at the primary care facilities offered clinical breast examination to women aged 40–69 years and cervical visual inspection with acetic acid to women aged 30–49 years. Screening coverage was moderate for breast cancer (63%) and low for cervical cancer (24%) in 2016. Detection rates of breast cancer (1 per 1000) and of cervical precancer and cancer (0.9 per 1000) were lower than expected.

Another SCR study demonstrated the large variability in colorectal cancer screening within the European Union (Senore et al., 2019); participation rates varied from 4.5% to 71.3%, and compliance with referral for colonoscopy assessment ranged from 64% to 92%. The detection rates of advanced adenomas and colorectal cancer were higher for the faecal immunochemical test programmes than for the guaiac faecal occult blood test programmes.

Table 2. Cervical precancer treatment success ratesa at 6 months follow-up in a randomized controlled trial, in Zambia, comparing battery-powered thermal ablator, cryotherapy, and large loop excision of the transformation zone. Reprinted from *The Lancet Oncology*, Pinder et al., Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial, Copyright 2019, with permission from Elsevier.

Participants	Number (%)				*P* value
	Cryotherapy (*n* = 250)	Thermal ablation (*n* = 250)	LLETZ (*n* = 250)	Total (*n* = 750)	
Eligible for 6-month follow-up	246 (98.4)	244 (97.6)	245 (98.0)	735 (98.0)	NA
Followed up at 6 months	206 (83.7)	197 (80.7)	204 (83.3)	607 (82.6)	NA
Overall					
Participants followed up[b]	200 (100.0)	192 (100.0)	199 (100.0)	591 (100.0)	NA
Participants with no evidence of disease[a]	120 (60.0)	123 (64.1)	134 (67.3)	377 (63.8)	0.311
HIV-negative at baseline					
Participants followed up	85 (100.0)	93 (100.0)	93 (100.0)	271 (100.0)	NA
Participants with no evidence of disease[a]	68 (80.0)	77 (82.8)	76 (81.7)	221 (81.5)	0.890
HIV-positive at baseline					
Participants followed up	109 (100.0)	95 (100.0)	101 (100.0)	305 (100.0)	NA
Participants with no evidence of disease[a]	50 (45.9)	42 (44.2)	55 (54.5)	147 (48.2)	0.297

HPV, human papillomavirus; LLETZ, large loop excision of the transformation zone; NA, not applicable; VIA, visual inspection with acetic acid.

[a] Treatment success was defined as either HPV type-specific clearance at 6 months among women positive for the same HPV type at baseline, or negative VIA test at follow-up if the baseline HPV test was negative.

[b] HPV reports were missing for 6, 5, and 5 women who received cryotherapy, thermal ablation, and LLETZ treatment, respectively; these patients were excluded from the analysis of treatment success rates.

Screening for noncommunicable diseases

An SCR study conducted in rural India demonstrated that community health workers could be trained to provide comprehensive noncommunicable disease detection services at home (Basu et al., 2019a) (Figure 6). High blood pressure and blood sugar were detected in 32.6% and 7.5% of participants, respectively (1988 men and 4997 women aged 30–60 years); hypertension and diabetes were confirmed in 42.3% and 35.0%, respectively, among those undergoing follow-up. Nearly 90.0% of women agreed to provide self-collected samples for HPV testing for cervical cancer screening, and 76.5% of the HPV-positive women attended a primary health centre for further evaluation and treatment.

Training of screening programme managers and service providers

SCR conducted training of programme managers and different levels of service providers in different countries (Bangladesh, Benin, China, Côte d'Ivoire, India, Senegal, and Zambia) (Figure 7).

Figure 6. Early detection of common noncommunicable diseases, including breast, cervical, and oral cancers, at home by community health workers in rural India. Community health workers performing check-ups of women at home. © IARC.

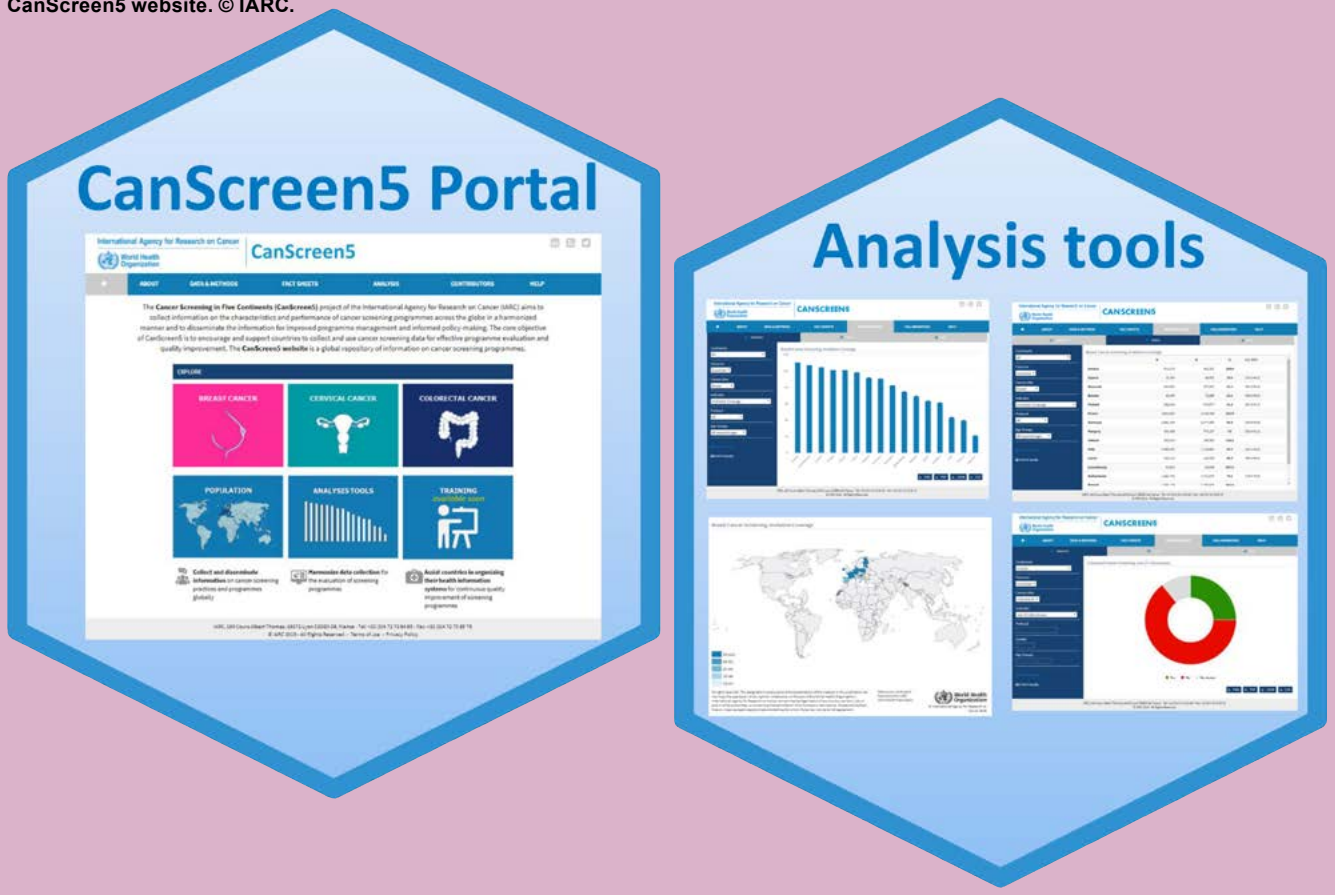
Figure 7. Snapshots from training programmes conducted by SCR: (left) in Cotonou, Benin, and (right) in Udaipur, India. © IARC.

Cancer Screening in Five Continents

The Cancer Screening in Five Continents (CanScreen5) project of SCR aims to uniformly collect, analyse, store, and disseminate information on the characteristics and performance of cancer screening programmes in different countries, with the core objective of motivating and supporting countries to collect and use cancer screening data in a consistent manner on a regular basis using an effective information system. A web-based open access platform (http://canscreen5.iarc.fr) was launched to facilitate access to and interpretation of data from the screening programmes, and to enable the individual programmes to compare their performance over time and with that of other similar programmes. The new initiative will impress upon the programme managers the value of monitoring and quality improvement of cancer screening programmes, and will also support capacity-building in the field.

CanScreen5 has led to two new projects: (i) a collaboration with the Centre for Global Health Inequalities Research (CHAIN) in Norway (supported by the Research Council of Norway) to evaluate how health inequalities affect cancer screening programmes in Latin America and identify evidence-based interventions to tackle such inequalities; and (ii) capacity-building of programme managers (supported by the National Institutes of Health, USA), focusing on improving data collection for better quality assurance of cancer screening programmes, to be attended by participants from 20 African countries.

CanScreen5 website. © IARC.

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Secretary
Ms Laurence Marnat

The Office of the Director comprises a small team that supports the Director in the implementation of the strategy of the Agency and its research activities. The Director is guided by the Medium-Term Strategy, which is developed in a large consolidation process with internal and external stakeholders and is refined and adopted in close collaboration with the IARC Scientific and Governing Councils.

In addition to providing administrative support to the Director's activities, the team in the Office of the Director assists with the coordination of a range of internal and external initiatives. This work includes supporting internal advisory groups and committees, contributing to the preparation of Governing and Scientific Council meetings and related initiatives with current and prospective IARC Participating States, coordinating cross-cutting resource mobilization and scientific initiatives and programmes with input from across the Agency, and assisting the Director in the development of strategic partnerships with the Agency's network of institutional collaborators, particularly the World Health Organization (WHO).

The bioethics and compliance team is also hosted in the Director's Office, to give it maximal independence from the scientific work conducted within the Agency. This team provides a dedicated secretariat to the IARC Ethics Committee, which is responsible for the efficient and transparent ethical evaluation of all IARC projects, and ensures the robust and consistent management of potential conflicts of interest of external experts who participate in IARC activities.

The Office of the Director provides the secretariat to the regular meetings of the Senior Leadership Team, and in February 2019 organized a 1-day off-site retreat where IARC senior staff discussed topics related to IARC's future scientific strategy, communications strategy, engagement with potential new Participating States, and IARC's values.

In line with the mandate of the Agency, several high-level partnership agreements were signed or renewed during the biennium, in order to promote collaborations with other cancer research institutes around the world, including with the African Academy of Sciences; the Danish Cancer Society; the German Cancer Research Center; the Centre Léon Bérard in Lyon, France; the Iranian Cancer Research Centre; the Istituto Superiore di Sanità, Italy; the National Cancer Center of the Republic of Korea; and the Union for International Cancer Control in Geneva, Switzerland.

In addition, with the creation of the senior position of Strategic Engagement

and Resource Mobilization Officer, the Agency has been increasing its efforts to raise the necessary funds for its future infrastructure and research programme.

The Office of the Director also assists with the cross-cutting coordination of collaborations with key partners in global policy development, technical cooperation, and advocacy for cancer prevention and control, including with WHO headquarters and regional offices and with other governmental and nongovernmental organizations.

Importantly, 2019 marked the first year that IARC was present at Regional Committee meetings of WHO. The Director received invitations to both the WHO Regional Office for Europe and the WHO Regional Office for the Eastern Mediterranean Regional Committee meetings, held in Copenhagen and Tehran, respectively.

An example of a cross-cutting project supported by the Director's Office is the Cancer Prevention Europe initiative, which aims to develop a strong rationale for promoting cancer prevention research in Europe in the coming years. This initiative started in 2017 and has continued to gain momentum during this biennium, establishing itself as an important voice in Europe on cancer prevention. The resounding success of this initiative has helped to make the European Commission Mission on Cancer a reality. The selection of the Director as one of the 15 experts on the Mission Board for Cancer highlights the important role of the Agency in setting the global cancer research agenda.

Cancer Prevention Europe (CPE)

Chair
Dr Joachim Schüz (head, Section of Environment and Radiation)

Coordinator
Dr Carolina Espina (scientist, Section of Environment and Radiation)

Secretariat
Ms Catherine Chassin (secretary, Section of Environment and Radiation)

Staff
Dr Rolando Herrero (head, Section of Early Detection and Prevention)
Dr Isabelle Soerjomataram (deputy head, Section of Cancer Surveillance)

Website
https://cancerpreventioneurope.iarc.fr/

The international and multidisciplinary consortium Cancer Prevention Europe (CPE) was created in 2018 to develop world-class prevention research to be translated into effective cancer prevention guidelines and policies at the national and international level. CPE is a consortium of leading European research institutions committed to prioritizing cancer prevention through cooperation between countries and programmes. Currently, CPE comprises the following 11 partner institutions: Cancer Research UK (CRUK), the Danish Cancer Society, the European Institute of Oncology (Italy), the German Cancer Research Center (DKFZ), IARC, Imperial College London (United Kingdom), Institut national du Cancer (INCa) (France), the Karolinska Institutet (Sweden), Maastricht University (The Netherlands), the UK Therapeutic Cancer Prevention Network, and World Cancer Research Fund International/ Wereld Kanker Onderzoek Fonds.

CPE draws on previous experience with the European Platform for Translational Cancer Research (EurocanPlatform), focuses on expanding preventive interventions, and takes the measures summarized in the fourth edition of the European Code Against Cancer (https://cancer-code-europe.iarc.fr) as a starting point. The mission of CPE is to reduce morbidity and mortality from cancer in European populations through prevention and earlier detection of the disease. This will be accomplished through (i) research into optimizing the implementation of known preventive strategies, (ii) the dissemination of established best practices in prevention, in order to see innovative research translated into effective cancer prevention guidelines and policies nationally and internationally, and (iii) research into the identification of novel targets for prevention.

The vision of CPE will be broad in scope, covering a spectrum of research topics from policy to the development of novel medical preventive agents. All aspects of primary, secondary, and tertiary prevention will be encompassed, and emphasis will also be placed on the research evaluation and advocacy dimensions of the prevention agenda. A core component of CPE will be economic evaluation of the cost–effectiveness of different interventions, in relation to costs of treatment, care, and productivity loss. Specific research topics for CPE may include the following: cancer registration, cancer etiology (including recurrence), development and evaluation of preventive interventions, and implementation

research to maximize the effectiveness of intervention programmes. These activities will be supported by a range of platforms, networks, and infrastructures, and will draw together a wide network of partners. Training and capacity-building will be integral to the CPE initiative.

Successful coordination of cancer prevention requires long-term vision, a dedicated research agenda, and funding for such research, as well as a sustainable infrastructure and cooperation between countries and programmes. CPE provides the opportunity to fill gaps in the evidence base for prevention, shape the European Union cancer research agenda, avoid common pitfalls in implementation, and share capacity for research training and quality improvement. With its large expertise in coordinating interdisciplinary research across countries and organizations, IARC hosts the secretariat of the CPE consortium, coordinating the development of the CPE priority actions within a 5-year strategic plan. The close working relationship between IARC and its parent organization, the World Health Organization, also enables the research findings to be translated effectively into timely policies for cancer control.

Resource Mobilization and Management Office (RMO)

Resource mobilization and management officer
Dr Olaf Kelm

Resource mobilization and management assistant
Ms Claire Salignat

Resource mobilization assistants
Ms Maud Bessenay
Ms Véronique Chabanis

Students
Ms Mathilde Boisserin
Ms Amandine Devouassoux (until November 2018)
Ms Daria Plotkina (until September 2018)
Ms Anna Schmutz

The Resource Mobilization and Management Office (RMO) works closely with the Office of the Director (DIR) and the Section of Support to Research (SSR) to guide the scientific Groups across the Agency in identifying and securing funding and in carrying out projects according to the highest project management standards. The team functions as the Agency's Project Management Office (PMO).

Resource mobilization activities

RMO supports the scientific Groups in identifying and responding to funding opportunities, and in securing extrabudgetary funding. Against a backdrop of decreasing success rates across a wide range of funders, the Agency has continued to be successful in attracting funding through research grants. The office pursues two main lines of activities. Novel funding sources are systematically identified and funding opportunities tightly monitored. The Group follows up on more than 100 funders, and publishes information on more than 250 funding opportunities every year. In addition, the Group collects funder intelligence and news, and supports the IARC researchers in targeting the relevant opportunities in the best possible manner. For such a tailored approach, the Group has put in place a bibliometric approach that enables appropriate funders to be identified using specific keywords on areas of interest.

In addition, RMO is increasingly called upon for proactive resource mobilization, for which a much more direct approach is required. To this end, RMO dedicates significant efforts in enhancing IARC's visibility with strategic partners, including current or potential new Participating States, organizing bilateral meetings, and launching open seminars and events. For example, RMO has worked with colleagues across the Agency to facilitate collaborations and meetings with researchers from more than 30 countries, and has organized scientific meetings with key partners; has followed up on a total of 20 memoranda of understanding or agreement; is disseminating a newsletter prepared by COM; coordinated three evenings for the general public; and organized a kick-off meeting for the Nouveau Centre campaign in the context of World Cancer Day on 4 February 2019, attended by representatives of the Ville de Lyon, the Metropole, the Region, and the Prefecture.

Project implementation (PMO)

A crucial element of any strategic engagement is to prove to be a reliable and trustworthy partner. In this context, it is of the utmost importance to ensure best-practice implementation of projects funded from extrabudgetary sources. RMO is tasked with supporting the scientific Groups in negotiating contract terms, facilitating contract signatures, and following up on an average of 140 active grants at the macro level regarding compliance with funder policies and implementation of project plans according to the agreed main deliverables. This work greatly benefits from the new Project Management Platform that was introduced at IARC in 2017. This online tool, referred to as the Project Portal, was developed entirely

in-house to meet the specific business needs of IARC, and has been widely adopted across the Agency as a key information and management tool.

The project management activities of RMO are continually expanding to better support the scientific Groups at both the pre-award and post-award level. Support across the portfolio of IARC projects includes: project management training; knowledge management; provision of reference policies, documents, and checklists; central programmatic, administrative, and financial follow-up and archiving; budget surveillance; and due diligence deliverables.

The mission of RMO is to increase the financial resources available to the Agency to enable the project-based implementation of IARC's mandate, and to strengthen and streamline the underlying administrative processes.

Communications Group (COM)

Group head
Dr Nicolas Gaudin

Secretary
Ms Sylvie Nouveau

Knowledge manager
Ms Teresa Lee

Managing editor
Dr Karen Müller

Scientific editor
Dr Heidi Mattock

Technical editor
Ms Jessica Cox

Communications officer
Ms Véronique Terrasse

Institutional webmaster
Ms Maria de la Trinidad Valdivieso Gonzalez

Web architect
Mr Danil Kister

Information assistants
Ms Latifa Bouanzi
Ms Freya Damrell (until July 2019)
Ms Elisabeth Elbers (until June 2018)
Ms Meaghan Fortune
Ms Fiona Gould
Ms Sylvia Lesage
Mr Nicholas O'Connor
Ms Solène Quennehen
Ms Morena Sarzo
Mr Othman Yaqoubi

The Communications Group (COM), as an integral part of the Director's Office, aims to present a clear and coherent image of IARC and its work to the scientific community, the media, and the general public. COM also provides information- and publication-related services to the research Sections. The COM Group Head also serves as External Relations Officer and Liaison with WHO management.

Digital strategy and dissemination

Streamlining and standardizing publishing workflows and making careful investments in technology continued to be priorities in the 2018–2019 biennium.

The internal Manuscript Clearance System, which was launched in March 2016 to provide greater oversight for external journal articles produced by Agency personnel, was significantly enhanced, and version 2 was launched in March 2018.

As part of a long-term strategy of consolidating IARC publications in one central portal, in 2019 the IARC Publications website (https://publications.iarc.fr/) gained prominence as the authoritative site for providing access to *IARC Monographs*.

In September 2019, the new digital subscription website, WHO Classification of Tumours Online (https://tumourclassification.iarc.who.int/), was released at the European Congress of Pathology, held in Nice, France. This much-anticipated digital subscription website brings together the complete digital contents of the six most recent volumes of this renowned series, along with whole slide images.

The Agency entered into an agreement with the United States National Library of Medicine (NLM) in 2015 for the deposit of its *IARC Monographs* and *IARC Working Group Reports* series in NLM's digital repository, NLM Bookshelf. Addenda to this deposit agreement in 2016 and again in 2019 have expanded the number of IARC titles eligible for deposit.

This biennium also saw the production of the new *World Cancer Report: Cancer Research for Cancer Prevention*, another IARC flagship publication. Considerable efforts were made to coordinate between this publication and the *Global Report on Cancer Policy* being produced by WHO. Both publications are due to be released in early 2020. In line with WHO's expansion of its Open Access policy to include WHO-published books, the new *World Cancer Report* will be one of IARC's first truly Open Access books.

Measuring impact through bibliometrics

Reporting requirements for the Agency's Medium-Term Strategy (2016–2020) gave COM an opportunity to experiment with new bibliometric tools and vendors. The Agency ran a 1-year trial of Altmetric that continued to July 2018, which yielded several interesting results showing social media attention to IARC research output.

Alignment with WHO publishing

The 2018–2019 biennium was a period of productive collaboration with WHO publishing. Recognizing the efficiencies and other benefits of aligning IARC publishing workflows with those of WHO headquarters, the Agency entered into an agreement with WHO Press for IARC authors' use of standing copyright agreements between WHO and major health publishers. Transactional permissions granted by IARC for the use of Agency-copyrighted materials have also been aligned with WHO practices. COM, WHO Press, and WHO Legal Counsel also worked jointly to harmonize copyright licenses with the United States National Institutes of Health (NIH), to facilitate the involvement of NIH authors in publications produced by WHO and IARC.

Information services

A less publicly visible but important function of COM is the provision of information services to Agency personnel and external visitors via the institution's library. In addition to providing access to journals and other materials in print and digital formats, the information services team plays a key role in training Agency personnel. In the 2018–2019 biennium, training topics in scholarly communications were expanded to encompass in-depth searching for systematic reviews, predatory journals, copyright, plagiarism, and more. The IARC library, as a part of the WHO Global Libraries Group, also participated in training WHO personnel more widely.

Open Access

Following the creation of an IARC Open Access fund in the amount of €50 000 per annum, the fund has supported 27 articles in 2018 and 26 articles in 2019 to date. Although comparative baseline figures are available only for 2014, tracking of IARC's Open Access journal article output since the establishment of the fund in 2015 suggests that the fund has a notably positive impact on Open Access publishing at the Agency.

During the 2018–2019 biennium, IARC published the following reference publications:

WHO Classification of Tumours

WHO Classification of Tumours of the Skin, 4th edition (print)
WHO Classification of Tumours of the Eye, 4th edition (print)
WHO Classification of Digestive System Tumours, 5th edition (print)
WHO Classification of Breast Tumours, 5th edition (print)

IARC Monographs

Volume 113, DDT, Lindane, and 2,4-D (print)
Volume 114, Red Meat and Processed Meat (print and PDF)
Volume 115, Some Industrial Chemicals (print and PDF)
Volume 116, Drinking Coffee, Mate, and Very Hot Beverages (print and PDF)
Volume 117, Pentachlorophenol and Some Related Compounds (print and PDF)
Volume 118, Welding, Molybdenum Trioxide, and Indium Tin Oxide (print and PDF)
Volume 119, Some Chemicals That Cause Tumours of the Urinary Tract in Rodents (print and PDF)
Volume 120, Benzene (PDF)
Volume 121, Styrene, Styrene-7,8-Oxide, and Quinoline (PDF)
Volume 122, Isobutyl Nitrite, β-Picoline, and Some Acrylates (PDF)

IARC Handbooks

Volume 16, Absence of Excess Body Fatness (print and PDF)
Volume 17, Colorectal Cancer Screening (print and PDF)

IARC Scientific Publications

Tumour Site Concordance and Mechanisms of Carcinogenesis, IARC Scientific Publication No. 165 (print and PDF)
Cancer in Sub-Saharan Africa, IARC Scientific Publication No. 167 (print and PDF)
Reducing Social Inequalities in Cancer: Evidence and Priorities for Research, IARC Scientific Publication No. 168 (print and PDF)

IARC Technical Publications

Thyroid Health Monitoring after Nuclear Accidents, IARC Technical Publication No. 46 (PDF)

Biennial Report

Rapport biennal 2016–2017 (PDF)

Non-series publications

Programme de dépistage des cancers du sein et du col de l'utérus du Maroc: Etat de la mise en œuvre, organisation et résultats
The Cancer Atlas, 3rd edition (print and website; joint publication with the American Cancer Society and the Union for International Cancer Control)
Cancer in Sub-Saharan Africa, Volume III (print and PDF; joint publication with the Union for International Cancer Control)

Electronic resources

WHO Classification of Tumours Online

Editing, layout, translation, and language services

The COM Editing and Layout team is responsible for the editing and layout of the *IARC Monographs*, the *IARC Handbooks*, and the *WHO Classification of Tumours* (also known as the WHO Blue Books) series, in addition to other established IARC Publications series and non-series publications. By ensuring high corporate standards, the team helps to maintain the reputation and image of the Agency. During the biennium, an Information Assistant for Layout joined the team when the layout of the WHO Blue Books was moved in-house. COM also produces various promotional materials about the Agency and its publications.

COM also provides English editing services for articles for submission to peer-reviewed journals, book chapters, and other manuscripts, as well as various materials for the IARC website, and provides training on writing and publishing. COM provides translation services for short documents and administers external translation services for longer documents. COM also organizes successful language courses for the Agency's personnel in English, French, and Spanish.

Media services

The IARC Communications strategy aims to increase the Agency's visibility among all stakeholders: the scientific community, governments, public health decision-makers, cancer research entities, the general public, and the media.

From January 2018 to September 2019, 186 news items and 21 press releases were published; of these, 86 news items and 12 press releases were posted since 1 January 2019.

In September 2018, a press conference for the launch of GLOBOCAN 2018 was organized with WHO at the Palais des Nations in Geneva, which led to extensive international media coverage.

During the biennium, an increased number of videos and infographics were produced by COM and promoted through IARC's social media (Twitter, YouTube) platforms to increasingly reach and engage all audiences.

IARC's database of media contacts continued to grow and was restructured to enable more precise targeting of content: complex scientific topics are pitched to scientific media or journals, and less technical topics are shared with general news media.

IARC also strived to increase its visual communications, with press releases and news items and events increasingly supported by video interviews, animations, and infographics.

In particular, events such as International Childhood Cancer Day, International Women's Day, World Cancer Day, and the 25th anniversary of the European Prospective Investigation into Cancer and Nutrition (EPIC) study were marked with coordinated multimedia communications packages. The media team also regularly supported resource mobilization initiatives, including through video interviews, photographs, and advice.

The IARC Media team continued its efforts towards a closer relationship and coordination with the WHO Department of Communications at all levels, with regular meetings, increased coordination on social media, sharing information, defining joint messages, and sharing communications materials.

The continued work of the Visual Designer and the integration of an Information Assistant for Communications have enabled and enhanced the effectiveness of the Agency's media services.

Web services

The Web services team has continued to advance and promote IARC's high-level research profile by disseminating timely and accurate cancer research information to a wide range of audiences, promoting external communications, providing access to interlinked online resources and databases, promoting activities of the Education and Training Group (ETR), and ensuring a consistent visual identity.

IARC website

As part of the IARC Communications strategy and to continue the improvement of the Agency's Internet presence, COM/Web services in collaboration with Information Technology Services (ITS) and ETR coordinated the development, by an external contractor, of the IARC content management system (CMS) using WordPress. The IARC CMS introduced a new look and feel based on modern trends in web design and focuses on the IARC website as a communications tool. The new look and feel enhances the visibility of the increasing multimedia production through the Media Centre page (https://www.iarc.fr/media-centre/), highlights in a more attractive way key IARC publications (e.g. *World Cancer Report*; https://www.iarc.fr/cards_page/world-cancer-report/), and advertises and promotes IARC seminars and meetings through the new Events webpage (https://www.iarc.fr/events/).

Also in the context of the development of the IARC CMS, the *IARC Monographs* website and the Education and Training website were migrated to the CMS with the new look and feel.

Efforts have been made to enhance the visibility of IARC's research work through the IARC website. These include the development of a "Just Published" feature where IARC journal articles indexed by PubMed are listed automatically on the IARC homepage (https://www.iarc.fr/), the addition to each scientist's staff page of a link to the PubMed listing of that scientist's record of publications (https://www.iarc.fr/who-is-who), and the creation of a new webpage that highlights the collaborative international research projects conducted by IARC (https://www.iarc.fr/cards_page/research-iarc-international-research-collaborations/).

In close collaboration with the Office of the Director of Administration and Finance (DAF) and the Resource Mobilization Office, the "Donate Now" and "IARC Newsletter" features were implemented, in support of the resource mobilization activities.

IARC Publications website

The Web services team finalized the second phase of the development of the IARC Publications website (https://publications.iarc.fr/), which included the consolidation of all IARC Publications series, including the *IARC Monographs*, on the IARC Publications website.

IARC research project websites

During the biennium, the Web services team coordinated and/or developed more than 10 research project and meeting websites.

The following websites were developed and launched:
6th Meeting on Emerging Issues in Oncogenic Virus Research: https://oncogenicviruses2020.iarc.fr/
Translational Studies of Head and Neck Cancer in South America and Europe (HEADSpAcE): https://headspace.iarc.fr/

SURVPOOL project (A Consortium on Risk Factors and Cancer Survival): http://survival.iarc.fr/Survpool/en/
Childhood Leukemia International Consortium (CLIC): https://clic.iarc.fr/

The following websites were validated and launched:
IARC Learning Portal: https://learning.iarc.fr
ICBP SURVMARK-2: Cancer Survival in High-Income Countries (SURVMARK-2) within the International Cancer Benchmarking Partnership (ICBP): http://gco.iarc.fr/survival-678ksdfs897/survmark/
IARC Cancer Screening in Five Continents (CanScreen5): http://canscreen5.iarc.fr/
Global Initiative for Cancer Registry Development (GICR): http://gicr.iarc.fr/
Cancer Prevention Europe (CPE): https://cancerpreventioneurope.iarc.fr/
Biobank Learning platform: http://biobanklearning.iarc.fr/
IARC Global Cancer Observatory (GCO): http://gco.iarc.fr/
Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine: http://gco.iarc.fr/resources/paf-france_en.php
Cancers Attributable to UV Radiation: https://gco.iarc.fr/causes/uv/home

Liaison and external relations

To bring the Agency's activities and processes in line with those of WHO, it is important to maintain adequate communication with the various WHO departments and key stakeholders, so that appropriate cross-representation is ensured on key panels and expert groups and there is no duplication of work. The ultimate goals are for WHO and its cancer agency to speak with one voice on cancer-related issues and for the cancer prevention research agenda of IARC to support the overarching WHO programme, as required by the standard operating procedures agreed to by the two organizations.

In addition, IARC Governance has requested that key developments be regularly communicated to IARC Participating States. This is why the COM Group Head, in addition to maintaining the contacts as outlined above, has been tasked with ensuring the provision of proper and timely updates on IARC activities to the Participating States' Permanent Missions in Geneva by organizing regular meetings with their representatives. The Group Head also represents the IARC Director as needed at the World Health Assembly and at WHO Executive Board and other high-level meetings, and acts as a first point of contact in identifying reputational risks to IARC and WHO headquarters in relation to areas of overlapping activities.

Education and Training Group (ETR)

Group head
Ms Anouk Berger

Senior visiting scientist
Dr Rodolfo Saracci
(until December 2018)

Assistant, fellowship programme
Ms Isabelle Battaglia

Assistant, courses programme
Ms Sandrine Montigny

Project assistant
Ms Dominique Meunier

Secretary
Ms Mira Delea

Trainees
Ms Lisa Berkani (until June 2018)
Mr Louis Fernez (until June 2018)
Ms Amélie Labaume
(until August 2019)
Mr Renzo Metail (until August 2018)

Affiliated staff
Dr Maribel Almonte (Scientific director, Summer School module on Implementing Cancer Prevention and Early Detection)
Dr Partha Basu (Scientific director, Summer School module on Implementing Cancer Prevention and Early Detection)
Dr Pietro Ferrari (Scientific director, Summer School module on Introduction to Cancer Epidemiology)
Dr Zdenko Herceg (Responsible officer, fellowship programme)
Dr Les Mery (Scientific director, Summer School module on GICR*Net* Master Class: Analysis of Population-based Cancer Registry Data)
Dr Catherine Sauvaget (Scientific director, Summer School module on Implementing Cancer Prevention and Early Detection)
Dr Isabelle Soerjomataram (Scientific director, Summer School module on GICR*Net* Master Class: Analysis of Population-based Cancer Registry Data)
Dr Kurt Straif (Scientific director, Summer School module on Introduction to Cancer Epidemiology) (until October 2018)

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

Key achievements of IARC's education and training programme during 2018–2019 are presented here. Whereas the Education and Training Group (ETR) coordinates the Agency's activities in these areas, many initiatives are led by the research Groups.

Research Training and Fellowship Programme

The programme offers researchers at different stages of their career (collectively referred to as Early Career and Visiting Scientists) opportunities to be trained at IARC in fields of research closely associated with the Agency's missions and activities, as well as to participate in collaborative research projects. Early Career and Visiting Scientists are supported either by project funds from IARC Groups or by IARC Fellowships. A total of 295 Early Career and Visiting Scientists from 62 different countries worked at IARC during the biennium, which represents a 16.6% increase compared with the previous biennium.

Hosting environment

The improvements made over the biennium regarding the terms and conditions under which Early Career and Visiting Scientists work while at the Agency have been monitored by ETR, in close collaboration with key players such as the Director of Administration and Finance, the Staff Physician, and the Early Career Scientists Association

(ECSA). In addition, an entirely revised version of the IARC Welcome Pack was released in 2019 (https://www.iarc.fr/cards_page/visitor-information/).

The internal programme of generic skills courses, developed within the framework of the IARC Postdoctoral Fellowship Charter and jointly managed by ETR and the Human Resources Office, offered 40 courses to Early Career and Visiting Scientists in 2018–2019 (Table 1), which were attended by more than 150 people. Since August 2018, Early Career and Visiting Scientists have had access to the WHO learning platform ilearn and Lynda.com, further expanding the learning opportunities. Continuing dialogue with ECSA has enabled the courses offered to be refined to address the needs of beneficiaries. For instance, Professional and Career Development Courses were held in both 2018 and 2019. To complement these courses, a Career Prospects Portal intranet site was jointly developed, providing a list of job offers maintained by ECSA, a selection of learning resources and tools, and a Job Application Clinic piloted by ETR in 2019.

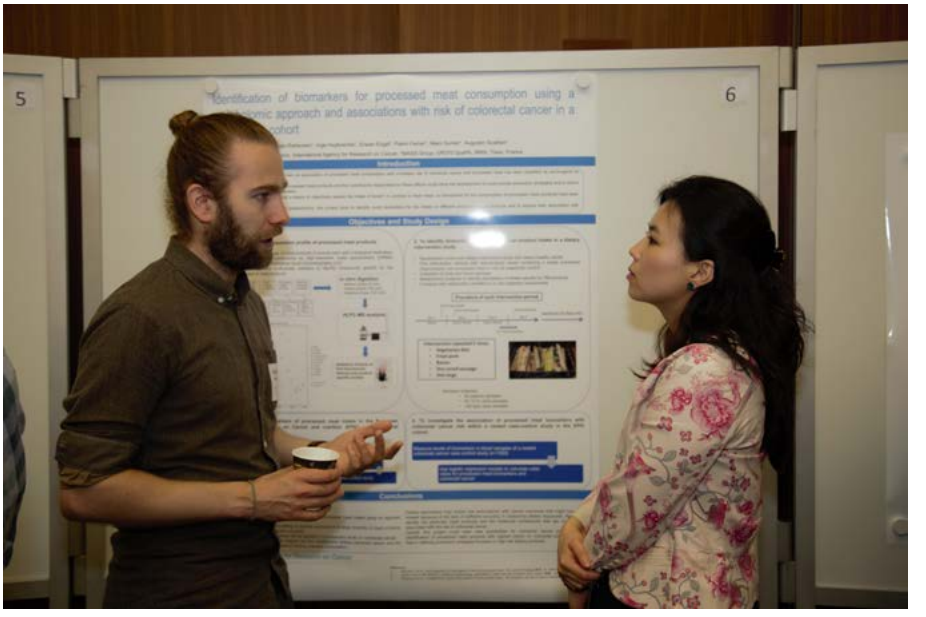
In addition to the exchanges described above, the Agency continued to support and work closely with ECSA on several areas to improve the quality of the training environment. Among other activities, ECSA continued to successfully hold its Scientific and Career Days in 2018 and 2019 (Figure 1), with a growing number of attendees, including through the Cancéropôle Lyon Auvergne Rhône-Alpes. Testimonials can be viewed online (https://www.youtube.com/watch?v=d6zLkeckMoo).

The relationship with local academic players has been strengthened, in particular through the opening of some of the above-mentioned courses to local students, including in partnership with the Cancéropôle Lyon Auvergne Rhône-Alpes. An example of such a course was "Nextflow: reproducible and portable bioinformatics data analyses", held at IARC in September 2019.

Table 1. Generic courses for Early Career Scientists, 2018 and 2019

Research skill development	Writing skills
Analysing TCGA data in the cloud	Copyright issues
Basic UNIX for handling large datasets	Documentation and in-depth searching to support systematic reviews
Data preparation and formatting	Effective scientific posters
Ergonomics in laboratories	EndNote basic (twice a year)
Good IARC laboratory practice (7 sessions)	EndNote advanced (three times)
Good pipetting practices	EndNote for systematic review (twice)
Introduction to biostatistics	Grant writing (twice)
Introduction to HPC and the IARC Linux clusters	Publishing in scientific journals
Introduction to geographic information systems (GIS) for epidemiology	PubMed workshop (twice a year)
Nextflow: reproducible and portable bioinformatics data analyses	Systematic reviews search methodology (three times)
Pathology of cancer: basic principles for non-pathologists	Web of Science
Statistical practice in epidemiology using R	Zotero (three times)
Using the IARC Nextflow bioinformatics pipelines	
IT skills	**Communication skills**
Electronic Laboratory Notebook (three times)	Dealing with conflicts in a multicultural environment
Electronic Laboratory Notebook outside laboratories	Dialogue on respect (WHO Office of the Ombudsman and Mediation Services)
Excel intermediate course (twice)	Instructor development course
REDCap for data collection (twice)	
REDCap for surveys (twice)	
SharePoint (twice)	
Career management and development	**Leadership and management**
Managing your career during the 4th industrial revolution (WHO Global Talent Management) (online)	Financial management
Networking	Make your research count
Professional and career development course (twice)	Project management (twice)
A holistic approach to career management (online)	Task management (twice)
Massive open online course (MOOC) reimbursement scheme offered for:	
Statistical skills and bioinformatics; Introduction to public speaking; Work smarter, not harder; Mindfulness for well-being and peak performance	

Figure 1. ECSA Scientific and Career Day 2018. © IARC/Sandrine Montigny.



Postdoctoral Fellowships

In 2018, the Agency awarded seven Fellowship extensions funded exclusively by the IARC Regular Budget. No new IARC Fellowships were awarded in 2018, because the call for applications was suspended in 2017 as a result of budgetary constraints. To maintain an effective programme while pursuing alternative funding, the Agency restricted the awarding of IARC Fellowships to candidates from low- and middle-income countries (LMICs). This led in 2019 to the awarding of six new Fellowships funded by the IARC Regular Budget. Fundraising efforts initiated in previous years started to pay off and one additional Postdoctoral Fellowship could be awarded in 2019, thanks to the financial support of the Terry Fox Foundation.

In 2018–2019, modest Research Return Grants were also awarded to six Fellows from LMICs, contributing to the establishment of their research activity in their own country.

Short-term fellowships

In collaboration with the Union for International Cancer Control (UICC), the UICC-IARC Development Fellowship enables a selected number of participants of the IARC Summer School to return to IARC for a period of 1 month for further training and collaborative work. In 2019, this fellowship was awarded to four researchers from LMICs.

Senior Visiting Scientist Award

Two Senior Visiting Scientist Awards were made in 2018–2019 (Table 2). Beyond the development of collaborative research projects, the Senior Visiting Scientist Award often leads to the expansion of important research initiatives or the joint production of key resources for capacity-building.

IARC Summer School in Cancer Epidemiology

Because of budget constraints, the IARC Summer School in Cancer Epidemiology was not held in 2018. The event was held in Lyon in June–July 2019, with the goal of improving the methodological and practical skills of more than 60 cancer researchers and health professionals from more than 40 countries, the vast majority of whom were from LMICs (Figure 2). The following modules were held: Introduction to Cancer Epidemiology, GICR*Net* Master Class: Analysis of Population-based Cancer Registry Data, and Implementing Cancer Prevention and Early Detection. Most sessions of the Summer School were recorded (https://videos.iarc.fr/channels/SummerSchool2019/), and some of those resources were viewed more than 1000 times between July and December 2019. Testimonials can be viewed online (https://training.iarc.fr/course-testimonials/summer-school2019/).

Table 2. Senior Visiting Scientist Awards, 2018 and 2019

2018	
Professor Torkjel Sandanger	Department of Community Medicine, Arctic University of Norway, Norway
2019	
Dr Rashmi Sinha	Division of Cancer Epidemiology and Genetics, National Cancer Institute, USA

Specialized and advanced courses

Specialized and advanced courses are organized by IARC's scientific Groups, sometimes with the support of ETR. Most of these courses are associated with collaborative research projects, in which IARC is transferring skills needed to conduct the projects and to enable the subsequent implementation of the research findings in the countries concerned. Specialized courses are often co-organized with external partners and are held at diverse locations worldwide (Table 3). During the biennium, more than 50 courses were organized, enabling the training of about 1700 scientists and health professionals.

Figure 2. IARC Summer School 2019 module on Implementing Cancer Prevention and Early Detection. © IARC/Amélie Labaume.

Table 3. Specialized and advanced courses, 2018 and 2019

Course title	Location	Number of participants	External collaborations
2018			
Cancer surveillance			
Basic cancer registration in Indonesia	Indonesia	60	
Basic cancer registration in Tanzania	United Republic of Tanzania	21	
Basic cancer registration in United Arab Emirates	United Arab Emirates	72	
CanReg5	Thailand	60	
Childhood cancer registration	Côte d'Ivoire	10	
GICR*Net* data quality train the trainers workshop	IARC	22	
SEER*Stat training workshop for the analysis and reporting of national mortality data	Trinidad and Tobago	10	
SurvCan-3: data collection for survival studies: data quality and assessment for survival analysis focusing on trace-back of DCO cases (Central and South American countries, Caribbean)	GoToWebinar	18	Cancer Institute (WIA), Chennai, India
SurvCan-3: data collection for survival studies: data quality and assessment for survival analysis focusing on trace-back of DCO cases (India and surrounding countries)	GoToWebinar	16	Cancer Institute (WIA), Chennai, India
SurvCan-3: data collection for survival studies: data quality and assessment for survival analysis (Central and South American countries, Caribbean)	GoToWebinar	18	Cancer Institute (WIA), Chennai, India
SurvCan-3: data Collection for survival studies: data quality and assessment for survival analysis (India and surrounding countries)	GoToWebinar	24	Cancer Institute (WIA), Chennai, India
Cancer prevention and early detection			
CICAMS-IARC Planning and implementing cancer control programmes, 2nd edition for ASEAN countries and China	China	42	Cancer Foundation of China, Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS)
IFCPC-IARC online training: colposcopy and the prevention of cervical cancer (in English) for India		15	International Federation of Cervical Pathology and Colposcopy (IFCPC)
IFCPC-IARC training course in colposcopy and the prevention of cervical cancer – objective structured clinical examination (OSCE)	India	20	International Federation of Cervical Pathology and Colposcopy (IFCPC)
IFCPC-IARC online training: colposcopy and the prevention of cervical cancer (in Russian and English)		30	International Federation of Cervical Pathology and Colposcopy (IFCPC), United Nations Population Fund-Eastern Europe Central Asia office (UNFPA-EECA)
Project ESTAMPA – Bolivia centre setup (4 sessions): project presentation, clinical samples collection, colposcopy and clinical management, laboratory procedures	Bolivia	63 (42 + 5 + 14 + 4)	
Projet Care4Afrique – Côte d'Ivoire – IVA et thermo-coagulation (in French)	Côte d'Ivoire	20	Ministère de la Santé et de l'Hygiène Publique; Institut National de Santé Publique, Abidjan, Côte d'Ivoire; Lalla Salma Foundation, Rabat, Morocco
Projet Care4Afrique – Sénégal – IVA et thermo-coagulation (2 sessions) (in French)	Senegal	46 (22 + 24)	Ministère de la Santé et de l'Action Sociale du Sénégal; Lalla Salma Foundation, Rabat, Morocco
Projet PAPRICA: ateliers d'information et de partage "Vaccination HPV" (3 sessions) (in French)	IARC	21	

Table 3. Specialized and advanced courses, 2018 and 2019 (continued)

Course title	Location	Number of participants	External collaborations
Training course for master trainers in cervical cancer prevention, early detection, and management (participants from Morocco, Burkina Faso, Chad, Côte d'Ivoire, and Senegal (in French)	India	23	Tata Memorial Centre Rural Cancer Project; Nargis Dutt Memorial Cancer Hospital (NDMCH), Barshi, Maharashtra, India; Lalla Salma Foundation, Rabat, Morocco
Cancer research infrastructure and methods			
B3Africa webinar series: mobile data collection, parts I and II	GoToWebinar	26 (18 + 8)	International Livestock Research Institute, Kenya
BELMED workshop: epidemiological principles (characteristics) of organized screening for breast cancer	Belarus	32	Belarus Ministry of Health, WHO Belarus
IARC workshop: an introduction to GIS mapping using QGIS; epidemiologic design: case–control studies; epidemiologic study design	Zambia	40 (20 + 10 + 10)	Society for Environmental Geochemistry and Health
GloboDiet transfer of knowledge to WHO-NCD	GoToWebinar	3	WHO-NCD in Moscow
Statistical practice in epidemiology using R	IARC	32	
ICAMA – taller de formación en patología e investigación en cáncer de mama (in Spanish)	Mexico	17	
2019			
Cancer surveillance			
IARC/National Cancer Center Korea Summer School on Cancer Registration: basic principles	Republic of Korea	22	National Cancer Center, Republic of Korea, GICR
IARC/WHO EMRO basic cancer registration course	Egypt	19	WHO Regional Office for the Eastern Mediterranean
IARC/WHO EURO advanced cancer registration course	Republic of Moldova	24	WHO Regional Office for Europe, GICR
International basic course for cancer registrars	Dominican Republic	18	Pan American Health Organization-Dominican Republic, Autonomous University of Santo Domingo, INCART (Ministry of Health of the Dominican Republic), GICR
Principles and practice of cancer registration course	Slovenia	50	Cancer Registry of the Republic of Slovenia, GICR
Site visit and cancer registration and CanReg training	Peru	6	Instituto Nacional de Enfermedades Neoplásicas (INEN), GICR
Site visit and cancer registration and CanReg training	Paraguay	6	Ministry of Health of Paraguay, GICR
Workshop on ESMO EMOO lung cancer data collection tool	Thailand	16	Chiang Mai Cancer Registry, Singapore Cancer Registry, ESMO, GICR
Workshop on registration of childhood cancer: challenges and opportunities	France	90	UICC
Cancer prevention and early detection			
BELMED workshop: cervical cancer prevention and screening in the Republic of Belarus	Belarus	27	
BELMED workshop for radiographers: principles of screening mammography	Belarus	20	Breast Screening Training Centre, St. George's University Hospitals, United Kingdom
BELMED workshop: multidisciplinary team	Belarus	45	Oxford University; University Hospitals of Derby and Burton; Addenbrooke's Hospital, Cambridge; Nottingham University (all United Kingdom)

Table 3. Specialized and advanced courses, 2018 and 2019 (continued)

Course title	Location	Number of participants	External collaborations
CICAMS-IARC Planning and implementing cancer control programmes, 3rd edition for ASEAN countries and China	China	40 (including 3 observers)	Cancer Foundation of China, Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS)
Colposcopy and treatment of precancers	India	25	Chittaranjan National Cancer institute, Kolkata, India
Formation en diagnostic et prise en charge du cancer du sein (in French)	Morocco	9	Institut National d'Oncologie, Rabat, Morocco; Fondation Lalla Salma, Prévention et traitement des cancers, Morocco
Genetic counselling for PRECAMA institutions and beyond (8 webinars)	Webinar	113 (19 + 13 + 14 + 6 + 17 + 15 + 15 + 14)	Hospital Sírio-Libanês, São Paulo, Brazil
Hands-on training on colposcopy and management of premalignant cervical lesions	India	8	GBH American Hospital and GBH Memorial Cancer Hospital, Udaipur, Rajasthan, India
IARC/WHO-EURO workshop on implementation of screening programmes	France	46	WHO Regional Office for Europe
IARC/WHO-EURO workshop on implementation research in cervical cancer elimination	Russian Federation	70	WHO Regional Office for Europe; N.N. Petrov National Medical Research Center of Oncology, Saint Petersburg State University, Russian Federation; Karolinska Institutet, Sweden
IFCPC-IARC training course in colposcopy and the prevention of cervical cancer – objective structured clinical examination (OSCE) (in Russian and English)	eLearning France	25	International Federation of Cervical Pathology and Colposcopy (IFCPC)
IFCPC-IARC training course in colposcopy and the prevention of cervical cancer – objective structured clinical examination (OSCE) (in Spanish)	eLearning Colombia	8	International Federation of Cervical Pathology and Colposcopy (IFCPC)
Project ESTAMPA – training for colposcopists and pathologists	Costa Rica	80	
Projet Care4Afrique – IVA et thermo-coagulation (in French)	Benin	27	Gouvernement de la Republique du Benin; Lalla Salma Foundation, Rabat, Morocco; Fondation Claudine Talon
Training course for master trainers in cervical cancer prevention, early detection, and management (participants from Morocco, Burkina Faso, Chad, Côte d'Ivoire, and Senegal) (in French)	India	13	Tata Memorial Centre Rural Cancer Project; Nargis Dutt Memorial Cancer Hospital (NDMCH), Barshi, Maharashtra, India; Lalla Salma Foundation, Rabat, Morocco
Cancer research infrastructure and methods			
Cours international francophone d'épidémiologie du cancer (in French)	Morocco	20	Institut de Recherche du Cancer, Fez; Fondation Lalla Salma, Morocco
Application of metabolomics in human health	South Africa	130	African Centre for Gene Technologies (ACGT)
Application of metabolomics in human health (hands-on)	South Africa	35	African Centre for Gene Technologies (ACGT)
EMBO practical course: metabolomics bioinformatics in human health	France	32	EMBO

Online Learning Portal

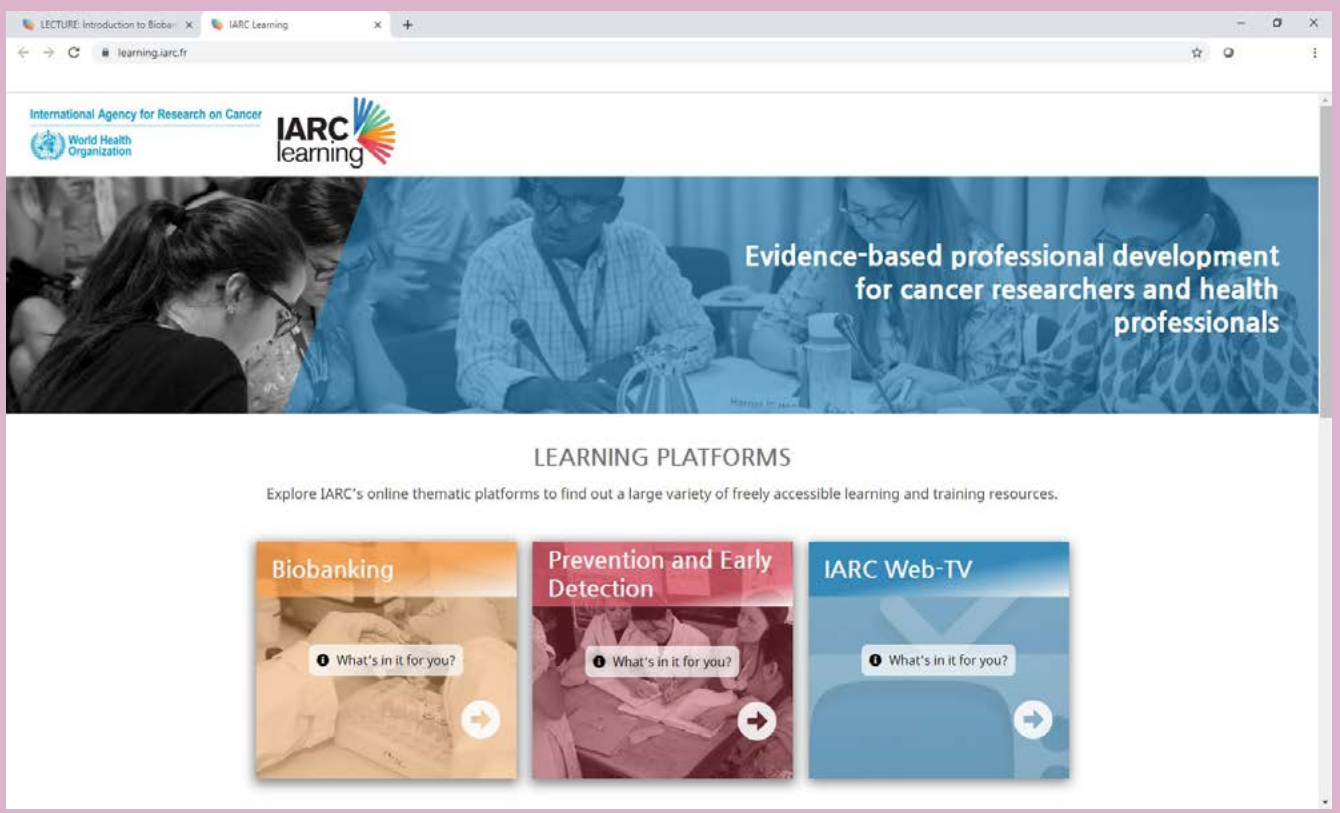
In 2018, an online learning platform was developed to host and disseminate resources produced in the framework of the Bridging Biobanking and Biomedical Research across Europe and Africa (B3Africa) project. The Biobank Learning platform (http://biobanklearning.iarc.fr/) was piloted in September 2018 and officially launched in February 2019. Between September 2018 and November 2019, the platform attracted 21 281 visitors, generating 89 542 hits (the IP addresses of visitors were from 147 countries).

On the basis of lessons learned from the launch and implementation of the Biobank Learning platform, the existing IARC Learning platform was migrated to a new information technology infrastructure with a revamped design and extended functionalities (e.g. easily searchable repositories of resources, centralized user management, decentralized content management, and enhanced technical and financial accessibility).

The new IARC Learning portal was launched in the last quarter of 2019, featuring two thematic platforms ready for registration: IARC Learning/Biobanking, with more than 80 self-learning resources for biobank-based research professionals, and IARC Learning/Cancer Prevention and Early Detection, with a variety of resources for researchers and health professionals in cancer prevention and early detection.

Four thematic platforms are under development: World Cancer Report, Cancer Surveillance, Human Exposome Assessment Platform, and IARC Summer School.

Screen capture of IARC Learning platform. © IARC.



Laboratory Services and Biobank Group (LSB)

Group head
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Secretary
Ms Sally Moldan

Data management assistant
Mr Ny Haingo Andrianarisoa (until October 2019)

Biobank process management assistant
Dr Elodie Caboux

Laboratory services management assistant
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Biobank technicians
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Ms Sophie Guillot
Mr Christophe Lallemand
Ms Gertrude Tchoua

Students
Ms Asma Benkhalfallah
Ms Amivi Dodji
Ms Sophie Jacquemot
Ms Nisrine Soltani
Ms Chiara Stellino

The Laboratory Services and Biobank Group (LSB) (Figure 1) works with IARC's Administrative Services Office (ASO) and research Groups to provide core laboratory and biobanking services to support the Agency's research activities. The Group also provides technical and safety advice to the Nouveau Centre project for the future laboratories and biobank.

Laboratory services

LSB ensures that optimal laboratory services are available, including a laboratory store providing consumables, glass-washing facilities, mycoplasma testing and quarantine, and pipette checking. In conjunction with the Laboratory Steering Committee, LSB oversees the common laboratory platforms and ensures equipment is well maintained. Interaction between laboratory-based and epidemiological research is enhanced through the upgrading, updating, and acquisition of state-of-the-art scientific instruments and the provision of sample storage capacity.

Figure 1. Laboratory Services and Biobank Group team photo. Courtesy of Xuexun Zhou.

Health and safety

Health and safety issues are managed in collaboration with the Occupational Health and Safety Committee (OHSC).

The safety manual has been completely rewritten to become a key document at IARC. Available online, it incorporates the latest international guidelines and is aligned with similar national and international documents. The first section applies to all persons working on or visiting the site. Information is given on the role of all personnel/service providers involved in safety and security at IARC, access conditions, general rules, emergency procedures, and medical services. The second section covers laboratory safety, including personal and collective protection guidelines, management of equipment and cold storage, transport procedures between laboratory floors, laboratory services offered, and good laboratory practice. Information is provided on biological and chemical risks; risks related to the handling of carcinogens, radioactive substances, or liquid nitrogen; and waste management.

Authorization for the restricted use of genetically modified organisms (GMO), and authorization to house and use radionuclides, has been renewed.

During the biennium, 204 general safety briefings for newcomers were provided, as well as 41 training sessions for newcomers working in the laboratory. LSB made 17 presentations to 186 laboratory personnel, covering good laboratory practice, good laboratory pipetting, working with liquid nitrogen, ergonomics, and the Electronic Laboratory Notebook. A further three presentations were made to other personnel involved with the laboratories, including ASO, Information Technology Services (ITS), cleaning personnel, and security guards.

IARC Biobank

The IARC Biobank maintains biological sample collections from international studies and operates a service platform for sample retrieval, sample inventories, DNA extraction, and the shipment of biological material worldwide.

The IARC sample management database (SAMI) stores information for more than 6 million biological specimens. During the biennium, almost 230 000 new samples were imported into SAMI and more than 145 000 samples were accessed for internal or external collaborators. SAMI is continuously being upgraded, and a web-based version 2.0 was developed.

Standard practices and procedures govern sample transfer from and to the Agency and the management of sample storage under optimal conditions. During the biennium, a procedure for fast-track material sharing was implemented and 156 Material Transfer Agreements for incoming and outgoing samples were verified. A procedure for the disposal of sample collections was developed in preparation for the move to the Nouveau Centre. LSB secured additional funding from the Governing Council to replace obsolete equipment and purchase new units to increase cold storage capacity to meet future needs as well as provide adequate back-up facilities. A new freezer-temperature monitoring system was piloted for future expansion to the Nouveau Centre.

Biobank services

The Biobank provides pre-analytical services on a cost-recovery basis. During the biennium, 16 projects were conducted relating to 24 requests from international institutions. This resulted in more than 13 880 sample retrievals from liquid nitrogen, 7790 DNA extractions, 7716 DNA aliquots, and 125 shipments to 24 countries worldwide.

An overview of the services provided as at September 2019 is presented in Figure 2.

The Biobank continues to participate in international proficiency schemes and scored very highly in the programmes of DNA extraction from whole blood, frozen tissue, and formalin-fixed, paraffin-embedded tissue and DNA quantification.

The Biobank provides support to research groups for incoming samples, from reception to uploading into the common database (SAMI).

BCNet

To address the underrepresentation of biological resources in low- and middle-

Figure 2. An overview of the services provided as at September 2019. © IARC.

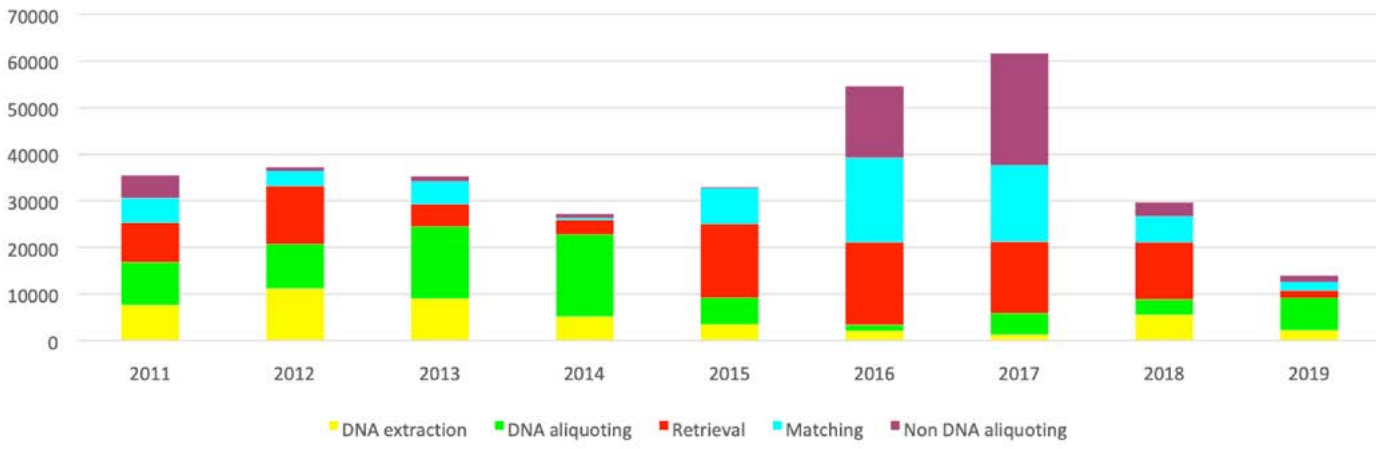
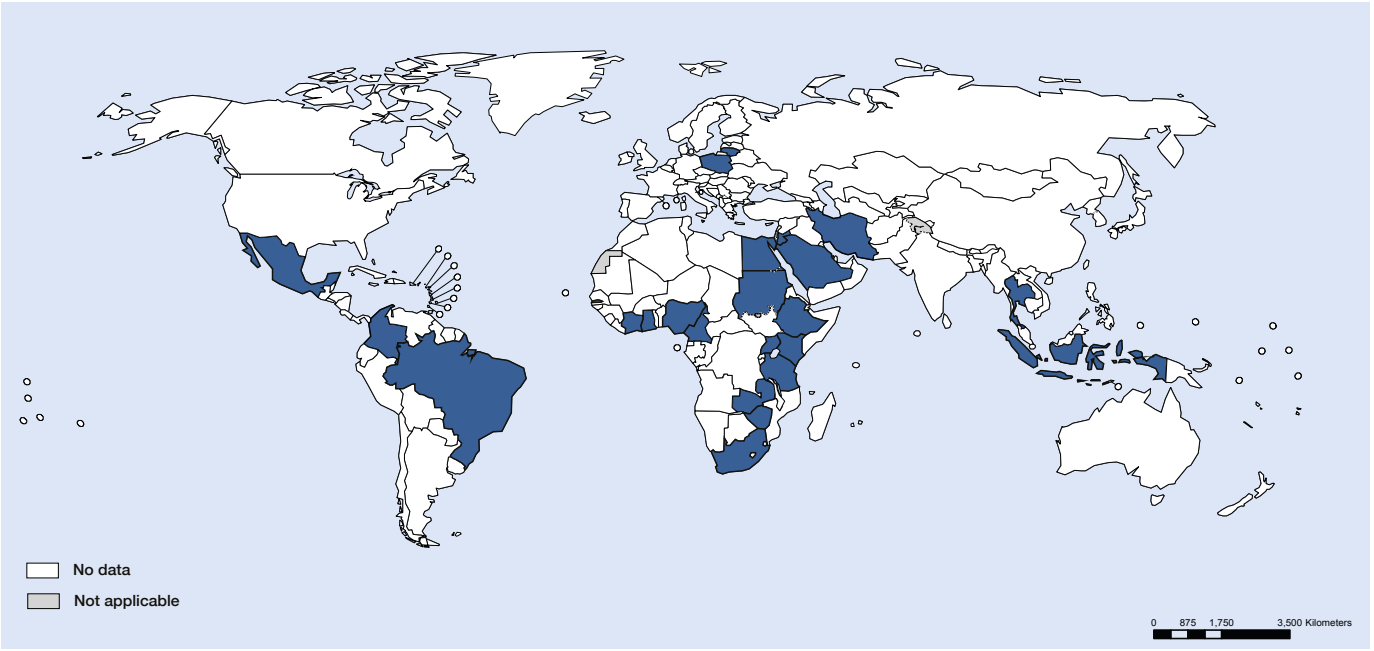


Figure 3. Map of BCNet member countries as at September 2019. © IARC.



World Health Organization

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement © WHO 2017 All rights reserved

Data Source: IARC
Map Production: IARC
World Health Organization (WHO)

income countries (LMICs) for research, the LMICs Biobank and Cohort Building Network (BCNet; http://bcnet.iarc.fr/) was established by IARC in 2013. Currently, 36 institutions from 23 countries are members of BCNet (Figure 3).

Training

Training workshops on biobanking were conducted in Indonesia (November 2018), Kenya (January 2019; Figure 4), Brazil (May 2019), and Romania (June 2019).

Collaborations

LSB represents IARC at the International Organization for Standardization (ISO) and at the Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium (BBMRI-ERIC) as an observer. IARC collaborates with BBMRI-ERIC members for international networking and interoperability issues to ensure that the structures and common services (CS) developed within Europe will be accessible to wider international communities. LSB also participates in working groups – for CS information technology (IT), CS ethical, legal, and social issues (ELSI), European Paediatric

Figure 4. Biobank training at Ampath Oncology Institute, Eldoret, Kenya, January 2019. Courtesy of Bonnie Oduor.

Translational Research Infrastructure (EPTRI), and Quality Management – and participates in international projects.

LSB continues to support the African Organisation for Research and Training on Cancer (AORTIC), linking the organization with BBMRI-ERIC and BCNet and other biobanking organizations in Europe and globally: the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB) and the International Society for Biological and Environmental Repositories (ISBER).

Grants

Four grant awards were received: (i) Implementation and operation of the gateway for health (ADOPT) into BBMRI-ERIC (EU-H2020 no. 676550), which aims to expand BBMRI beyond Europe (October 2015–September 2018); (ii) Bridging Biobanking and Biomedical Research across Europe and Africa (B3Africa) (EU-H2020 no. 654404), for which IARC is leading the Training and Dissemination work packages (July 2015–June 2018); (iii) a grant for BCNet projects from the United States National Cancer Institute Center for Global Health (NCI-CRDF-2016); and (iv) a grant from the EPTRI (May 2019–December 2019).

In addition, there are three research projects with budget allocation for biobank services: (i) HPV genomics, from Institut national du Cancer (INCa), France; (ii) Fat–ovarian, from INCa; and (iii) Impact of HBV genetic variability on liver disease in West Africa, from Agence nationale de recherches sur le sida et les hépatites virales (ANRS), France.

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Support staff
Mr Bruno Amara (Maintenance)
Mr Thomas Cler (Laboratory maintenance)
Mr Yannick Condomines (Reception)
Mr Henri Cordier (Laboratory and administration)
Mr José Garcia (Laboratory and administration) (until July 2018)
Mr William Goudard (Space maintenance)
Mr Antoine Hernandez (Driver)
Mr Michel Javin (Reprography)
Mr Hafed Lamouchi (Electronic maintenance)

Trainee
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Resource mobilization and grant officer
Dr Olaf Kelm (until March 2019)

Budget officer
Ms Editta Odame

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Mr Thomas Odin
Ms Madeleine Ongaro
Mr Franck Rousset

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Mr Samuel Billard
Mr Pascal Binet
Mr Christian Mah
Ms Laurence Piau
Ms Adèle Séguret

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Ms Véronique Chabanis (until March 2019)
Ms Claire Salignat (until March 2019)

Trainees (Resource mobilization)
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Ms Amandine Devouassoux (until November 2018)
Ms Daria Plotkina (until September 2018)
Ms Anna Schmutz (until March 2019)

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Human resources officer
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Associate human resources officer
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Ms Julie Buguet
Ms Julianna Soos (Training)

Secretary
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Central Secretarial Services (CSS)
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Ms Séverine Coutelier
Ms Nandini Deleu
Ms Jennifer Nicholson (until October 2019)
Ms Andreea Spanu

Staff physician
Dr Michel Baduraux (Consultant)
Dr Chantal Ferracin (until May 2019)

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

Relocation assistant
Ms Christine Astier

Information Technology Services

Head, Information Technology Services
Mr Francisco Lozano

IT officers
Mr Philippe Boutarin
Mr Christopher Jack

Assistants (Informatics)
Mr Sébastien Agathe
Ms Lucile Alteyrac
Mr Hafed Lamouchi
Mr Nicolas Tardy (Bioinformatics)
Mr Rémi Valette

Support staff
Mr Théodore Cholin (Web development) (until June 2019)
Mr Benjamin Danet (User support)

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

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: (i) Resource Mobilization, Budgeting, and Financial Management; (ii) Human Resources Management; (iii) Procurement, Conference Services, Office Administration, and Building Management; and (iv) Information and Communications Technology. SSR ensures that the Agency's activities meet the highest standards of management, efficiency, and accountability in the use of the funding made available by its Participating States and donors.

In addition to the regular provision of services, during 2018–2019 the achievements of the SSR team in four areas have contributed substantively to the continued efforts to maintain IARC's status as a leader in the ever-changing international research environment.

During the biennium, SSR continued to spearhead the review of IARC's key administrative processes in an effort to simplify, streamline, and re-engineer the workflows of the most frequently used contractual modalities. The enhanced automated eWorkflow environment based on SharePoint aims to further increase efficiency, accelerate clearance procedures, and reduce administrative burden across the Agency. IARC's reporting tools have been further improved through the launch of an automated Business Intelligence (BI) solution, which enables close-to-real-time reporting of fund status, human resources statistics, procurement statistics, and asset information. Complemented by an innovative IARC Management Dashboard, the BI solution has further strengthened the monitoring and oversight capacity of the Agency.

Notable progress has been made, in cooperation with our host country, in preparing for the construction of a new state-of-the-art IARC headquarters building in Lyon: the Nouveau Centre. In May 2016, the public tender for a combined design–build project was launched by the Métropole de Lyon. In January 2018, the contract was awarded to the design–build team presenting the offer with the best value for money. IARC has actively participated in the assessment, shortlisting, and decision-making process, and is also part of the expert panel providing input on design. The design studies were under development between January 2018 and September 2019. Work will start in 2020, and the new building is scheduled to be inaugurated in 2022. Alongside working towards the construction of IARC's future premises, SSR continued to ensure that IARC's scientific activities were not interrupted for more than a couple of days by the continued technical failures experienced in the current premises.

In view of several incidents with varying degrees of severity, a formal IARC Business Continuity Plan and Disaster Recovery Plan has been put in place to ensure a smooth response to anticipated and unexpected events. With regard to the escalating international terrorist threat, and specifically events in France during 2018–2019, significant efforts have also been made towards reinforcing IARC's security measures and response capacity.

The IARC Specific Guide on Engagement with Non-State Actors was developed to provide clear operational guidance, complementing the implementation of the WHO Framework of Engagement with Non-State Actors (FENSA) at the Agency. SSR continued to support the

Aerial view of the future IARC Nouveau Centre. © ART & BUILD, architect s.a.

Director in efforts to mobilize additional external financial resources to deliver the approved programme of work, in line with the IARC Medium-Term Strategy for 2016–2020. These included work on funder intelligence, monitoring of funding opportunities, and outreach before the transfer of the Resource Mobilization Office to the Office of the Director in March 2019.

SSR continues to ensure effective management of IARC accounts, retaining compliance with the International Public Sector Accounting Standards (IPSAS), validated by WHO external auditors on an annual basis.

Several measures were implemented aimed at maximizing the professional and personal potential of personnel and fostering a work environment that supports collaboration and excellence. The revised IARC Learning and Development Framework comprises innovative approaches to ensure that IARC personnel are equipped with the required competencies to meet the current and evolving objectives and needs of the Agency. In light of budget constraints, face-to-face training sessions were complemented with online courses and novel group-based learning methods. Furthermore, a learning credit approach is being piloted over a 2-year period with the aim of encouraging and recognizing the participation of all personnel in formal and informal learning activities that strengthen and develop leadership, performance, and team and/or group management skills.

During the second part of the biennium, the Quality of Work Life (QWL) at IARC work plan was developed and launched. The plan aims to ensure and promote the following four pillars of QWL at the Agency: (i) a respectful and harmonious environment; (ii) opportunities for growth and development; (iii) well-being and a work–life balance; and (iv) a culture of collaboration and teamwork (team and performance management). The work plan is being implemented by SSR in collaboration with the Staff Association Committee (SAC) and the Early Career Scientists Association (ECSA) to ensure harmonization of various Agency-wide initiatives contributing to QWL.

SSR remains committed to the principle of continuous quality improvement, striving to further enhance the Agency's processes and support services, inter alia by collecting feedback through regular service surveys. SSR also holds biannual town hall meetings to communicate the Section's objectives and planned activities, and holds information sessions when required to explain new policies and procedures.

Committees

Laboratory Steering Committee (LSC)

Laboratory research is essential to support the various epidemiological projects conducted at IARC on the causes and mechanisms of cancer. It involves six Groups at IARC (BMA, EGE, GCS, ICB, LSB, and MMB). The IARC Laboratory Steering Committee (LSC) oversees the IARC core laboratory facilities and advises the Director on their most efficient use.

Significant tasks of the LSC over the biennium, conducted in close collaboration with LSB, have concerned the coordination of the acquisition of new items of equipment (one robot for DNA extraction, one system for high-throughput nucleic acid quality control, one automated immunohistochemistry system, and software for metabolomic analyses), the overall maintenance of laboratory equipment, the design of laboratories in the Nouveau Centre, new safety procedures, the archiving of laboratory notebooks, the transformation of some laboratories to match changing needs, the organization of seminars on new laboratory technologies, and the update of the Laboratory Services website on the intranet. An inventory of all maintenance contracts for laboratory equipment was carried out, and priorities were established for the corresponding costs under the LSB budget.

Biobank Steering Committee (BSC)

The role of the IARC Biobank Steering Committee (BSC) is to support biobanking activities at the Agency and advise the Director regarding the strategic development of the Biobank, both internally and with external collaborators and projects.

The BSC welcomed the new head of LSB. During the biennium, the committee advised on the future biobank facilities in the Nouveau Centre, a new fast-track Material Transfer Agreement process, a revised price structure for the biobank services, the upgrade of storage capacity through the purchase of new freezers, and a new automated liquid nitrogen tank. The committee also discussed the review, management, or disposal of old sample collections in preparation for the move to the Nouveau Centre.

Computational Biology, Bioinformatics, and Biostatistics (C3B) Steering Committee

The IARC Computational Biology, Bioinformatics, and Biostatistics (C3B) Steering Committee has continued to oversee the Agency's activities in these areas. Three working groups – Bioinformatics (headed by Dr Matthieu Foll [GCS] and Dr Magali Olivier [MMB]), Biostatistics (headed by Dr Pietro Ferrari and Dr Vivian Viallon [NMB]), and Information Technology (headed by Mr Christopher Jack [ITS] and Dr Matthieu Foll [GCS]) – have overseen activities in these areas, reporting to the C3B twice a year.

The key activity has been the expansion of IARC's scientific computing capacity, resulting in a 3-fold increase in computational power and a 6-fold increase in storage capacity; the system now has 70 users across the Agency. The C3B also coordinated seminar series (30 seminars attended by about 30 individuals) to discuss areas of bioinformatics, statistics, and computational biology, and the continued application of these areas in the Agency's research programme. Technical discussions, blogs, and training sessions have also been developed in collaboration with the Education and Training Group (ETR).

Ethics Committee (IEC)

The IARC Ethics Committee (IEC) ensures that research conducted or supported by IARC conforms to international ethical standards for research involving humans. The IEC ethical review is complementary to local and/or national ethical approval. Over the biennium, the IEC was composed of 10 senior individuals from diverse backgrounds and nationalities. The IEC is chaired by Professor Samar Al-Homoud, supported by Dr Angeliki Kerasidou as vice-chair and assisted by Dr Chiara Scoccianti as secretary. An external Ethics Advisory Group (EAG) provides guidance on an ad hoc basis on areas where specialist expertise is required.

During the 2018–2019 biennium (up to June 2019), the IEC evaluated 69 new projects and 55 resubmissions of projects previously reviewed by the IEC. IEC templates and procedures were further updated on the basis of feedback from IARC staff, disclosure requirements set by the IARC/WHO Policy on Clinical Trials Registration and Public Disclosure of Results, and the minimum criteria for data protection set by the General Data Protection Regulation. A course on biomedical research ethics for IARC Early Career Scientists was delivered. The EAG was consulted on the potential ethical implications of study design and methods, ethical issues related to data collected on religion, ethnicity, and language, and the IEC position on the Asbest study (Occupational exposure to chrysotile in workers in mines and processing facilities in Asbest, Russian Federation).

Occupational Health and Safety Committee (OHSC)

The mission of the Occupational Health and Safety Committee (OHSC) is to ensure, in close collaboration with the Staff Physician, the IARC administration, and LSB, that optimal working conditions are provided for all IARC personnel.

The activities of the OHSC during 2018–2019 include (i) a critical review of the IARC safety manual; (ii) participation in the development of new procedures to improve working conditions and mitigate associated risks, such as the transport of biological materials; and (iii) a new procedure for hosting scientific visitors working in IARC laboratories for a short duration. The committee also contributed to the organization of regular and specific training, such as courses on chemical hazards and biological risks, and an ergonomics training course for laboratory workers.

After the success of the first IARC pedometer challenge, organized in 2017 to fight sedentary behaviour at work, the OHSC launched a second challenge, which attracted high participation rates. Finally, the committee was involved in the setting of technical parameters for the new IARC building.

Governing and Scientific Councils

The International Agency for Research on Cancer (IARC) was established in May 1965, through a resolution of the Eighteenth World Health Assembly, as an extension of the World Health Organization, after a French initiative. Its governance is effected through the IARC Governing and Scientific Councils.

Governing Council

IARC's general policy is directed by a Governing Council, composed of the Representatives of Participating States and of the Director-General of the World Health Organization. It meets every year in ordinary session in Lyon, usually the week before the World Health Assembly. The Governing Council elects IARC's Director for a 5-year term. The Council elected Dr Elisabete Weiderpass in May 2018 to serve for a 5-year term as from 1 January 2019. 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 4-year terms by the Governing Council. The Scientific Council reviews the scientific activities of the Agency and makes recommendations on its programme of permanent activities and priorities. The Scientific Council meets every year in ordinary session in late January/early February.

Budget

IARC activities are partially funded by the regular budget contributions paid by its Participating States. In addition, substantial funding comes from extrabudgetary sources, mainly grant awards, both national and international. The regular budget for the 2020–2021 biennium was approved in May 2019 at a level of €44 149 793.

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