- Top left: "International Agency for Research on Cancer" with WHO logo "World Health Organization"
- Title: "BIENNIAL REPORT"
- "20/21"
- Bottom: "INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 2020–2021"

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BIENNIAL REPORT

20/21

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER   2020–2021

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Biennial Report
2020–2021

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Introduction – from the IARC Director

This Biennial Report covers the period 2020–2021 and showcases a selection of the work conducted by the International Agency for Research on Cancer (IARC) in collaboration with its global network of experts. This time, the Biennial Report has an associated webpage (https://www.iarc.who.int/biennial-report-2020-2021web/) that highlights key cancer data and key figures on IARC. Furthermore, in line with the changing environment and the Agency's efforts to "green the blue", IARC is no longer providing paper copies of its Governance documents, and this Biennial Report is the first to be produced in electronic format only.

IARC's latest estimates show that the global cancer burden rose to 19.3 million new cases and 10.0 million cancer deaths in 2020. Cancer is expected to surpass cardiovascular disease as the leading cause of premature death in most countries during this century. One of IARC's most striking discoveries is that, for the first time, female breast cancer has overtaken lung cancer as the most commonly diagnosed cancer worldwide. IARC predicts that by 2040 cancer incidence will almost double, to 30.2 million new cases. This Biennial Report highlights several studies that show the long-term beneficial impacts of preventive interventions, emphasizing the tremendous potential for prevention to invert the projected trends in cancer incidence and mortality.

Because of the COVID-19 pandemic, the past two unprecedented years have brought IARC many challenges. From March to May 2020, we adapted to working remotely. IARC's operations continued thanks to the outstanding commitment of its personnel and significant investment in the digitalization of its activities. Subsequently, there was a gradual return to on-site operations, with most personnel (~70%) working remotely for the following months. Despite the challenges, IARC successfully conducted most of its research remotely and deployed innovative tools and technologies such as digital signatures and online conferencing solutions. For the first time in IARC's history, all meetings were successfully transformed into virtual meetings, including five *Monographs* meetings, two *Handbooks of Cancer Prevention* meetings, the IARC Scientific Council session in 2021 and the IARC Governing Council sessions in 2020 and 2021, in addition to various other scientific events. Unfortunately, the COVID-19 pandemic had a negative impact on IARC's fundraising activities and resulted in the suspension of certain activities and projects that could not be conducted remotely, such as fieldwork.

In response to the pandemic, IARC assessed its impact on health at the national level and on the outcomes of current and future patients with cancer. IARC participated in the COVID-19 and Cancer Global Taskforce and became a founding partner of the COVID-19 and Cancer Global Modelling Consortium, with a remit to co-develop tools and provide evidence to aid decision-making during and after the pandemic. IARC was able to clearly assess the negative impact that the pandemic has had; it interrupted registry operations, disrupted screening programmes, and delayed patient diagnosis and initiation of treatment. The long-term, large-scale cancer aftershock will be strongly felt in the coming years.

Despite the pandemic, IARC continued to fulfil its mission, and after more than a year of external consultation, reflection, and discussion, the IARC Medium-Term Strategy 2021–2025 was finalized and adopted by the IARC Governing Council in May 2021. This exciting new roadmap will guide IARC for the next 5 years. The Medium-Term Strategy is based on the IARC Statute and an objective that has guided IARC's work since 1965: *to promote international collaboration in cancer research*. In 2021–2025, IARC will focus its work on areas where it has the greatest public health impact and where it can make the biggest difference to

people's lives. This ambition has forged IARC's future strategy and defined its fundamental and emerging priorities.

IARC continues to address its *fundamental priorities*: Data for Action (to describe the occurrence of cancer), Understanding the Causes (to identify cancer risk factors), From Understanding to Prevention (to effectively implement cancer research), and Knowledge Mobilization (to share knowledge about cancer). In addition to its fundamental priorities, IARC has identified three *emerging priorities* that are important and evolving global issues for cancer prevention research: Evolving Cancer Risk Factors and Populations in Transition, Implementation Research, and Economic and Societal Impacts of Cancer. IARC will gradually strengthen its engagement in these three emerging priorities, increasing its activity in *implementation research*.

Aiming for a more agile organization, IARC's organizational structure was reviewed and revised to enable greater flexibility in resource management and to promote collaboration across the Agency. In 2021, the former Section and Group structure (as reflected in this Biennial Report) was replaced by a Branch structure. This structure is complemented by the conceptual idea of four scientific Pillars representing IARC's four fundamental research priorities, as described above.

The adoption of the Medium-Term Strategy was a major milestone, and one of IARC's greatest achievements during this biennium was to welcome China as a new Participating State in May 2021. I am confident that this engagement will further strengthen international cooperation and the strategic coordination of scientific research for cancer prevention and control.

With a new Medium-Term Strategy and a new Participating State, IARC looks forward to an exciting move to its Nouveau Centre building, a new state-of-the-art headquarters from which to undertake its mission to reduce the burden of and suffering from cancer, now and for future generations. Cancer research that matters.

Dr Elisabete Weiderpass. © IARC.

International Agency for Research on Cancer
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1 December 2020

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Group
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Dr I. Cree

Section
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IARC LECTURES

In 2020 and 2021, IARC was honoured and delighted to host seminars that were delivered by some of the world's most eminent speakers in the fields of cancer research, prevention, implementation science, and health inequalities, as well as cancer initiatives currently under way at both the European and global levels.

7TH IARC CANCER AND SOCIETY LECTURE

March 2020   Emily Banks (Australian National University, Australia) – Cancer control: public health solutions to our greatest challenges

Professor Emily Banks

IARC DISTINGUISHED SPEAKER SERIES

These distinguished speakers were invited to present topics of interest within the framework of regular Town Hall meetings, which were broadcast online after March 2020 because of the COVID-19 pandemic.

January 2020   Rashmi Sinha (National Cancer Institute, USA and IARC Senior Visiting Scientist Awardee, NME) – New Year Lecture: moving microbiome research into population studies

February 2020   Lin Fritschi (Curtin University, Australia and IARC Senior Visiting Scientist Awardee, IMO) – Occupational cancer epidemiology

June 2020   Christine Friedenreich (Cancer Control Alberta and University of Calgary, Canada) – Physical activity across the cancer continuum: epidemiologic evidence and biologic mechanisms

January 2021   Paolo Vineis (Imperial College London, United Kingdom and the Italian Institute of Technology, Italy) – Cancer and the Green New Deal

February 2021   Benjamin O. Anderson (World Health Organization (WHO), Breast Health Global Initiative (BHGI), Fred Hutchinson Cancer Research Center, and University of Washington, USA) – Global Breast Cancer Initiative (GBCI): a catalyst for change in global oncology and noncommunicable diseases (NCDs)

April 2021 — David A. Chambers (National Cancer Institute, USA) – Advancing implementation science in cancer: progress, assumptions, and next steps

April 2021 — Anne F. Rositch (Johns Hopkins Bloomberg School of Public Health, USA) – Dissemination and implementation science: research to reduce the global burden of cancer

May 2021 — Karen Canfell (The Daffodil Centre and University of Sydney, Australia) – The journey towards cervical cancer elimination: how far have we come, and how far is there to go?

June 2021 — Michael G. Marmot (University College London, United Kingdom) – Social justice and health equity

September 2021 — Mark Jonathan Caulfield (Queen Mary University of London, United Kingdom) – Transforming cancer genomics in healthcare

September 2021 — Véronique Trillet-Lenoir (European Parliament, Belgium) – Strengthening Europe in the fight against cancer: towards a comprehensive and coordinated strategy

October 2021 — Christine Chomienne (Institute de Recherche Saint Louis, Université de Paris) – Horizon Europe Cancer Mission: preparation and launch of the implementation plan

November 2021 — Ophira Ginsburg (New York University Grossman School of Medicine, USA and IARC Senior Visiting Scientist Awardee, CSU) – Women, power, and the cancer divide

November 2021 — Arash Etemadi (National Cancer Institute, USA) – Biomarkers: the lingua franca of global cancer research

Ranking of CVD/cancer as
leading cause of premature death

CVD 1st, Cancer 2nd (73)
Cancer 1st, CVD 2nd (54)
CVD and Cancer rank in top 3 (49)
Other (7)

No data   Not applicable

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

Data source: GHE 2016
Map production: CSU
World Health Organization

World Health
Organization

Probability of dying (%)

Cancer
Cardiovascular
diseases

2000

2019

Middle-income countries

High-income countries

Mexico Costa Rica Colombia Mauritius Uzbekistan Philippines Brazil Bulgaria Kazakhstan Ukraine

Japan Australia Chile Norway Italy New Zealand U.K. U.S. France Slovakia
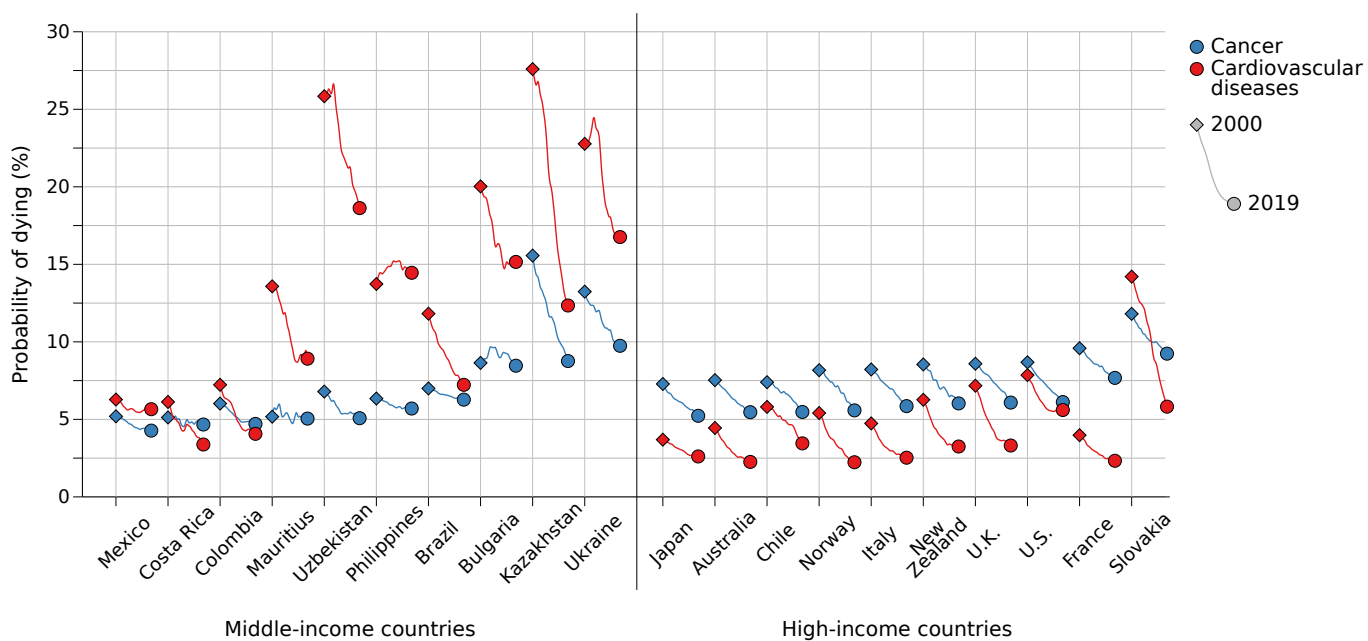
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With long-standing expertise in cancer registration and descriptive epidemiology, the Section of Cancer Surveillance (CSU) serves as a reference to the global cancer community in the provision of national cancer indicators, developed through a collaborative research programme. The research activities are complemented by support and advocacy for local data collection, and a key aim of CSU is the provision of measurable improvements in the coverage, quality, and networking capacity of population-based cancer registries (PBCRs) in low- and middle-income countries (LMICs). The core priorities of CSU are:
• to consolidate the role of IARC as a definitive source of data and statistics describing the global cancer burden in children, adolescents, and adults;
• to ensure that locally recorded high-quality cancer data are available to governments in LMICs, to inform priorities for national cancer control;
• to describe and interpret the changing magnitude and the transitional nature of cancer profiles around the world; and
• to advocate the health, social, and economic benefits of cancer prevention, through a systematic quantification of the future impact of effective interventions.

With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, CSU was renamed as the Cancer Surveillance Branch. A brief summary of CSU activities during the 2020–2021 biennium is provided here.

Cancer registry support and collaboration

CSU provides the Secretariat for the International Association of Cancer Registries (IACR; http://www.iacr.com.fr), the professional society dedicated to fostering the aims of PBCRs worldwide through meetings, advocacy, and developing registry standards and tools. An IACR survey revealed the operational impact of the COVID-19 pandemic on PBCRs in the early months of the crisis; two thirds of the respondents reported disruptions. With international travel on hold, the 42nd IACR Annual Scientific Conference was held virtually over 3 days in October 2021; this free event was attended by more than 400

members worldwide. A major focus was facilitating the recording of comparable cancer staging data internationally.

The Global Initiative for Cancer Registry Development (GICR; https://gicr.iarc.fr/) brings together agencies committed to working collaboratively to improve surveillance worldwide. A virtual IARC–GICR course on tumour–node–metastasis (TNM) staging and the Essential TNM was held for participants from 11 Eastern Mediterranean countries in November 2020. The CanStaging⁺ tool was launched by IARC in August 2021 (Figure 1) (Ervik et al., 2021) as part of the International Cancer Benchmarking Partnership (ICBP SURVMARK-2), and a Perspective was published in *The Lancet Oncology* (Soerjomataram et al., 2021b). Several ICBP SURVMARK-2 studies sought to better understand variations in staging, histology, and registry practices in the context of international survival comparisons (Cabasag et al., 2020a, 2021; Myklebust et al., 2020; Andersson et al., 2021a; Araghi et al., 2021a; Morgan et al., 2021a). CSU participated in the IARC/WHO Committee for the International Classification of Diseases for Oncology (ICD-O), tasked with updating the ICD-O-3 morphology included in revised editions of the *WHO Classification of Tumours* (also known as the WHO Blue Books), and disseminating

the resulting changes to the registry community. Finally, the call for data for Volume XII of the joint IACR–IARC publication *Cancer Incidence in Five Continents* (covering diagnoses made during 2013–2017) was launched in July 2021, combined with the SURVCAN-4 call for selected registries.

The GICR*Net* continued to expand its network of IARC–GICR Regional Trainers. To compensate for the limited opportunities to meet in person during the biennium, 14 e-learning modules were developed together with Vital Strategies and the African Cancer Registry Network (AFCRN), supported by Bloomberg Philanthropies. In July 2021, the second IARC–GICR Summer School was held virtually in collaboration with the National Cancer Center of the Republic of Korea. The introduction of GICR Partner Countries provided greater focus on registries, and there are strong prospects for further improvement. In addition, regional support was increased through the integration of IARC–GICR Collaborating Centres to complement the work of the Regional Hubs.

From June 2020, IARC entered into a bilateral agreement with St. Jude Children's Research Hospital (USA) to implement the Targeting Childhood Cancer through the GICR (ChildGICR) project, an

Figure 1. Screenshot of the CanStaging⁺ tool (https://canstaging.org/). © IARC.
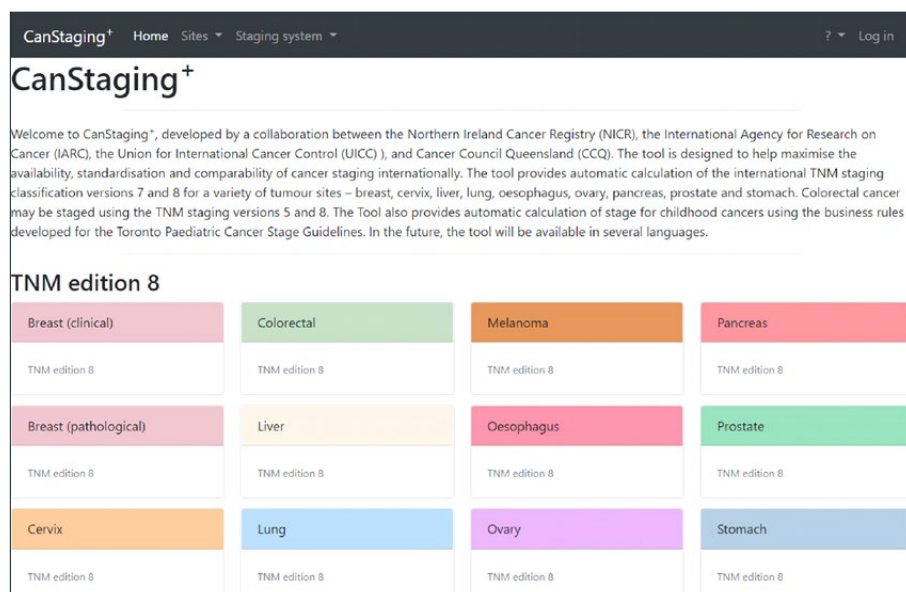
extension of the GICR programme to build national childhood cancer surveillance capacity in LMICs via implementation, education, and research. Networking workshops involving local stakeholders were held virtually in four target countries: Georgia, Mexico, South Africa, and Viet Nam. An educational highlight was the online ChildGICR Masterclass that started in April 2021. Over 12 weeks, 22 GICR*Net* participants worked together with global leaders to jointly co-develop educational materials on the principles of childhood cancer registration (Figure 2); the participants continue to actively network to build regional capacity.

In collaboration with WHO regional offices, CSU developed several position papers discussing surveillance data to inform policies in Latin America (Piñeros et al., 2021a) and the Eastern Mediterranean (Znaor et al., 2021a). CSU also developed roadmaps for the surveillance of cervical cancer (Figure 3) (Piñeros et al., 2021b) and childhood cancer (Piñeros et al., 2021c), to complement the scale-up of the respective WHO signature initiatives. Collaborative studies examining the status of registration in China (Wei et al., 2020) and the Russian Federation (Barchuk et al., 2021a) were published. CSU also participated in the *Lancet Oncology* Commission on sustainable care for children with cancer (Atun et al., 2020).

The Global Cancer Observatory: linking research to action

CSU disseminates global cancer statistics through the Global Cancer Observatory (https://gco.iarc.fr/), an interactive web-based platform comprising multiple subsites. The Cancer Today subsite was updated with the GLOBOCAN estimates of national incidence, mortality, and prevalence in 185 countries for 2020. Studies reviewing data sources and methods and regional variations in cancer profiles worldwide (Sung et al., 2021) were published, the latter in *CA: A Cancer Journal for Clinicians*, which retains the highest impact factor of all journals ranked by the International Scientific Indexing (ISI) server.

The Cancer Tomorrow subsite provides tools to predict future cancer incidence and mortality up to 2040, and it was updated to incorporate user-defined trends-based projections of the future burden. The Cancer Causes subsite provides estimates of population attributable fractions (PAFs) for major risk factors, to assist national decision-makers in setting priorities for cancer prevention; alcohol consumption was added in 2021, based on a recent collaborative publication (Rumgay et al., 2021). In collaboration with WHO regional offices, updates of the alcohol-related burden were disseminated in various media formats (Figure 4). The Cancer Survival subsite has been continuously updated over the biennium to incorporate recent site-specific results from numerous studies published as part of ICBP SURVMARK-2 (Cabasag et al., 2020a, 2021; Araghi et al., 2021a; Rutherford et al., 2021).

In collaboration with the Association of the Nordic Cancer Registries (ANCR), a complete revamp of the NORDCAN website was undertaken; NORDCAN 2.0 (https://nordcan.iarc.fr/) enables dynamic comparisons of cancer statistics for the Nordic countries, supported by the Nordic Cancer Union (NCU). Harnessing some of the same technology, the Cancer Over Time subsite was launched in November 2021 to enable joint analyses of cancer incidence and mortality trends in about 60 countries around the world.

Descriptive studies: a focus on impact, to aid decision-making

CSU expanded its research programme to ask questions that support the commitments of countries to tackle

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Figure 2. Trainers participating in the online ChildGICR Masterclass, in April 2021. Over a period of 12 weeks, working groups developed the necessary teaching materials to cover seven key topics in childhood cancer registration. © IARC.
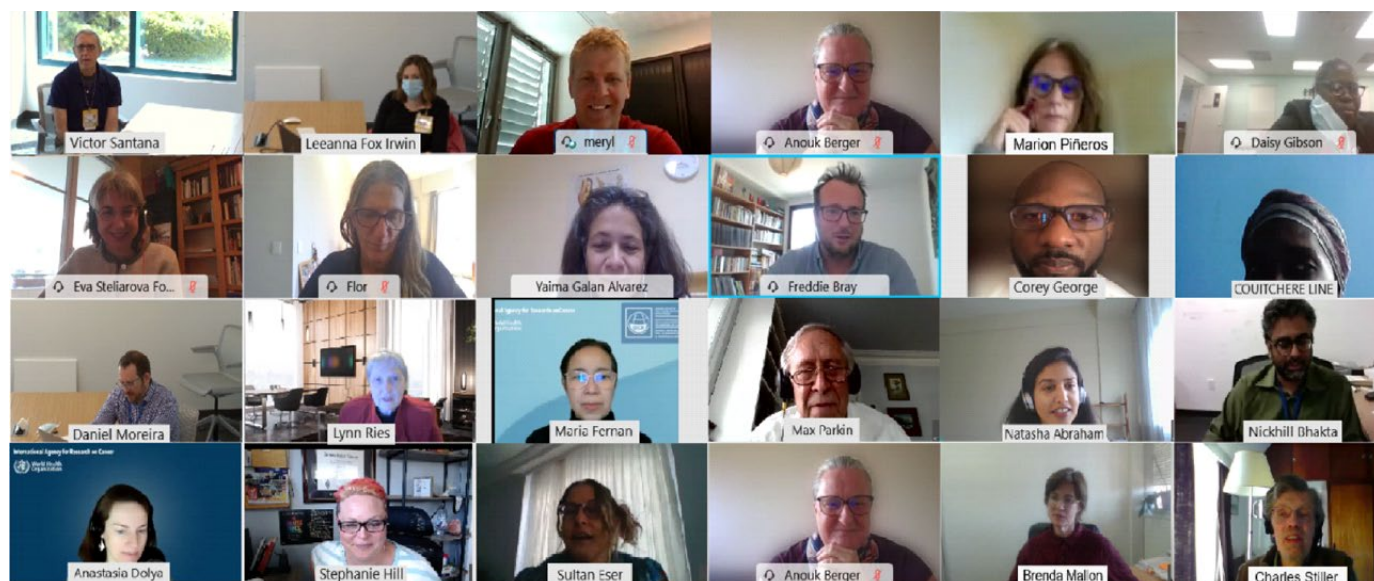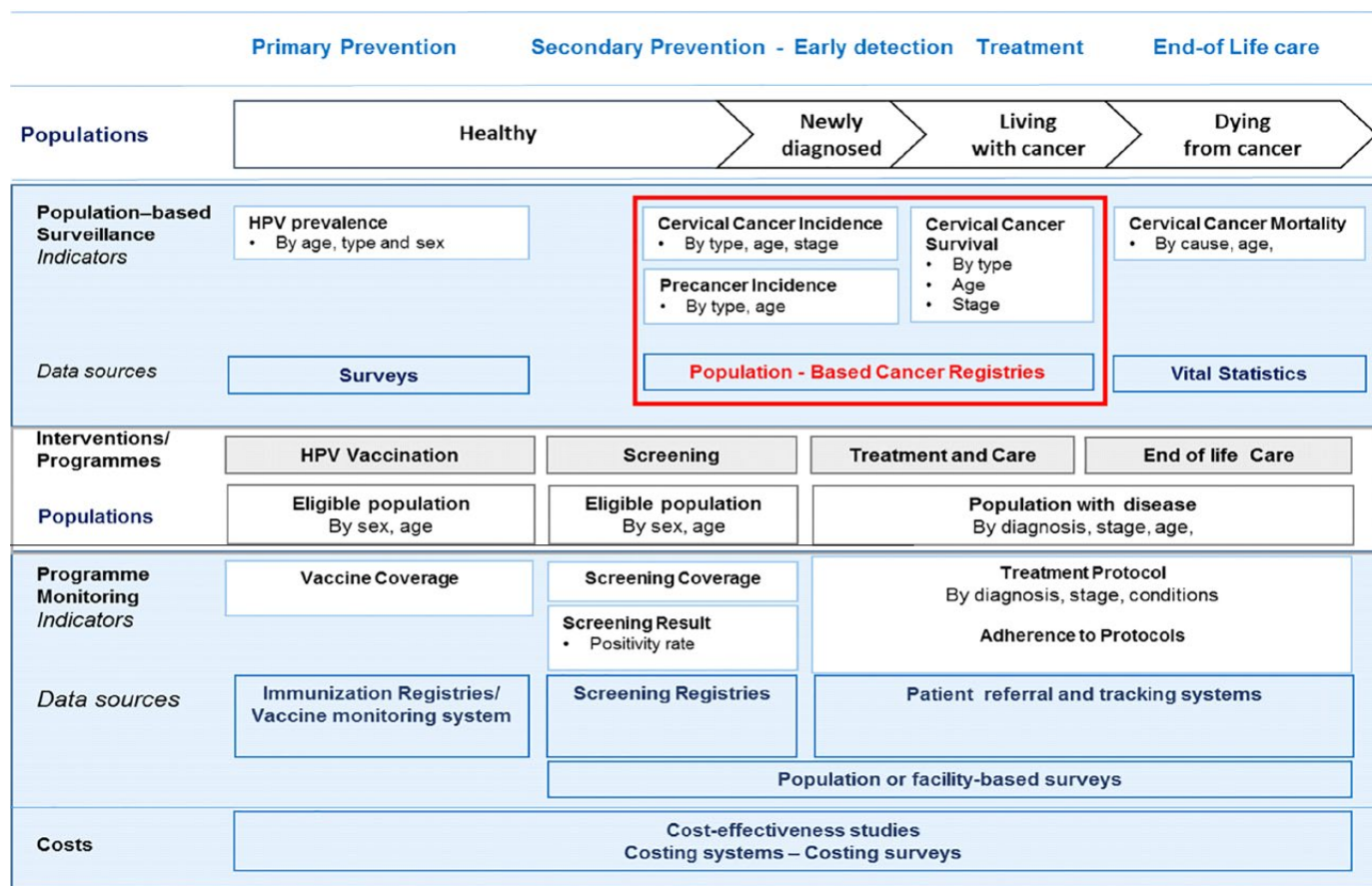
Figure 3. A framework for the surveillance and monitoring of a scaled-up cervical cancer control programme, including the central role of population-based cancer registries. Reproduced with permission from Piñeros et al. (2021b). © 2020 The Authors. Published by Elsevier Inc.

the rising cancer burden. A focus was the measurement of the impact of the COVID-19 pandemic on the health of nations and on the outcomes of current and future patients with cancer. CSU participated in the COVID-19 and Cancer Global Taskforce and in spring 2021 became a founding partner of the COVID-19 and Cancer Global Modelling Consortium (https://ccgmc.org/), with a remit to co-develop tools and provide evidence to aid decision-making during and after the pandemic (Figure 5).

CSU continued to highlight cancer transitions worldwide. Cancer is expected to surpass cardiovascular disease as the leading cause of premature death in most countries during this century (Bray et al., 2021a). Furthermore, a recent study compared trends in premature death from cardiovascular disease and cancer during 2000–2019 in 20 diverse countries to examine whether the countries will meet Target 3.4 of the United Nations

Sustainable Development Goals: a reduction by one third in premature deaths from noncommunicable diseases by 2030. National progress was highly variable and tended to be more apparent in high-income countries compared with middle-income countries, and for the control of cardiovascular disease compared with cancer (Bray et al., 2021b).

With IARC's unique focus on cancer prevention, several studies have highlighted the long-term beneficial impact of preventive interventions. As well as predicting the future burden up to 2070, CSU recently quantified the long-term impact on global cancer incidence of a reduction in the prevalence of tobacco smoking, overweight and obesity, and human papillomavirus (HPV) infection in different settings (Soerjomataram and Bray, 2021). Recent estimates of the impact of tobacco use and alcohol consumption on the cancer burden

sought to advocate the prioritization of their control; CSU has shown that optimal implementation of evidence-based tobacco control policies could prevent 1.65 million new cases of lung cancer in Europe by 2037 (Gredner et al., 2021). CSU also estimated that almost 750 000 (~ 4%) of the new cases of cancer worldwide in 2020 could be attributed to alcohol consumption (Figure 4) (Rumgay et al., 2021a); this figure could be reduced by various control strategies, including increasing alcohol taxation.

CSU continued to develop in-depth collaborative assessments of the descriptive epidemiology of specific cancer types, including cancers of the oral cavity (Miranda-Filho and Bray, 2020) and gastrointestinal tract (Arnold et al., 2020a, 2020b; Rumgay et al., 2021b; Rutherford et al., 2021), and sex-specific cancers (Bray et al., 2020a; Znaor et al., 2020a). CSU also published the results of several studies examining the current
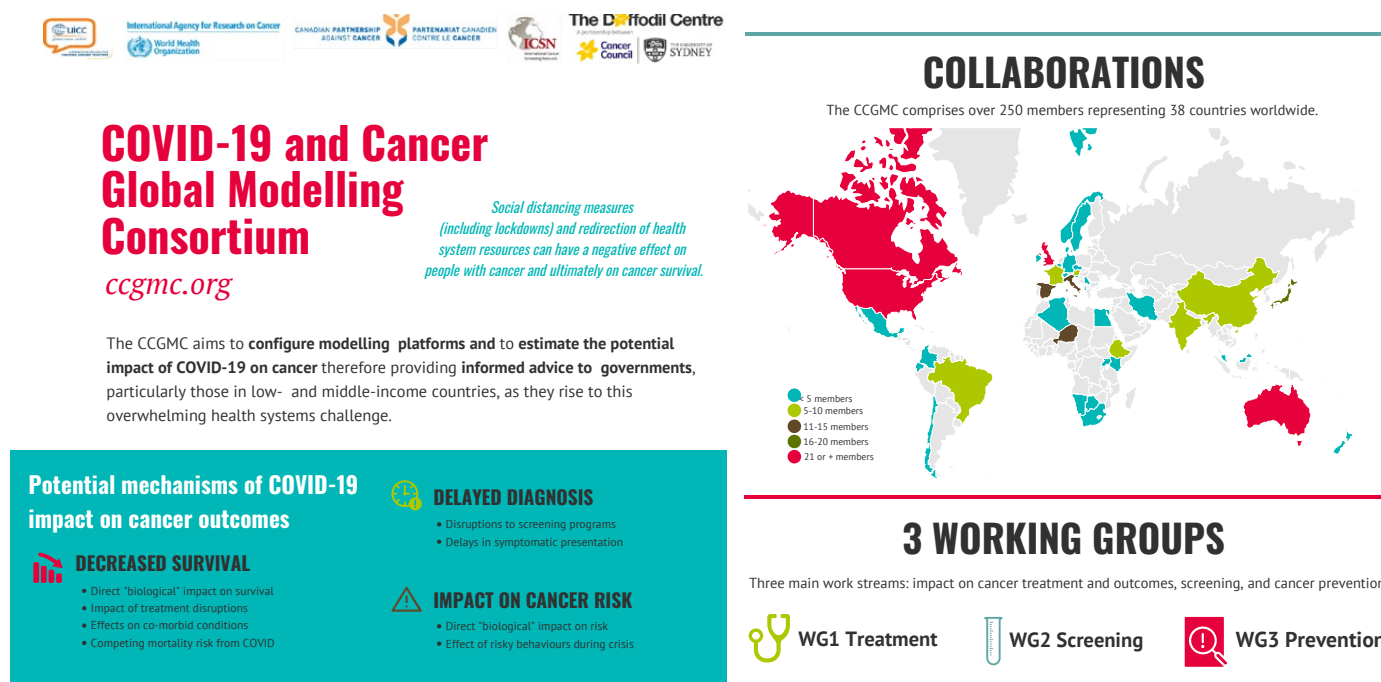
and future burden of cervical cancer in relation to scaling up the WHO global initiative to eliminate cervical cancer as a public health problem (Arbyn et al., 2020a; Brisson et al., 2020; Canfell et al., 2020; Pilleron et al., 2020; Bonjour et al., 2021; Ryzhov et al., 2021; Stelzle et al., 2021; Znaor et al., 2021b), as well as the impact of overdiagnosis on thyroid cancer incidence and mortality (Li et al., 2020a, 2020b, 2021a; Miranda-Filho et al., 2021a; Vaccarella and Dal Maso, 2021; Vaccarella et al., 2021a). Specific in-country studies examined the current and future patterns of cancer in the Islamic Republic of Iran (Roshandel et al., 2020, 2021), Thailand (Sangrajrang et al., 2020), Ukraine (Ryzhov et al., 2020), and Uruguay (Musetti et al., 2021).

In line with the emerging priority areas as set out in the IARC Medium-Term Strategy 2021–2025, CSU developed two teams in 2021 that aim to develop and expand cancer research activities that focus on social inequalities (Lortet-Tieulent et al., 2020) and on descriptive economics.
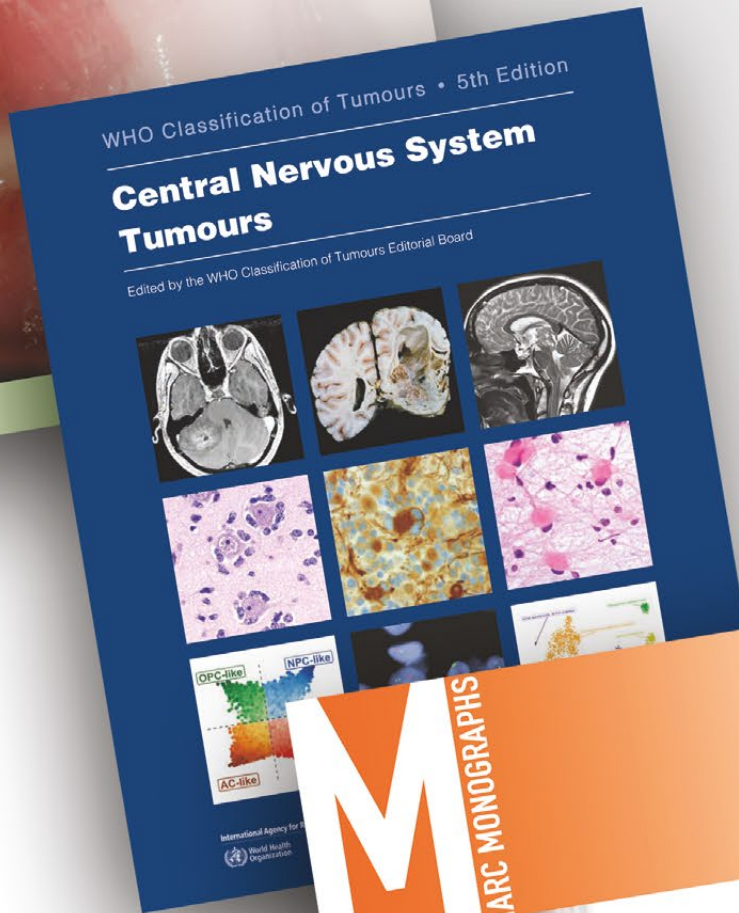
Figure 4. Infographic on alcohol and cancer produced as part of the release of the publication on the global cancer burden attributable to alcohol. © IARC.
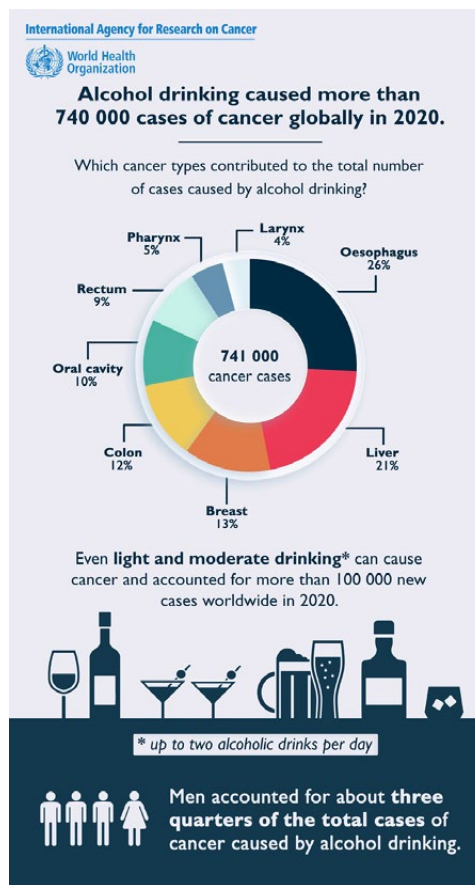
Figure 5. The COVID-19 and Cancer Global Modelling Consortium. This infographic was designed by CSU. For more information about the consortium, please visit https://ccgmc.org/.

IARC HANDBOOKS

CERVICAL CANCER
SCREENING
VOLUME 18

WHO Classification of Tumours • 5th Edition

Central Nervous System
Tumours

Edited by the WHO Classification of Tumours Editorial Board

OPC-like   NPC-like

AC-like

International Agency for Research on Cancer
World Health Organization

IARC MONOGRAPHS

ACROLEIN, CROTONALDEHYDE,
AND ARECOLINE
VOLUME 128

IARC MONOGRAPHS
ON THE IDENTIFICATION
OF CARCINOGENIC HAZARDS
TO HUMANS

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World Health Organization

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Trainee
Mr Javier Del Aguila

The Section of Evidence Synthesis and Classification (ESC) comprises three Groups: the IARC Monographs Group (IMO), the IARC Handbooks Group (IHB), and the WHO Classification of Tumours Group (WCT). With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, ESC was renamed as the Evidence Synthesis and Classification Branch.

The IARC Monographs Group (IMO) 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) 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) produces the *WHO Classification of Tumours* series (also known as the WHO Blue Books). Now in its fifth edition as a series of 14 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 Handbook on Cervical Cancer Screening

At the World Health Assembly in May 2018, WHO Director-General Dr Tedros Adhanom Ghebreyesus made a global call for action towards the elimination of cervical cancer. The *IARC Handbooks* programme responded to this call with the preparation of Volume 18: Cervical Cancer Screening. This volume updates the evaluations of the effectiveness of the current methods of cervical cancer screening and provides statements of the comparative effectiveness of these methods.

This *Handbook* was prepared in close collaboration with WHO headquarters, for the updating of the *WHO Screening and Treatment Recommendations to Prevent Cervical Cancer*. Preliminary steps involved the identification of topics for contribution to the recommendations, harmonization of the protocols for systematic review, and coordination of the calendars so that the two projects would evolve in parallel. The outcome of the collaboration was that the *IARC Handbooks* evaluations of the effectiveness of screening with human papillomavirus (HPV) DNA testing, cytology, and visual inspection with acetic acid (VIA), and the statements of their comparative effectiveness, served as a basis for the WHO recommendations.

Announcement of the webinar held on 6 July 2021. Reproduced from https://www.who.int/news-room/events/detail/2021/07/06/default-calendar/reaching-2030-cervical-cancer-elimination-targets, Copyright 2021.

Such collaboration represents a major milestone for the *IARC Handbooks* programme, and a similar collaboration is currently under way with the WHO Regional Office for South-East Asia for the preparation of Volume 19: Oral Cancer Prevention.

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 cancer in humans. Since the inception of the *Monographs* programme in 1971, 1032 agents have been evaluated one or more times 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 2020–2021 biennium. Because of the travel restrictions put in place during the COVID-19 pandemic, all of the meetings were held fully remotely, and they were extended beyond 8 days to accommodate the time zones associated with global remote participation. The agents evaluated at the five Working Group meetings included several that had been recommended as priorities for evaluation:
• Volume 127: Some Aromatic Amines and Related Compounds (25 May–12 June 2020)
• Volume 126: Opium Consumption (11–20 September 2020)
• Volume 128: Acrolein, Crotonaldehyde, and Arecoline (29 October–13 November 2020)
• Volume 129: Gentian Violet, Leucogentian Violet, Malachite Green, Leucomalachite Green, and CI Direct Blue 218 (22 February–5 March 2021)

Figure 1. *IARC Monographs* Volume 126: Opium Consumption. © IARC.
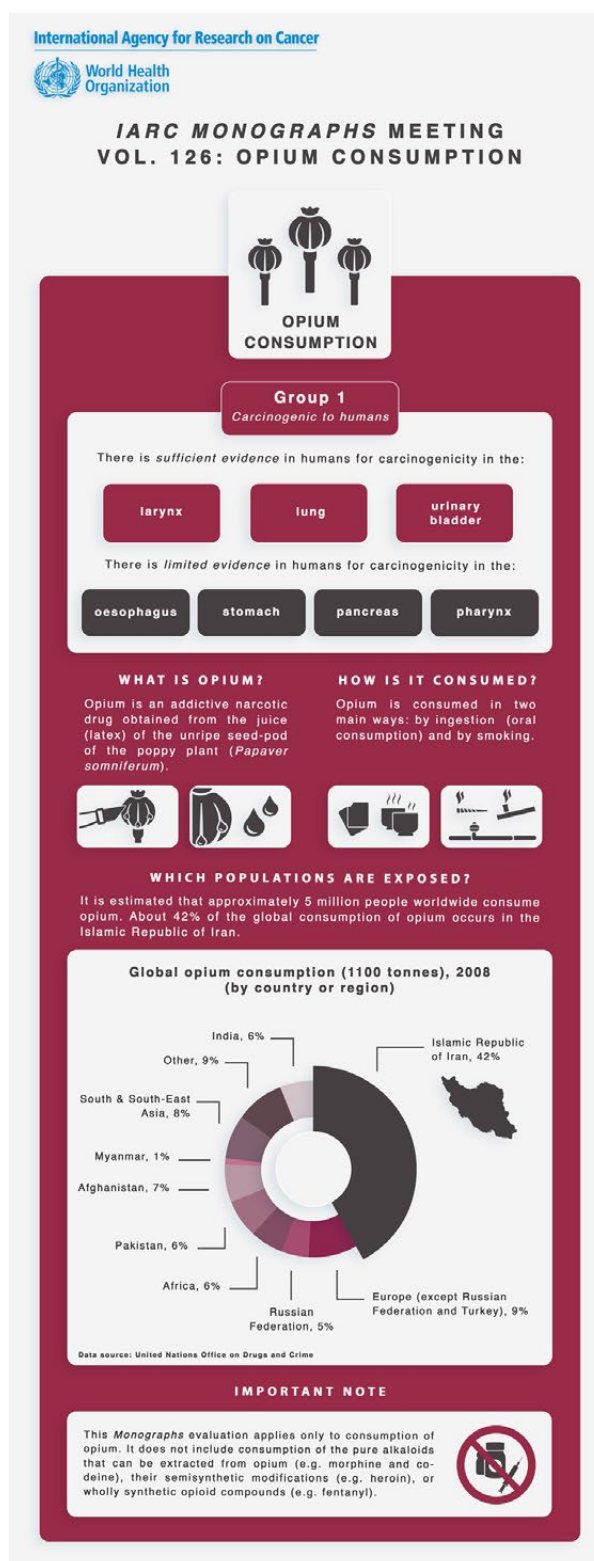
- Volume 130: 1,1,1-Trichloroethane and Four Other Industrial Chemicals (7–22 October 2021).

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 opium consumption (Figure 1).

The evaluations reached in these meetings included 20 classifications, comprising 14 agents never before evaluated by IARC and re-evaluations of 6 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 *Monographs* volume, which is expected to be published about a year after each meeting. Both are available to download for free from the IARC Publications website (https://publications.iarc.fr/).

PUBLICATIONS

During the 2020–2021 biennium, the following *IARC Monographs* volumes were published:
Volume 128: Acrolein, Crotonaldehyde, and Arecoline (2021)
Volume 127: Some Aromatic Amines and Related Compounds (2021)
Volume 126: Opium Consumption (2021)
Volume 125: Some Industrial Chemical Intermediates and Solvents (2020)
Volume 124: Night Shift Work (2020)
Volume 123: Some Nitrobenzenes and Other Industrial Chemicals (2020).

Table 1. Summary of evaluations from the five *Monographs* meetings held in 2020–2021

Agent (Volume)	Evaluation[a]	Strength of evidence of cancer in humans (tumour type provided for *limited* or *sufficient* evidence)	Strength of evidence for carcinogenicity in experimental animals	Key characteristics of carcinogens with strong evidence[b]
Opium Consumption (Volume 126)				
Opium consumption	Group 1	*Sufficient* (larynx, lung, urinary bladder) *Limited* (oesophagus, stomach, pancreas, pharynx)	*Sufficient*	2
Some Aromatic Amines and Related Compounds (Volume 127)				
Aniline[c]	Group 2A	*Inadequate*	*Sufficient*	Multiple (1, 2, 5, 10)
Aniline hydrochloride[c]	Group 2A	*Inadequate*	*Sufficient*	Multiple (1, 2, 5, 10)
ortho-Anisidine[c]	Group 2A	*Inadequate*	*Sufficient*	Multiple (1, 2, 10)
ortho-Anisidine[c] hydrochloride	Group 2A	*Inadequate*		Multiple (1, 2, 10)
ortho-Nitroanisole[c]	Group 2A	*Inadequate*	*Sufficient*	Multiple (1, 2, 10)
Cupferron	Group 2B	*Inadequate*	*Sufficient*	2
Acrolein, Crotonaldehyde, and Arecoline (Volume 128)				
Acrolein	Group 2A	*Inadequate*	*Sufficient*	Multiple (1, 2, 3, 5, 6, 7, 10)
Crotonaldehyde	Group 2B	*Inadequate*	*Limited*	Multiple (1, 2, 5, 6)
Arecoline	Group 2B	*Inadequate*	*Limited*	Multiple (1, 2, 3, 5)
Gentian Violet, Leucogentian Violet, Malachite Green, Leucomalachite Green, and CI Direct Blue 218 (Volume 129)				
Gentian Violet	Group 2B	*Inadequate*	*Sufficient*	None
Leucogentian Violet	Group 3	*Inadequate*	*Inadequate*	None
Malachite Green	Group 3	*Inadequate*	*Limited*	None
Leucomalachite Green	Group 2B	*Inadequate*	*Sufficient*	None
CI Direct Blue 218	Group 2B	*Inadequate*	*Sufficient*	None
1,1,1-Trichloroethane and Four Other Industrial Chemicals (Volume 130)				
1,1,1-Trichloroethane	Group 2A	*Limited*	*Sufficient*	None
Hydrazobenzene	Group 2B	*Inadequate*	*Sufficient*	None
N-Methylolacrylamide	Group 2B	*Inadequate*	*Sufficient*	None
Diphenylamine	Group 2B	*Inadequate*	*Sufficient*	None
Isophorone	Group 2B	*Inadequate*	*Sufficient*	None

[a] Group 1, carcinogenic to humans; 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] This agent was determined to belong to a class of aromatic amines for which several members (including *ortho*-toluidine, 2-naphthylamine, and 4-aminobiphenyl) have been classified as *carcinogenic to humans* (Group 1).

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. *Handbook* evaluations have included chemopreventive agents, preventive actions, effectiveness of screening, and effectiveness of tobacco control measures. The *Handbooks* are used worldwide by public health representatives to set guidelines and recommendations for cancer prevention.

Major accomplishments

IHB organized two meetings during the 2020–2021 biennium: the Working Group meetings for *IARC Handbooks* Volume 18 (Cervical Cancer Screening) and Volume 19 (Oral Cancer Prevention). Because of the COVID-19 pandemic, both meetings were held fully remotely.

Volume 18: Cervical Cancer Screening (June–October 2020)

Cervical cancer screening was re-evaluated by the *IARC Handbooks*. The Working Group considered new screening technologies, including human papillomavirus (HPV) testing, and provided statements of the comparative effectiveness of established screening methods (Figure 2). This *Handbook* was published in response to the WHO Cervical Cancer Elimination Initiative, which was launched after the WHO Director-General's call for action at the World Health Assembly in May 2018. This was the first close collaboration between the *Handbooks* programme and WHO headquarters, and it enabled the development and updating of WHO recommendations.
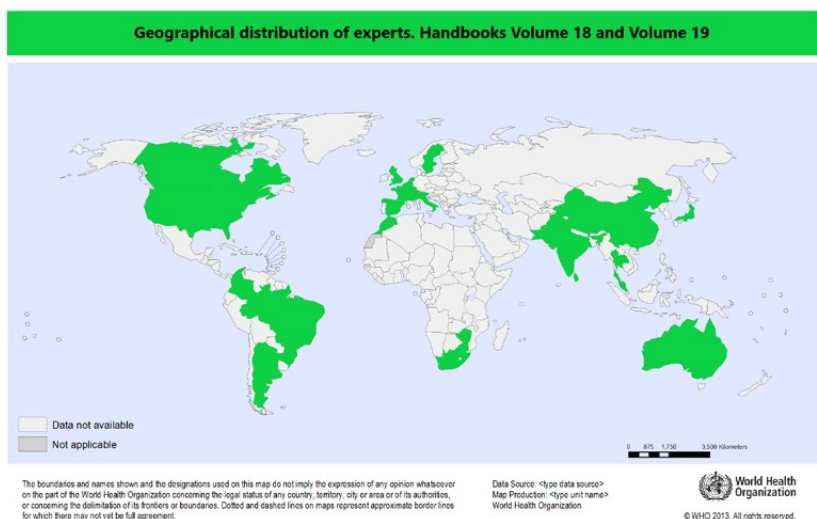
A summary of the outcome of the meeting, which took place remotely between June and October 2020, was published in *The New England Journal of Medicine* in November 2021 (Bouvard et al., 2021).

Volume 19: Oral Cancer Prevention (September–December 2021)

This *Handbook* is a first-time evaluation of all approaches to oral cancer prevention, with a special emphasis on low- and middle-income countries and on oral cancer associated with the use of smokeless tobacco and products derived from the areca nut. This *Handbook* will cover primary prevention through the evaluation of whether reduction of exposure to the established (IARC Group 1) risk factors leads to reduced incidence or mortality, primary prevention through interventions aiming to reduce exposure to smokeless tobacco or products derived from the areca nut, and secondary prevention through screening.

A scoping meeting for Volume 19 took place in February 2021, and the meeting took place fully remotely between September and December, first in subgroups and then in plenary sessions. The evaluations reached at this *Handbooks* meeting will lead to the development of tools and recommendations for the implementation of prevention measures in those countries most in need.

Figure 2. The Working Group for *IARC Handbooks* **Volume 18: Cervical Cancer Screening, the geographical distribution of the participants, and the summarized outcomes of the meeting. All © IARC.**

WHO CLASSIFICATION OF TUMOURS GROUP (WCT)

The work of the WHO Classification of Tumours Group (WCT) encompasses the *WHO Classification of Tumours* series (also known as the WHO Blue Books), the IARC histopathology laboratory, and the International Collaboration for Cancer Classification and Research (IC³R).

WHO BLUE BOOKS

Tumour classification is a major scientific endeavour of considerable importance, underpinning the diagnosis of all cancer worldwide. In recent years, the series' adoption of a relational database approach and a hierarchical classification according to Linnaean principles has vastly improved the standardization of tumour classification across anatomical sites, requiring authors to consider all characteristics of each tumour and highlighting the increasingly multidisciplinary nature of cancer diagnosis.

During the 2020–2021 biennium, the following volumes were published:
- *Soft Tissue and Bone Tumours*, fifth edition (2020)
- *Female Genital Tumours*, fifth edition (2020)
- *Thoracic Tumours*, fifth edition (2021).

A fourth volume (*Central Nervous System Tumours*, fifth edition) is almost complete. The 14-volume fifth edition of the *WHO Classification of Tumours* series is well under way, with a further five volumes in various stages of production. The books and the accompanying website (WHO Classification of Tumours Online; https://tumourclassification.iarc.who.int/) have both been very well received, and use of the classification is expanding in the wider biomedical community (e.g. among radiologists). Production of the *WHO Classification of Tumours* series continues to be funded by book sales and website subscriptions alone.

HISTOPATHOLOGY LABORATORY

During this biennium, thanks to the IARC Scientific Council and Governing Council Special Funds (2021), the histopathology laboratory has modernized its equipment, with a corresponding increase in capacity and capability. It continues to operate with a single scientist but provides technical support to a wide range of projects across the Agency, including providing whole slide images for the WHO Blue Books (Figure 3). The laboratory is increasingly involved in

Figure 3. A lymphoepithelial carcinoma of the lung showing a syncytial growth pattern of tumour cells with large vesicular nuclei (whole slide image). © IARC.
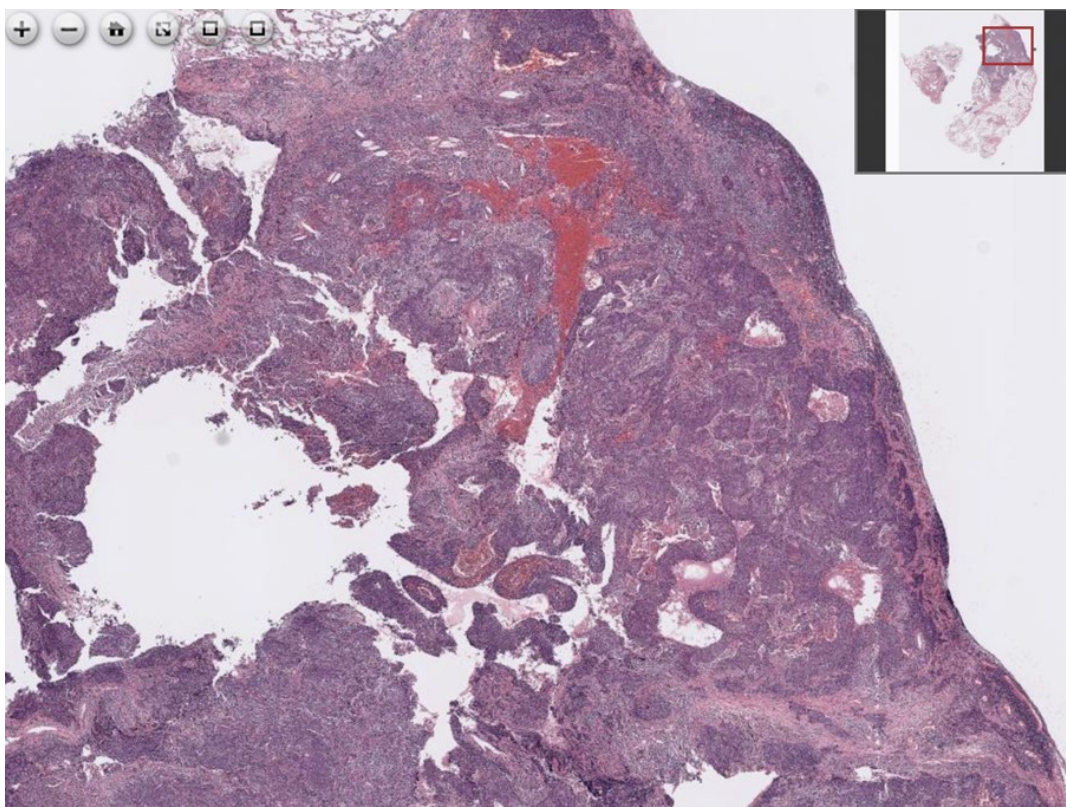
all aspects of digital and computational pathology, including artificial intelligence and machine learning projects. Its capacity to produce high-quality immunohistochemistry for research projects has been enhanced by the acquisition of an automated immunostainer, and older equipment used to produce slides and frozen sections is being updated. All of the laboratory's equipment will eventually be moved to the Nouveau Centre building, which will have a dedicated histopathology laboratory similar to the one currently in use. Collaborations with Centre Léon Bérard and other institutions continue to expand.

INTERNATIONAL COLLABORATION FOR CANCER CLASSIFICATION AND RESEARCH (IC³R)

The translation of research findings into practice is never easy, and the sheer volume of information produced each year can be daunting for those involved. Crucially, scientific information must be of high quality to be of use. Unlike in other branches of medicine, the translation of cancer research into diagnostic practice is largely in the hands of its users, through incorporation into the WHO Classification of Tumours (with the exception of health technology assess-

ment, which is the remit of health-care services within individual countries).

The International Collaboration for Cancer Classification and Research (IC³R; https://ic3r.iarc.who.int/) was established to bring cancer research institutions together to improve research quality and to meet the need for evaluation and synthesis of research findings (Figure 4). Currently, 22 institutions are involved in IC³R, and it is funded by membership dues.

Figure 4. The WHO Classification of Tumours (WCT) is run by an Editorial Board composed of standing members nominated by major societies, and expert members selected for each volume. The International Collaboration for Cancer Classification and Research (IC³R) has been formed to bring together cancer research institutes around the world interested in diagnosis to improve the evidence base for the classification. The classification can also be used to identify gaps and priorities for future research. © IARC.
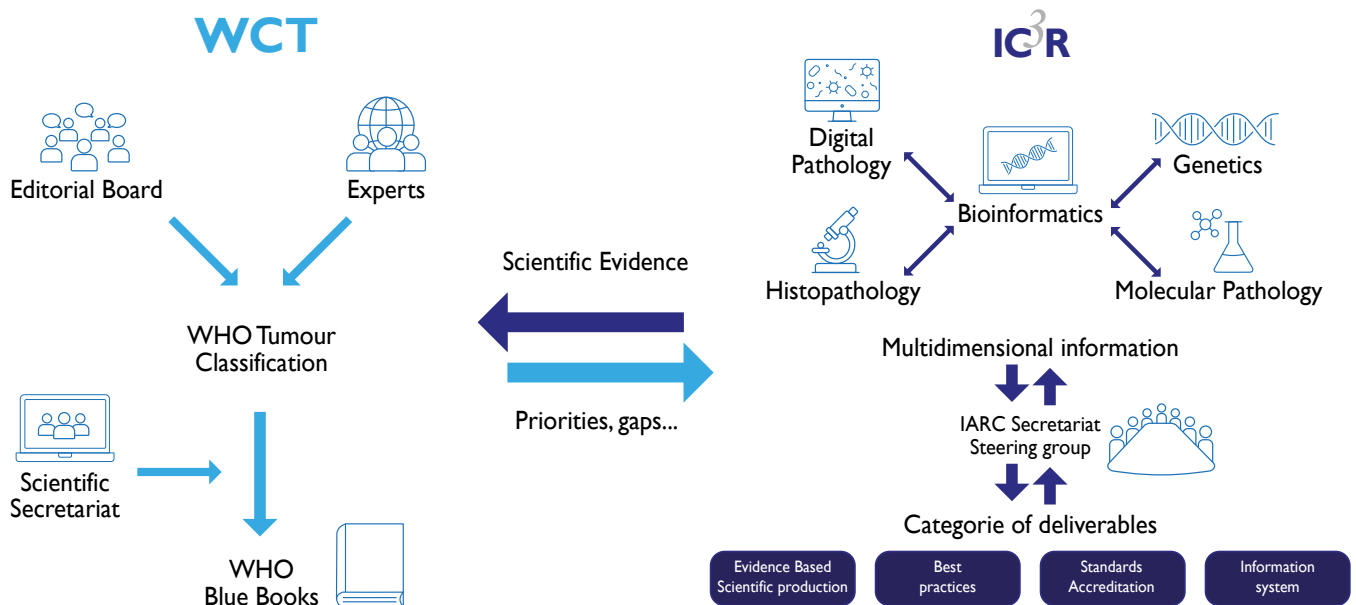
Studying (epi)genome deregulation and environmental origins of cancer

Risk factors

Endogenous processes
- Hormones
- Microbiome
- Metabolome
- Inflammation
- Aging...

External exposures
- Smoking
- Air Pollution
- Nutrition
- Biol. Agents
- Endocrine disruptors...

Timing of exposures

In utero life

Birth

Childhood

Adulthood

(Epi)genome responses

Epigenome

Genome

Epigenetic changes as "sensors" of exposure & "mediators" of outcomes

Consequences

Hallmarks of cancer

Angiogenesis

Reprograming energetics

Immortality

Proliferation

Inflammatory signals

Genome instability

Resisting death

Invasiveness

Evade immune destruction

Evading suppressors

Causality

Identifying causal pathways linking environ. exposures to cancer (**biological plausibility**)

Outcome

Cancer

Section of Mechanisms of Carcinogenesis (MCA)

Section head
Dr Zdenko Herceg

Epigenetics Group (EGE)

Group head
Dr Zdenko Herceg

Scientists
Dr Rosita Accardi (died 13 May 2020)
Dr Akram Ghantous
Dr Rita Khoueiry

Secretariat
Ms Elizabeth Page

Postdoctoral fellows
Dr Zainab Awada
Dr Felicia Chung (until April 2021)
Dr Andrea Halaburkova
(until November 2020)
Dr Farah Nassar
Dr Alexei Novoloaca
(until December 2020)
Dr Grace Akinyi Odongo
Dr Alexandra Sexton-Oates
(until January 2020)
Dr Natalia Spitz Toledo Dias
Dr Fazlur Talukdar (until August 2020)

Doctoral students
Ms Maria Boskovic
Ms Mariana Gomes da Silva Araujo
Mr Antonin Jay
(until November 2020)
Ms Francesca Manara
Mr Thanos Mouchtaris-Michailidis
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Ms Aurélie Salle

Senior research assistant, data management/analysis
Mr Vincent Cahais

Trainees
Ms Cédrine Milesi
(until September 2020)
Ms Farah Ramadan
(until December 2020)
Ms Ling Wei (until March 2020)

Molecular Mechanisms and Biomarkers Group (MMB)

Group head
Dr Jiri Zavadil

Scientists
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Dr Magali Olivier (until August 2020)

Senior research assistant, data management/analysis
Dr Claire Renard

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Ms Marie-Pierre Cros
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Secretariat
Ms Karine Racinoux

Postdoctoral fellow
Dr Samrat Das

Students
Ms Liesel Claeys
(until November 2021)
Ms Shefali Thakur

Trainees
Ms Bérénice Chavanel
(until August 2021)
Ms Xinyue Jiang (until August 2020)
Mr Stéphane Keita
(until August 2021)

Identifying the causal pathways that link environmental or lifestyle exposures to tumorigenesis and gaining insights into the molecular mechanisms that underlie the associations observed in epidemiological studies (biological plausibility) provide a foundation for studies of cancer etiology, carcinogen evaluation and classification, and ensuring evidence-based cancer prevention. The Section of Mechanisms of Carcinogenesis (MCA) conducts hypothesis-driven and data-driven studies aimed at advancing the understanding of cancer causation and the mechanisms of tumorigenesis, as well as promoting international collaborations, as the core mission of IARC.

The studies of MCA are interdisciplinary in nature, and the major MCA programmes promote and advance synergistic collaborations with other IARC scientists and evidence synthesis experts. Key elements of MCA's strategy include developing innovative state-of-the-art molecular and cell biology and functional epigenomics research methodologies, and bioinformatics and biostatistics tools, applicable to experimental cancer models and human samples from population-based studies. The Section comprises two Groups – the Epigenetics Group (EGE) and the Molecular Mechanisms and Biomarkers Group (MMB) – whose corresponding research programmes are complementary with respect to methodological approaches and the shared ultimate objective of identifying causal links between environmental factors and cancer. With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, MCA was renamed as the Epigenomics and Mechanisms Branch.

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 and endogenous processes 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 (Halaburkova et al., 2020; Pashayan et al., 2020; Ghantous et al., 2021; Sklias et al., 2021). 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 (Merid et al., 2020; Karabegović et al., 2021; Sorroche et al., 2021; Talukdar et al., 2021).

Epigenome-wide profiling of oesophageal squamous cell carcinoma from high-incidence regions identifies crucial genes and potential cancer markers

Oesophageal squamous cell carcinoma (ESCC) is one of the most aggressive and lethal forms of cancer in the world, with the highest incidence rates in low- and middle-income countries. EGE conducted the largest epigenome-wide (DNA methylome, DNAme) profiling of the collection of ESCC samples from high-incidence populations worldwide (Figure 1), with the aim of understanding ESCC etiology and identifying early biomarkers. DNAme changes in ESCC samples and normal tissue adjacent to the tumours (NAT) from patients with cancer in nine high-incidence countries in Africa, Asia, and South America were studied by using the Infinium MethylationEPIC array (Talukdar et al., 2021). Methylome analysis comparing tumour tissue and NAT identified 6796 differentially methylated positions (DMPs) and 866 differentially methylated regions (DMRs). Most of the identified DMPs and DMRs were hypermethylated in tumours. Top genes identified in the discovery phase were prioritized for validation, and their putative functional impact on gene transcription was analysed using RNA-seq data from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) project. The specificity and sensitivity of these DNAme events in discriminating tumours from NAT were then assessed. EGE identified and prioritized genes and pathways involved in the development of ESCC, and proposed an early detection marker panel, which could serve as a reference for tests to improve the early detection of this cancer type in low-resource settings (Talukdar et al., 2021).

Epigenetic markers of breast cancer risk in a prospective cohort study

Epigenetic alterations are a near-universal feature of malignancy; however, much of the current evidence is based on findings in retrospective studies, which may reflect epigenetic patterns influenced by the onset of the disease. Studying breast cancer, EGE established genome-scale DNA methylation profiles of prospectively collected buffy coat samples from a case–control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study using reduced representation bisulphite sequencing (RRBS) (Figure 2). For a subset of these individuals, EGE also profiled primary tumours and tumour-adjacent tissue samples. EGE observed cancer-specific DNA methylation events in both the breast tissue and buffy coat samples, each characterized by sample type-specific differences but with a shared enrichment for genes in specific biological pathways. Notably, increased DNA methylation in genomic regions associated with specific genes was linked to the length of time to diagnosis in prospectively collected buffy coat DNA from individuals who subsequently developed breast cancer

(Figure 2). Using machine learning methods, EGE piloted a DNA methylation-based classifier that predicted case–control status in a held-out validation set with high accuracy, in some cases up to 15 years before diagnosis. The findings suggest a model of gradual accumulation of cancer-associated epigenetic patterns in peripheral blood, which may be detected long before the clinical manifestation of cancer. Such changes may provide useful markers for risk stratification and, ultimately, personalized cancer prevention.

Figure 1. Genome-wide DNA methylation profiling of oesophageal squamous cell carcinoma (ESCC) from high-incidence populations of the world enables the identification of functionally relevant and robust DNA methylation markers for early detection in low-resource settings. (a) Overview of study design and sample characteristics. Country-wise sample distribution in percentages. Dots in the map showing sample collection sites and their respective countries are coloured. Reprinted from Talukdar et al. (2021), with permission from the American Association for Cancer Research. (b) Collaborators attending the Oesophageal Squamous Cell Carcinoma African Prevention research (ESCCAPE) network meeting (coordinated by Dr Valerie McCormack, IARC) held in Eldoret, Kenya. © IARC.
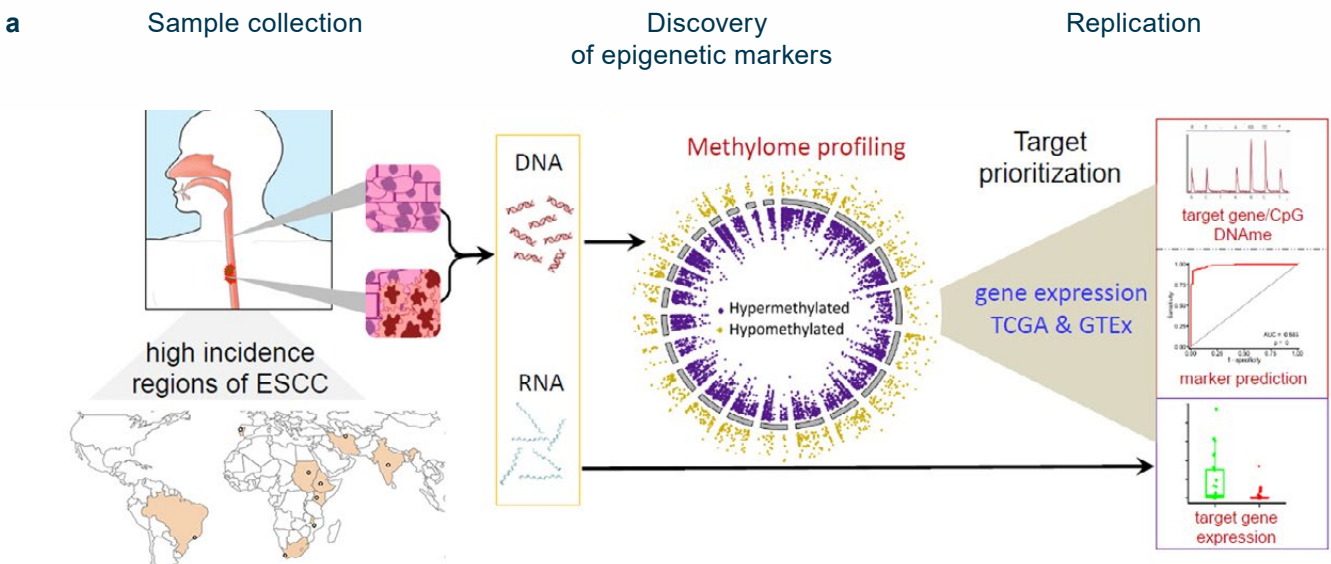
Figure 2. Identifying epigenetic markers of breast cancer risk in a prospective cohort (EpiMark study). (a, b) Schematic of the study design and analytical methods. (a) A nested case–control study was constructed within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Blood samples and lifestyle information were collected from apparently healthy participants upon enrolment. Participants who were diagnosed with breast cancer during the follow-up period were matched on a one-to-one basis with individuals who were cancer-free over the follow-up period. Buffy coat lysates derived from blood samples collected at enrolment as well as tumour tissue and adjacent normal tissue from cases were analysed by reduced representation bisulphite sequencing (RRBS). **(b)** Five-fold nested cross-validation was used to train and evaluate classifier models for their ability to discriminate individuals who developed breast cancer from those who were cancer-free over the follow-up period. The best-performing model was selected and trained on the full cross-validation data set of 340 pairs, to finalize model parameters. The final model was used to predict case–control status in a held-out validation set of 68 matched pairs. Differential methylation analyses and functional enrichment analyses were conducted in parallel. **(c, d)** The global DNA methylation landscape in breast tumours, and breast cancer-specific DNA methylation patterns in breast tissue. **(c)** Unsupervised clustering of methylation in the 6713 most variable regions according to the k-means algorithm and Euclidean distance. **(d)** Four consensus clusters of tumour tissue were identified and are denoted as clusters 1–4, in order of overall DNA methylation levels across CpG islands, gene bodies, and promoters compared with DNA methylation at the same sites in tumour-adjacent normal tissue (NT). **(e–h)** Prediction of case–control status in prospectively collected blood tissue using a prediction analysis for microarrays (PAM) classifier. **(e)** The receiver operating characteristic (ROC) curve and the corresponding area under the curve (AUC) statistics for the PAM classifier applied on the validation cohort, against a background of 100 label-shuffled control data sets that were subjected to the same model training and testing process. A t-distributed stochastic neighbour embedding (t-SNE) plot was generated using the 49 genomic regions used in the PAM classifier, coloured by **(f)** case–control status and **(g)** length of time from sample collection to diagnosis (by quartile). **(h)** Schematic of the classification results from the final PAM model on the held-out validation set alongside length of time to diagnosis (quartiles). **(i)** Diagram of documented functional and physical interactions between possibly perturbed transcription factors in both blood and tissue differentially methylated region (DMR) sets. © IARC.
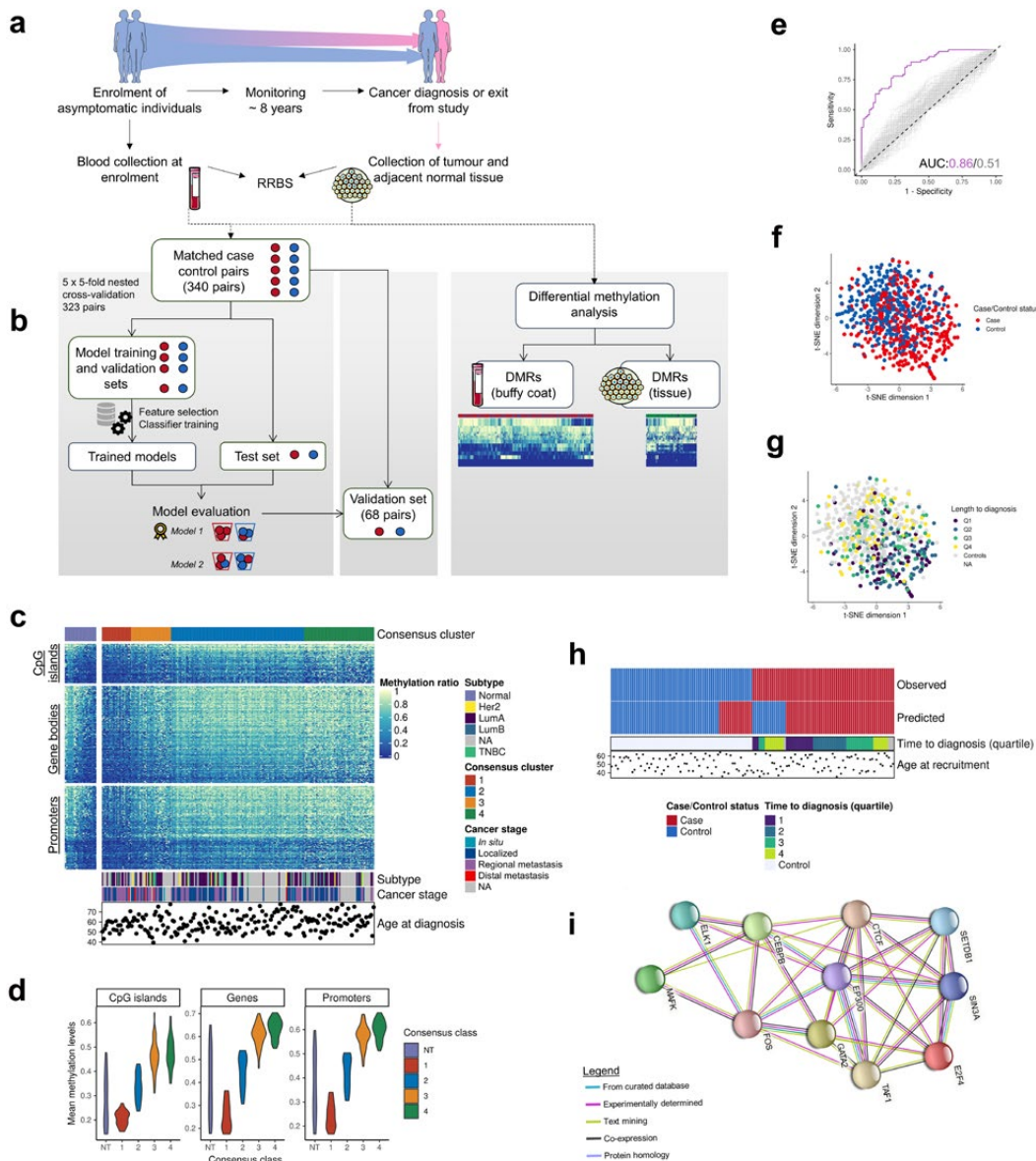
Figure 3. Understanding estrogen receptor (ER) pathway regulation in breast cancer cells and revealing potential mechanisms underlying the roots of resistance to anti-estrogen therapy. (a) Breast cancers are classified into different molecular subtypes mainly according to the presence of ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), and their expression tends to determine the treatment approach. Most (70%) breast cancers are ER-positive (ER+) and are subjected to anti-estrogen therapy. However, patients regularly develop a non-reversible resistance to anti-estrogen therapy. (b) In vitro optimized protocol adapted for studying estrogen deprivation and re-stimulation using MCF-7 breast cancer cells. MCF-7 cells cultured in control conditions (CTR, charcoal-stripped serum + estradiol E2) were deprived of E2 for 4 and 14 days (E2D) or deprived of E2 for 4 days then re-stimulated with E2 for 10 days (ReSt, blue dashed line). (c) Heat map of differentially methylated positions (DMPs) between CTR and E2-deprived (E2D) MCF-7 cells with at least 10% differential methylation (Δβ) detected after methylome analyses using an 850K array, which measures the DNAm levels across more than 850 000 CpGs. (d) Analyses of histone post-translational modification (PTM) by ChIP-sequencing of H3K27 acetylation (H3K27ac), a mark associated with enhancer regions. Analysis showed a global decrease of histone acetylation in E2D compared with CTR. (e) Results of transcriptome analysis (RNA-sequencing). Upper left: Distribution of $-\log_{10}(P)$ of differentially expressed genes (DEGs) in E2D versus CTR according to $\log_2$ fold change (FC) of expression. Coloured dots represent downregulated and upregulated DEGs with an absolute $\log_2(FC) > 1$ (blue and red) and a false discovery rate (FDR) < 0.05 (dashed horizontal). DEGs that were differentially expressed with an absolute $\log_2(FC) < 1$ are shaded dark grey. Upper right: Gene set enrichment analysis of downregulated and upregulated DEGs (MSigDB, database H, hypergeometric test). Lower: Significant differential expression of three epigenetic remodelling factors, HDAC9, PADI4, and TET2, in response to E2 deprivation. (f) Partial reversibility of epigenomic and transcriptomic changes after E2 deprivation and re-stimulation. Left: Distribution of hypermethylated DMPs in response to E2 deprivation and re-stimulation for CTR, E2D, and ReSt at day 14 (CTR vs E2D, *n* = 950; FDR < 0.05, Δβ > 10%). Box plot: centre lines, median (Q2); box boundaries, 25% and 75% quartiles (Q1 and Q3); top and bottom whiskers, minimum and maximum (Q0 and Q4). For each pairwise comparison (ReSt–CTR and CTR–E2D), the quartiles are connected with red lines. In each interquartile range, the mean Δβ between the compared interquartile groups is shown in red. The mean of each group is shown with a red cross. Asterisks mark significant differences of ReSt and E2D means compared with CTR. Upper centre: Overlap of differential H3K27ac regions between CTR versus E2D and CTR versus ReSt regions, showing 207 common peaks. Lower centre: H3K27ac signal in $\log_2$-normalized reads of the 207 peaks. Right: Non-reversibility of expression of AP-1 transcription factor inducer TNIK and AP-1 target gene MMP13 for CTR condition (green squares), E2D (orange diamonds), and ReSt (blue triangles) on day 14. Differential expression analysis was performed after RNA-sequencing by contrasting CTR versus ReSt groups among E2-deprivation DEGs with FDR < 0.05 and |$\log_2$FC| > 1. Reproduced from Sklias et al. (2021). © 2021, Oxford University Press.
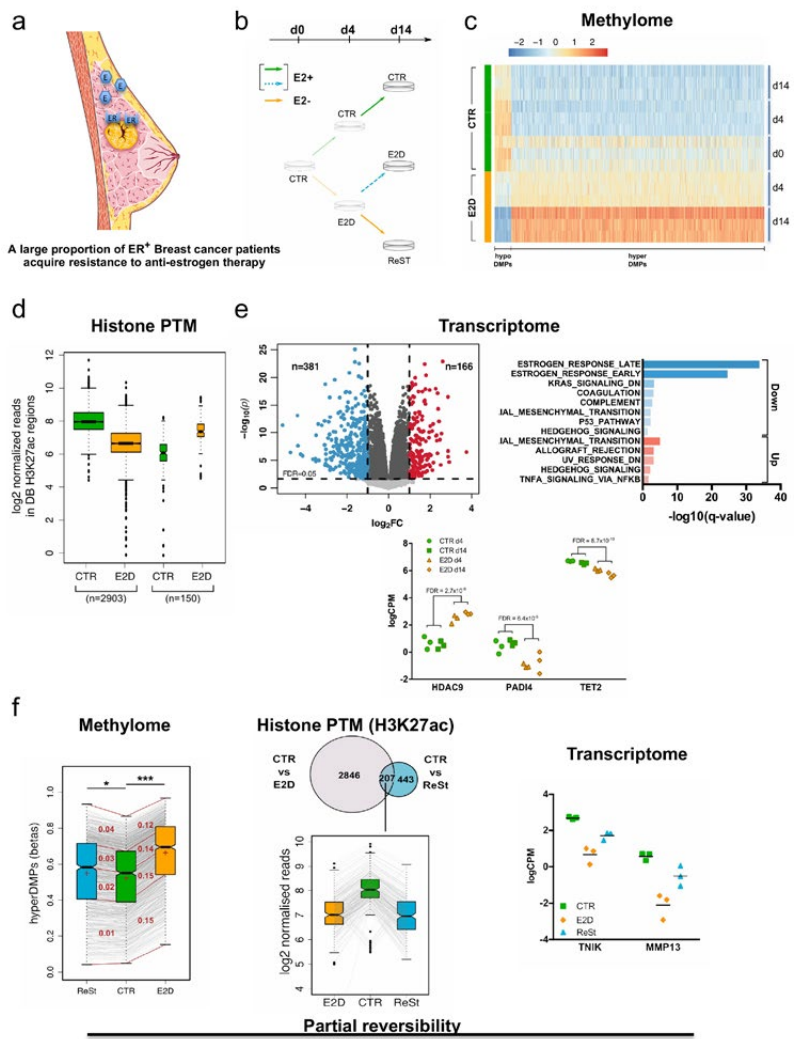
Epigenetic changes induced by estrogen hormones as a potential mechanism underlying endocrine resistance in ER-positive breast cancer

Estrogen hormones are implicated in the development of most breast cancers, and estrogen receptor (ER) alpha, the main nuclear factor that mediates estrogen signalling, orchestrates a complex molecular circuitry, which is poorly understood. EGE combined a novel in vitro protocol adapted for studying estrogen deprivation and re-stimulation with the latest epigenomics and bioinformatics tools, which enabled a genome-wide interrogation of the epigenome and transcriptome changes associated with modifications in ER pathways. The results showed that prolonged estrogen deprivation and re-stimulation result in time-dependent epigenetic changes across diverse genomic regions and changes in gene expression associated with specific biological pathways (Figure 3). Remarkably, many of the observed changes upon estrogen deprivation were also detected in breast cancer cells that developed resistance in response to anti-estrogen therapy (Sklias et al., 2021). Finally, the study revealed a selective reversibility and persistence of epigenetic and gene transcription changes observed after estrogen deprivation and re-stimulation, suggesting a potential mechanism underlying the roots of endocrine resistance that develops in response to anti-estrogen therapy (Figure 3) (Sklias et al., 2021).

Molecular Mechanisms and Biomarkers Group (MMB)

The overarching objective of the Molecular Mechanisms and Biomarkers Group (MMB) is to improve the knowledge base for mechanistic molecular studies of modifiable cancer causes and for relevant cancer prevention measures. Innovative experimental approaches assist in the discovery of molecular cancer markers (Melki et al., 2020). MMB conducts molecular cancer epidemiological studies (Karabegović et al., 2021; the MODARC study on the role of dietary acrylamide in renal carcinogenesis; the EVAMOVAIRE2 study) and participates in IARC's carcinogen evaluation (Samet et al., 2020) and cancer classification efforts (Cree et al., 2021a). During the biennium, MMB performed integrative toxicogenomic analyses of selected candidate carcinogens and their roles in oncogenesis (Claeys et al., 2020). MMB also collaborated with the IARC Monographs on systematic cancer hazard assessments (Barupal et al., 2021).

Evamovaire2: mutational signatures of asbestos exposure in ovarian tumours

Epidemiological studies of geographical variations in ovarian cancer incidence have suggested a causal role for environmental factors, prompting the IARC Monographs to classify asbestos fibres as an ovarian carcinogen in 2009. MMB explored the link between asbestos exposure and ovarian cancer histological subtypes by integrating epidemiological data, exposure assessment, and whole-genome sequencing to determine the potentially carcinogenic effects of exposure to asbestos. Among 254 patients with ovarian cancer in the study, 13.4% had been exposed to asbestos occupationally and 16.5% had possibly been exposed indirectly, via a close relative. The direct exposure prevalence appeared to be higher than in the general population.

MMB conducted whole-genome sequencing of tumour–normal tissue pairs of 25 cases with established exposure mode, probability, and levels. Several exposure-specific mutational signatures were observed, all of an endogenous nature, alongside a signature of BRCA1/2 deficiency and lower rates of the *TP53* gene mutations associated with tumours of unexposed patients (Figure 4). Chrysotile asbestos treatment of cell model systems induced prominent, dose-dependent cytotoxicity and genome-wide mutagenesis indicative of oxidative DNA damage (Figure 4). The EVAMOVAIRE2 study has provided new insights into environmental and occupational exposure to asbestos as an important risk factor for ovarian carcinogenesis.

Genomic DNA damage induced by tobacco-specific nitrosamines

Epidemiological studies have linked tobacco use to numerous cancer types, including cancer of the lung, oral cavity, pharynx, larynx, oesophagus, pancreas, urinary bladder, and liver. The tobacco-specific nitrosamines (TSNAs) 4-methylnitrosamino-1-(3-pyridyl)-1-butanone (NNK) and *N′*-nitrosonornicotine (NNN) are recognized human carcinogens (IARC Group 1). However, the complex composition of tobacco smoke and a lack of molecular exposure markers mask the precise roles of TSNAs in human oncogenesis. NNK and NNN might contribute to the mutagenic effects of tobacco smoke, but the mutational signatures of TSNAs have not yet been described.

Figure 4. Mechanisms of asbestos-associated ovarian carcinogenesis investigated in 25 patients with epithelial ovarian cancer, using whole-genome sequencing of DNA derived from the formalin-fixed, paraffin-embedded (FFPE) tumour specimens. (a) In the included exposed patients (*n* = 17), enrichments of mutational signatures were observed, indicating increased cell proliferation (SBS1, SBS5), fingerprints of APOBEC-driven mutagenesis (SBS2, SBS13), higher rates of DNA replication errors (ID1, ID2), and ovarian-specific signature ID16. (b) Mutational signature SBS3 and TP53 mutations were enriched in the unexposed patients compared with the exposed patients. (c) Acute and chronic effects of chrysotile asbestos treatment on mutagenesis in cultured cells manifested through elevated mutational signature SBS18 (red arrows) formed by oxidated deoxyguanosines (8-oxo-2′-deoxyguanosine, 8-oxo-dG), consistent with increased exposure-related oxidative DNA damage. The top panel shows a background signature SBS17, and the bar graph shows the increase in the SBS18 versus SBS17 ratio after treatment with chrysotile. © IARC.
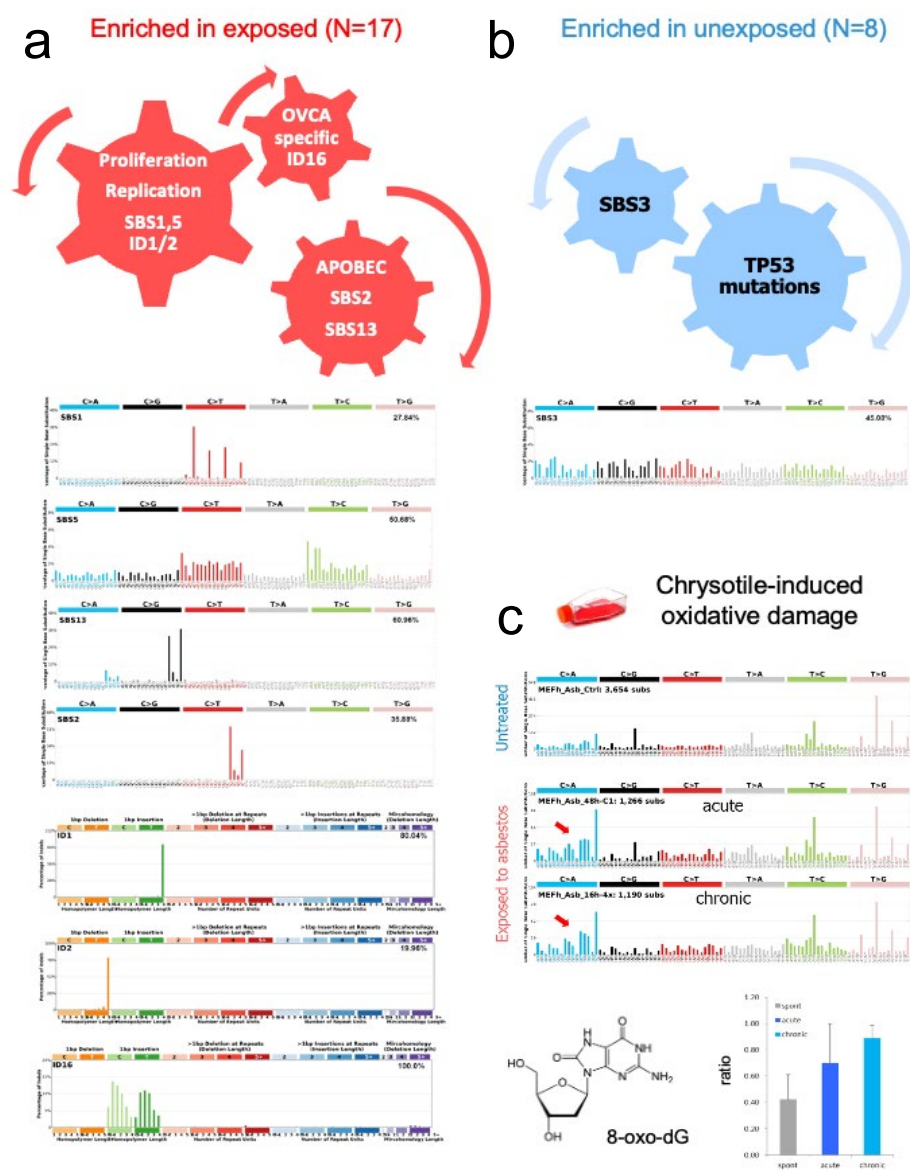
MMB characterized such mutational signatures induced by TSNAs in a human lung cell line and in a rat bioassay. DNA adduct analysis revealed major damage on thymidine (O2-POBdT) and guanine (7-POBG) residues (Figure 5). Genome-scale sequencing of TSNA cell clones and of rat tumours yielded highly similar mutational signatures (Figure 5), indicating the convergent effects of the two related nitrosamine compounds. The hallmark T > N mutations enriched on the untranscribed strand are consistent with the thymidine damage via O2-POBdT adduct formation. The newly identified signatures provide a valuable molecular marker for follow-up in silico studies of the mutagenic effect of TSNA exposure in thousands of human cancer genomes, to ultimately address the contribution of TSNAs to the mutation spectra of tobacco-related cancers.

Figure 5. (a) Levels of pyridoxobutyl DNA adducts in the A549 lung cell line exposed to 25 μM or 50 μM 4-[(acetoxymethyl) nitrosamino]-1-(3-pyridyl)-1-butanone (NNKOAc) and in rat oesophageal tumour tissue from animals treated with 4 ppm or 8 ppm *N'*-nitrosonornicotine (NNN) in the drinking-water (*n* = 3). The DNA adducts analysed are shown on the left. O6-POBdG was not measured in 4 ppm NNN-treated rat samples. DNA was isolated and analysed by liquid chromatography–tandem mass spectrometry (LC-MS/MS). (b) Mutational signature analysis in cells and animal tumours, showing the 192-channel mutational signatures extracted by non-negative matrix factorization from the NNKOAc-exposed A549 lung cell line (top panel) and from the NNN-induced rat oesophageal tumours. © 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.

The functional studies of ICB during the 2020–2021 biennium were focused on the characterization of the biological properties of oncoproteins from several human viruses, in particular cutaneous beta human papillomavirus (HPV) types (Gupta et al., 2020a; Minoni et al., 2020; Romero-Medina et al., 2020; Magnotti et al., 2021). With regard to epidemiological studies, ICB developed a highly sensitive diagnostic assay for a large number of infectious agents, with the final aim of (i) evaluating the contribution of infections to human carcinogenesis; and (ii) identifying novel algorithms for early

diagnosis of human cancers driven by infections (Amorrortu et al., 2020, 2021; Galati et al., 2020a, 2021; Tagliabue et al., 2020; Rollison et al., 2021; Simoens et al., 2021).

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 HPV vaccine in LMICs and to characterize the role of mucosal high-risk (HR) HPV infection in the etiology of head and neck cancer.

With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, INF became part of the newly created Early Detection, Prevention, and Infections Branch.

GASTRIC CANCER PREVENTION IN THE REPUBLIC OF KOREA: THE HELPER STUDY

Helicobacter pylori is the most important infectious cause of cancer worldwide. In 2013, IARC and the National Cancer Center of Korea launched the HELPER study, a multicentre double-blind randomized controlled trial in the Republic of Korea, to assess the effect of *H. pylori* eradication in gastric cancer prevention. HELPER has recruited about 12 000 middle-aged participants from the general population, including 5269 *H. pylori*-positive participants, who were subsequently randomized to eradication with bismuth quadruple therapy or placebo. Biennial endoscopic follow-up is continuing within the Korean National Cancer Screening Programme, and an interim analysis is planned for 2026.

HELPER Investigators' Workshop, Seoul, Republic of Korea. © IARC.

This trial is expected to determine to what extent *H. pylori* eradication reduces the risk of gastric cancer in the general population, while also providing important data on how to optimize the allocation of the resources devoted to gastric cancer control in the Republic of Korea. Globally, the study will have major public health implications by providing leads for gastric cancer prevention in populations with elevated rates of gastric cancer, particularly in Asian countries.

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. They are subdivided into genera and species in the HPV phylogenetic tree according to the DNA genome sequence. A subgroup 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. Using in vitro and in vivo experimental models, studies by ICB and other groups have highlighted the transforming properties of E6 and E7 from several cutaneous beta HPV types. In a recent study, ICB characterized a novel mechanism of virus-mediated p53 inactivation. Beta HPV38 E6 and E7 promote accumulation of a wild-type p53 form in human keratinocytes, promoting cellular proliferation. Inactivation of p53 by different means strongly decreases the proliferation of HPV38 E6 and E7 human keratinocytes. This p53 form is phosphorylated at S392 by the double-stranded RNA-dependent protein kinase PKR, which is highly activated by HPV38. PKR-mediated S392 p53 phosphorylation promotes the formation of a p53–DNMT1 complex, which inhibits expression of integrin alpha 1 (ITGA1), a repressor of epidermal growth factor receptor (EGFR) signalling (Romero-Medina et al., 2020) (Figure 1). These findings reveal the existence of a specific wild-type p53 form that displays pro-proliferation properties and are in agreement with a model in which beta HPV E6 and E7 proteins and ultraviolet (UV) radiation intimately cooperate in promoting skin carcinogenesis (Figure 2). A recent study by ICB showed that UV irradiation per se increases the beta HPV positivity in the skin, most likely because of its inhibitory activity on the immune system. In turn, by targeting key cellular pathways, beta HPV types act as facilitators of HPV UV-induced DNA mutations. However, after the accumulation of DNA mutations and the development of skin lesions, the expression of the HPV38 E6 and E7 genes is dispensable for the maintenance of the malignant phenotype of skin cancer cells (Lambert et al., 2020a).

In agreement with this working model, a prospective study showed that baseline beta HPV detection significantly predicted the development of cutaneous squamous cell carcinoma (Rollison et al., 2021).

Figure 1. HPV38 alters wild-type p53 activity to promote cell proliferation via the downregulation of integrin alpha 1 (ITGA1) expression. EGFR, epidermal growth factor receptor. © IARC.
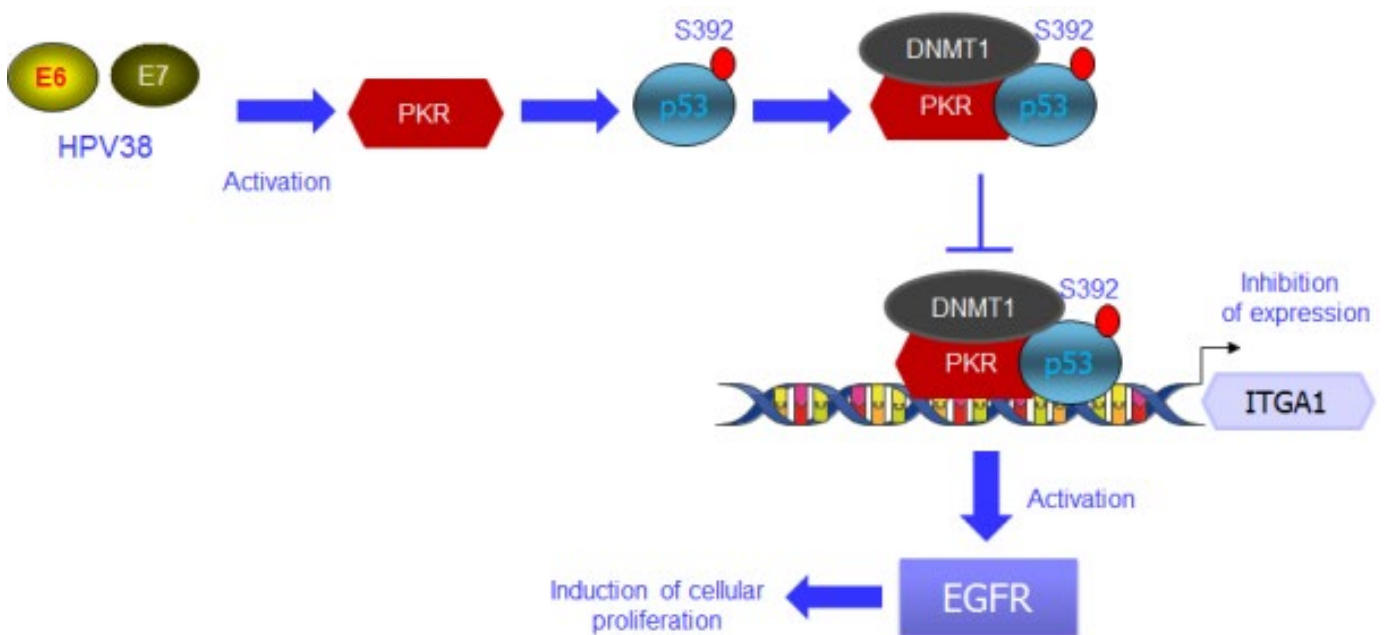
Figure 2. Model for cooperation between some beta human papillomavirus (HPV) types and ultraviolet (UV) radiation in promoting cutaneous squamous cell carcinoma (cSCC). Under physiological conditions, UV irradiation of the skin induces DNA mutations in keratinocytes and immunosuppression. The UV-induced damage results in (i) cell-cycle arrest and repair of DNA mutations or (ii) apoptosis if the DNA damage is unrepairable. Beta HPV early proteins, E6 and E7, can alter the cellular response to UV-induced stress, maintaining alive DNA-damaged cells that have a high risk of evolving into cancer cells. After accumulation of mutations in oncogenic driver genes (e.g. cellular tumour suppressor genes or oncogenes), the expression of the viral genes becomes dispensable. Reproduced from Lambert et al. (2020a). Copyright © 2020, The Authors, under exclusive licence to Springer Nature Limited.
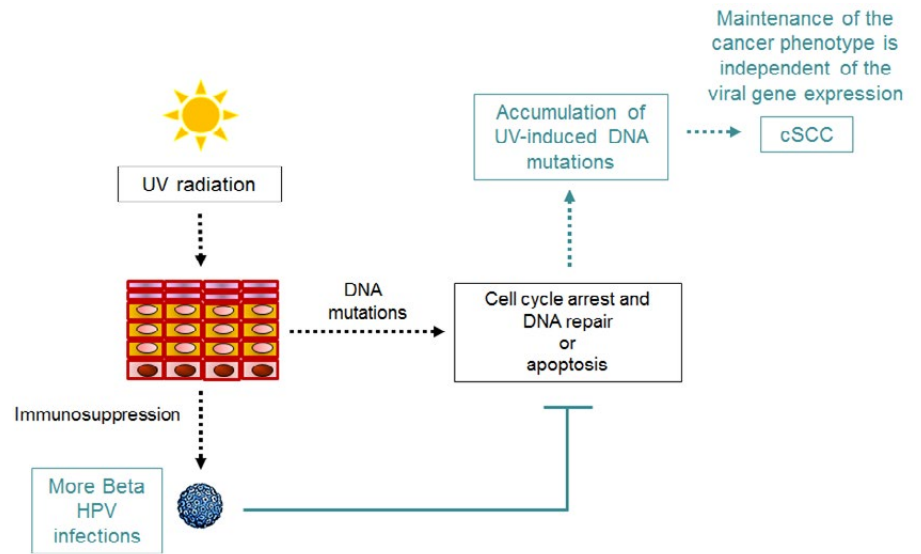
INFECTIONS AND CANCER EPIDEMIOLOGY GROUP (ICE)

## GLOBAL BURDEN OF CANCER ATTRIBUTABLE TO INFECTIOUS AGENTS

Given the amenability of infections to prevention, estimates of infection-attributable cancer burden are key public health indicators. ICE updated estimates of infection-attributable cancer burden at the country, regional, and global level with the most pertinent exposure assessment tools and the latest global cancer incidence data for 11 infectious carcinogens (viruses, bacteria, and parasites) (de Martel et al., 2020) (Figure 3). This work estimated that in 2018, 2.2 million infection-attributable cancer cases were diagnosed worldwide, corresponding to an age-standardized incidence rate (ASIR) of 25.0 cases per 100 000 person-years. Primary causes were *H. pylori* (810 000 cases; ASIR, 8.7), HPV (690 000 cases; ASIR, 8.0), hepatitis B virus (360 000 cases; ASIR, 4.1), and hepatitis C virus (160 000 cases; ASIR, 1.7). The infection-attri-butable ASIR was highest in eastern Asia (37.9) and sub-Saharan Africa (33.1) and lowest in northern Europe (13.6) and western Asia (13.8) (de Martel et al., 2020) (Figure 3). China accounted for one third of global cancer cases attri-butable to infection, driven by the high ASIR of *H. pylori* (15.6) and hepatitis B virus (11.7) infections. HPV-attributable cancer incidence showed the strongest relationship with income level, from ASIR of 6.9 in high-income countries to ASIR of 16.1 in low-income countries. Follow-up analyses focused on the global burden of cervical cancer attributable to HIV infec-tion (Stelzle et al., 2021) and on the HPV-related cancer burden in China (Duan et al., 2020). These findings are important to raise awareness for the control of oncogenic infections, particularly in an era where global cancer prevention is seen within the context of noncommuni-cable diseases.

ANAL CANCER EPIDEMIOLOGY AND PREVENTION

Understanding the burden and natural history of HPV-related anal squamous cell carcinoma (ASCC) is needed to raise awareness and inform prevention initiatives. Globally every year, an estimated 29 000 people, predominantly women, are diagnosed with ASCC (de Martel et al., 2020). An ASCC risk scale was developed, based on a meta-analysis of anal cancer incidence, to help prioritize high-risk groups for anal cancer prevention programmes, most notably people living with HIV, men who have sex with men, women diagnosed with HPV-related gynaecological precancerous lesions or cancer, and recipients of solid organ transplants (Clifford et al., 2021) (Figure 4). A collaborative re-analysis of individual-level data of almost 30 000 men from 64 studies comprehensively described the age-specific epidemiology of anal HPV infection and high-grade

Figure 3. Global burden of cancer attributable to infections in 2018: 2.2 million cases (13% of all cancers). HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus. Reproduced from de Martel et al. (2020). © 2019 International Agency for Research on Cancer; licensee Elsevier.
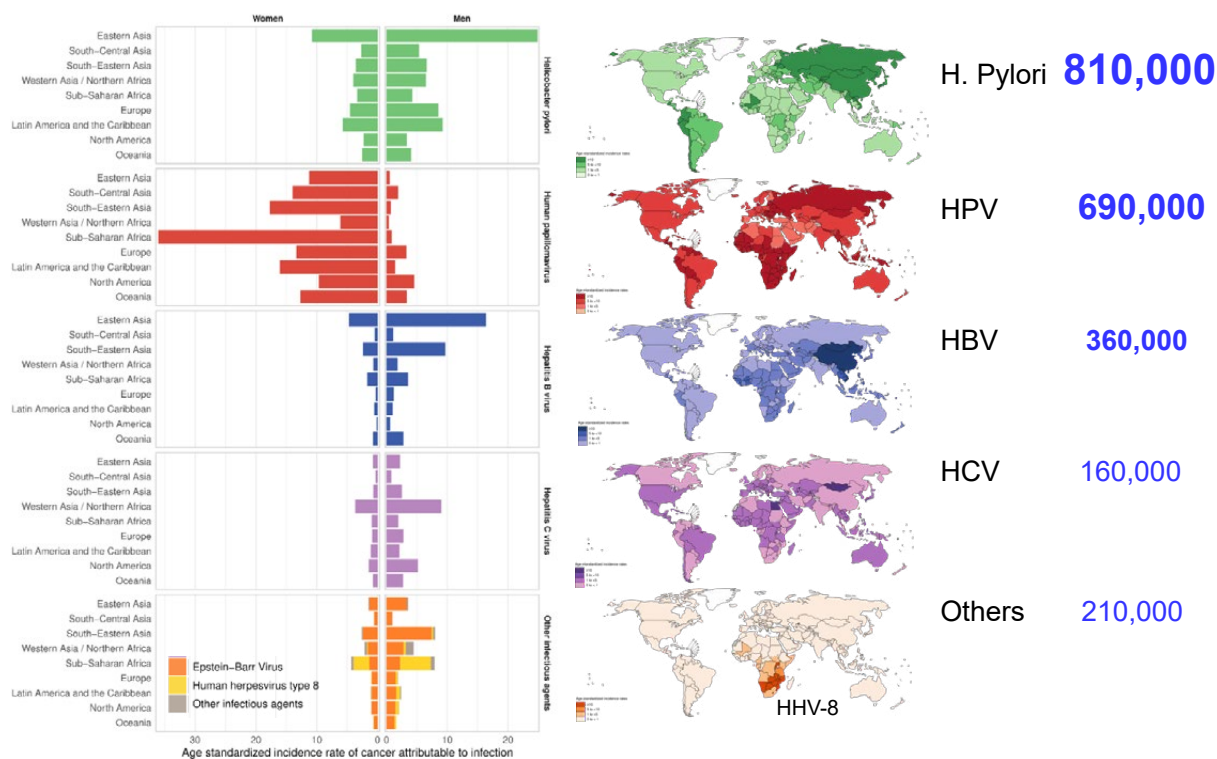
Figure 4. Anal cancer risk scale, showing estimates for people living with HIV, men who have sex with men (MSM), women diagnosed with HPV-related gynaecological precancerous lesions or cancer for different age groups, and solid organ transplant recipients (SOTR) for different periods since transplant; yrs, years; yst, years since transplant. Reproduced from Clifford et al. (2021). © 2020 International Agency for Research on Cancer (IARC/WHO); licensed by John Wiley & Sons Ltd on behalf of Union for International Cancer Control.
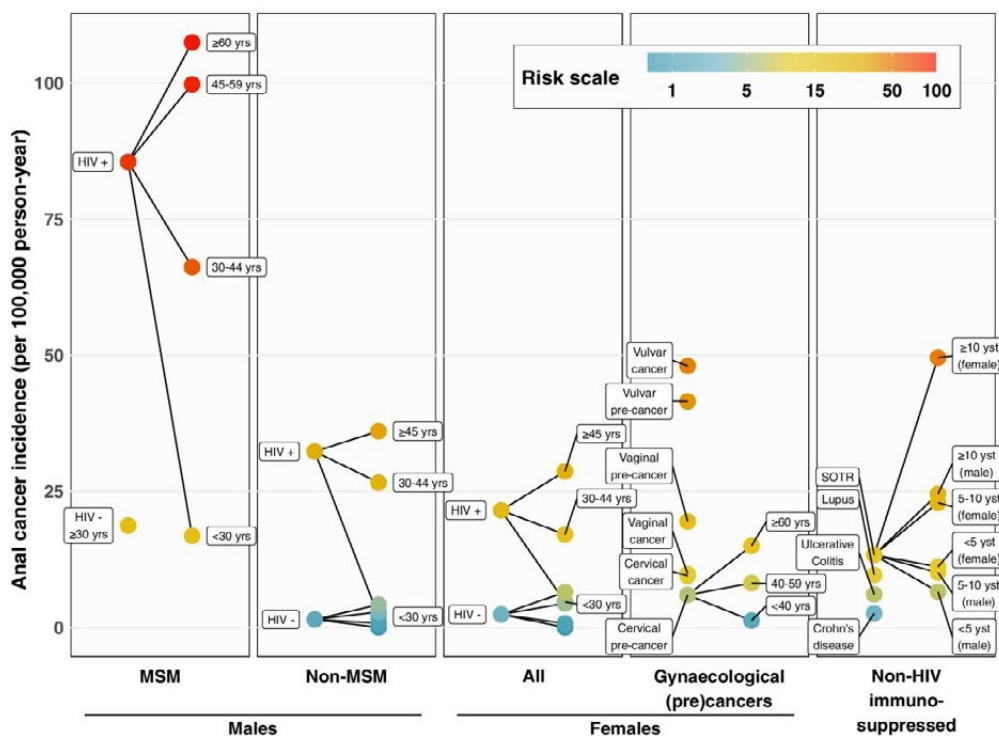
precancerous lesions according to the main known determinants of male ASCC risk, namely HIV status and sexuality (Wei et al., 2021a). Another meta-analysis focused on describing anal HPV, anal lesions, and cancer in recipients of solid organ transplants (Albuquerque et al., 2020). Clinical studies also continue to provide information about natural history in these high-risk groups, including anal HPV prevalence in HIV-positive women in China, the utility of HPV16 E6 antibodies to stratify people living with HIV for risk of anal cancer in the Swiss HIV Cohort Study (Combes et al., 2020), and a longitudinal study of anal HPV16 and HPV18 incidence and clearance in the APACHES study of 500 HIV-positive men who have sex with men in France (Alberts et al., 2020a).

HPV vaccination impact in LMICs: public health decision modelling

Effective prophylactic vaccines against HR HPV types have shown high safety and efficacy, and vaccination programmes are cost-effective in high-income countries. However, the introduction of HPV vaccination in LMICs remains challenging and requires the long-lasting commitment of local public health authorities. To support HPV vaccination in LMICs, ICE is conducting field studies to monitor the local impact of HPV vaccination and is developing predictive algorithms to project, at a global scale, the expected reduction in cervical cancer incidence as a result of vaccination. In Rwanda and Bhutan, ICE has demonstrated HPV vaccination effectiveness through urine-based HPV prevalence surveys in schools (Baussano et al., 2021) and cytology-based surveys in

Figure 5. Type- and age-specific HPV prevalence in baseline and repeated surveys in Bhutan. Vaccine types are HPV6, HPV11, HPV16, and HPV18; non-vaccine types are 42 types detected by GP5+/6+, excluding the 4 vaccine types. Error bars represent 95% confidence intervals. From Baussano et al. (2020a). Copyright © 2020 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.
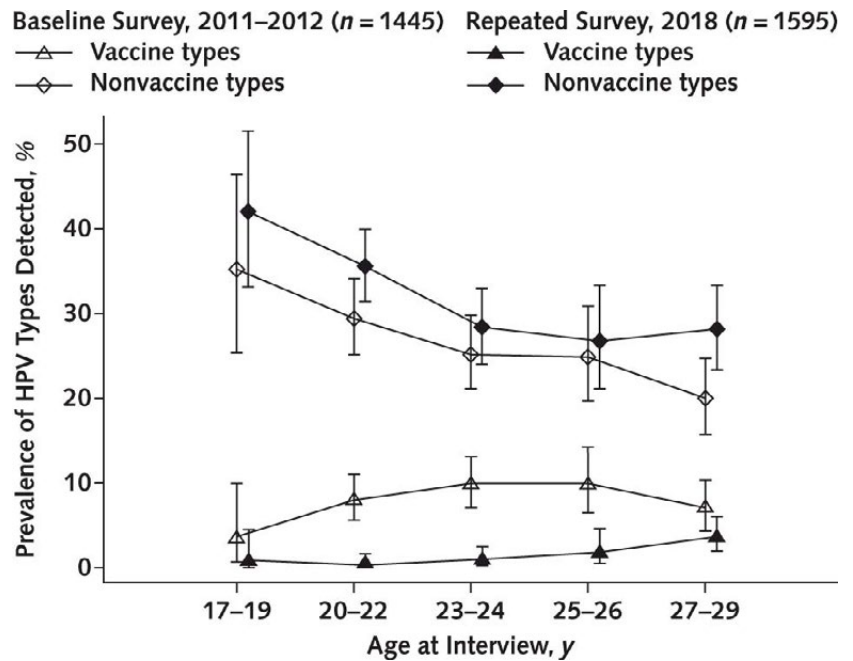
the general population (Baussano et al., 2020a) (Figure 5). In Rwanda, ICE has concomitantly assessed the nationwide cohort-specific coverage of vaccination (Sayinzoga et al., 2020). Meanwhile, to support the introduction of HPV vaccination at a global scale, ICE has estimated expected and preventable cervical cancers among women born between 2005 and 2014 in 185 countries (Bonjour et al., 2021; Piñeros et al., 2021b) (Table 1). To assess the local burden of cervical cancer in settings where

cancer registry data are not available, ICE has also developed a procedure to estimate cervical cancer incidence from population-based HPV prevalence data. Finally, in collaboration with colleagues from other leading institutions worldwide, ICE has assessed optimal HPV vaccination strategies to prevent cervical cancer in limited-resource settings (Drolet et al., 2021). These studies support the WHO global initiative to eliminate cervical cancer as a public health problem.

Table 1. Number of women at risk and number of expected and preventable cervical cancer cases among women born between 2005 and 2014 by continent, cervical cancer burden category, and 2018 Human Development Index

	Number of women at risk	Cases expected in the absence of vaccination		Cases preventable through vaccination	
		Number (95% UI)	Percentage of total cases in each category	Number (95% UI)	Percentage of total cases in each category
Continent					
Africa	165 606 523	5 648 149 (5 428 370–6 021 112)	48.7	4 162 782 (4 000 569–4 437 821)	73.7
Asia	344 978 554	4 486 109 (4 372 716–4 643 003)	38.7	3 480 802 (3 380 678–3 608 856)	77.6
Europe	38 508 937	416 241 (410 384–423 343)	3.6	332 124 (327 352–337 944)	79.8
Latin America	52 222 051	863 532 (835 639–919 393)	7.4	605 918 (586 145–644 957)	70.2
North America	22 124 133	140 961 (137 550–144 461)	1.2	111 009 (107 869–114 330)	78.8
Oceania	3 061 127	42 855 (39 073–47 384)	0.4	35 485 (32 318–39 271)	82.8
Cervical cancer burden[a]					
Very high	292 719 493	5 949 749 (5 745 857–6 186 696)	51.3	4 568 726 (4 405 526–4 755 927)	76.8
High	136 428 165	2 808 840 (2 671 891–3 045 844)	24.2	2 062 358 (1 961 833–2 236 491)	73.4
Medium	77 561 473	1 697 817 (1 597 925–1 890 372)	14.6	1 231 586 (1 158 349–1 372 443)	72.5
Low	106 942 955	1 027 948 (992 516–1 118 556)	8.9	778 124 (752 326–844 285)	75.7
Very low	12 849 239	113 492 (109 602–120 963)	1.0	87 326 (84 360–93 058)	76.9
Human Development Index[b]					
Low–middle	352 464 260	8 025 880 (7 794 459–8 447 380)	69.2	6 117 421 (5 939 136–6 430 904)	76.2
High	186 108 791	2 775 193 (2 720 782–2 837 271)	23.9	1 994 697 (1 954 640–2 039 514)	71.9
Very high	87 928 274	796 774 (786 593–810 166)	6.9	616 002 (607 835–626 440)	77.3
Total	626 501 325	11 597 847 (11 366 107–12 027 739)	100.0	8 728 120 (8 549 700–9 049 217)	75.3

UI, uncertainty interval.

[a] Individual countries were sorted according to the expected number of cervical cancer cases, then grouped into the following categories: very high burden (8 countries accounting for up to 50% of all cases worldwide), high burden (17 countries accounting for the next 25% of all cases), medium burden (25 countries accounting for the next 15%), low burden (68 countries accounting for the next 9%), and very low burden (67 countries accounting for the remaining 1%).

[b] Low–middle, < 0.70; high, 0.70–0.79; very high, ≥ 0.80.

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The main programme of work of the Section of Environment and Radiation (ENV) encompasses environmental, occupational, and radiation-related cancer, and lifestyle and cancer etiology and prognosis in low- and middle-income countries (LMICs), as well as the implementation of cancer prevention research. With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, ENV was renamed as the Environment and Lifestyle Epidemiology Branch, to better capture its broad scope of activities.

ENV focuses its endeavours on four main areas: (i) research in settings where levels of exposure to putative or established carcinogens in the environment, in the workplace, or related to people's lifestyles are high, and research is thus warranted; (ii) studies of common cancer types and of specific environmental, occupational, or lifestyle exposures that occur in underresearched settings; (iii) studies evaluating the role of broader social and biological factors throughout the course of the disease and its prognosis; and (iv) catalysing all new knowledge on lifestyle, environmental, occupational, and radiation-related risk

factors, and on screening and vaccination with the respective collaborators, into recommendations at the individual and population level. The objectives of ENV are achieved through the conduct of collaborative international epidemiological studies, including coordination of international consortia or through the initiation of focused individual and multicountry analytical epidemiological studies. In selecting programmes of research, an effort is made to ensure that the involvement of the Agency serves a specific and substantial function, by facilitating international collaboration, by overcoming political barriers, by

initiating new studies through assisting local collaborators with IARC's unique expertise in and beyond ENV and increasing 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 (WHO).

With a strong focus on environmental (including occupational and radiation-related) and lifestyle risk factors, ENV fills a major research gap to further identify factors and to understand the cancer burden attributed to these factors. ENV has steered its research focus to LMICs in particular, a direction that is consistent with the Agency's international remit and is warranted because in these settings, levels of environmental pollution are often higher and protection measures are often less developed. Another focus of ENV is to identify and investigate previously unstudied lifestyle habits and exposures unique to LMICs and other settings that may affect carcinogenesis. Capacity-building, as well as establishing research platforms, is another mission of IARC to which ENV contributes extensively. ENV also plays a key role in the translation of research findings into applied cancer prevention by, for example, informing the respective international and national authorities on worker protection, especially against radiation. Most directly, ENV is conducting cancer prevention research through the World Code Against Cancer initiative, which is developing sets of regional recommendations on primary and secondary prevention of cancer, and by chairing the newly established Cancer Prevention Europe platform, which had an influential role in shaping Europe's Beating Cancer Plan.

Manus sordidae, mens pura (dirty hands, but a clean mind)

At the heart of the cancer studies carried out by ENV is the conduct of fieldwork in underresearched areas of the world, in particular in low-income countries that have a scarcity of available data but unique and never-studied exposures (many not yet even identified as candidates) and combinations of exposures, higher exposures in workplaces and in the environment, and less protection of workers, communities, and environments compared with high-income countries. High-quality studies in these settings can be initiated only if the collaboration between the local and international scientists is respectful and is driven by shared scientific curiosity and open-mindedness and addresses questions, exposures, and exposure circumstances relevant to the local setting. This requires not only a mutual understanding of each group's expertise and how it contributes to the joint success of the project but also an appreciation of how epidemiological methods from
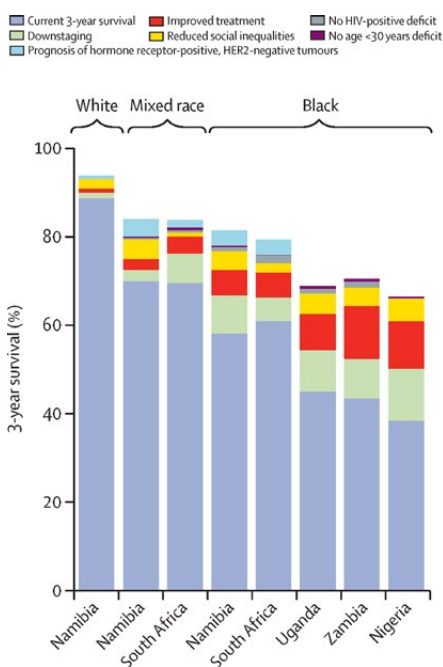
A scene from ESCCAPE fieldwork, illustrating the challenge of percentage ethanol estimation in local distillations. This is an artisanal *kachasu* (maize-based) distillation setup in Malawi. The ethanol content of this unregulated spirit varies according to the distillation process and between distillers, and differs between the regular and *mutu* (strong) *kachasu*. Although the first research implicating the role of *kachasu* in the incidence of oesophageal cancer was published in 1969, evidence of its contribution to the oesophageal cancer burden in East Africa is only now beginning to emerge. © IARC.

textbooks are put into practice and, for the international scientists, an appreciation of the local context, culture, and environment. The setting up of protocols, including methods of study conduct and interpretation of results, is full of pitfalls and barriers. However, more than 50 years of experience has shown IARC that such barriers can be minimized by regular and frequent mutual visits and joint explorations, which no virtual platform in the world can replace. With such a focus on hands-on studies, ENV is closely following Geoffrey Rose's motto of *manus sordidae, mens pura* ("dirty hands, but a clean mind"; https://www.bmj.com/content/bmj/2/6143/1006.full.pdf). The continuing COVID-19 pandemic has had a large impact on such activities. ENV pledges to make all efforts to enable fieldwork research that is informative and scientifically sound, and not diluted and misleading.

The ABC-DO study

The African Breast Cancer – Disparities in Outcomes (ABC-DO) study is an ENV-initiated programme of work aimed at addressing multiple dimensions of a major cause of cancer death in women in sub-Saharan Africa: low breast cancer survival. This common cancer type in women has a very good prognosis in high-income settings; therefore, improving survival should be a priority in cancer control plans in all LMICs. To examine the major barriers to improving breast cancer survival, ENV set up a five-country breast cancer cohort (https://abc-do.iarc.who.int), which continues to follow up 2200 women who were newly diagnosed with breast cancer during 2014–2017. Mobile-health (mHealth) real-time data collection and follow-up protocols were uniquely adopted in this study, ensuring few losses to follow-up (Foerster et al., 2020a). Recent findings showed that breast cancer survival is alarmingly low in Black African women (Figure 1). At 3 years after diagnosis, survival was 90% in White Namibian women, 58% in Black Namibian and Black South African women, 46% in Ugandan and Zambian women, and 36% in Nigerian women (McCormack et al., 2020). The largest contributors to low survival were late stage at diagnosis and a lack of access to surgery and systemic therapy, which particularly affected women in lower socioeconomic groups. In contrast, the relatively high proportions of young-onset breast cancer (age < 30 years at diagnosis), HIV-positive women, and more aggressive tumour subtypes made only a small contribution to low overall survival (McCormack et al., 2020).

The drivers of late stage at diagnosis have also been identified and include extensive delays between presentation at a first-line health provider and diagnosis (Foerster et al., 2021), as well as the geospatial element driving later stage at diagnosis in women living farther away from diagnostic centres (Togawa et al., 2021a). ABC-DO has also, for the first time, revealed the extent of the inter-generational effect of such high patient mortality rates by quantifying the number of maternal orphans associated with each breast cancer death (Galukande et al., 2021). The ABC-DO cohort continues to be followed up, and current research is studying the impact of additional morbidities (hypertension, HIV, and obesity) on survival (Ayeni et al., 2021). The comprehensive multidimensional insights gained through ABC-DO are helping to show the impact of breast cancer deaths and to shed light on the most effective pathways to improving survival, as part of WHO's 2021 launch of the Global Breast Cancer Initiative.

Figure 1. Three-year overall survival (%) of patients with breast cancer in sub-Saharan Africa. Observed survival (blue) and predicted survival if the following improvements had been made, by site and race: downstaging to improved distributions of earlier stage at diagnosis (green), improved treatment so that all women receive surgery and systemic therapy (red), reduction in survival deficits attributed to social inequalities (orange), and elimination of survival deficits attributed to increased mortality in HIV-positive women (dark grey), being young (< 30 years) (purple), and not having estrogen receptor (ER)-positive or progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative tumour subtypes (light blue). Reproduced from McCormack et al. (2020), Copyright Elsevier (2020).

Codes Against Cancer

The European Code Against Cancer was launched in 1986, and IARC was mandated to lead the development of its fourth edition. The IARC methodology to develop the cancer prevention recommendations has been refined and expanded to include information on successful interventions, as described in a roadmap laid out within the European Union (EU) Innovative Partnership for Action Against Cancer (iPAAC); this roadmap now forms the basis for the development of the fifth edition within Europe's Beating Cancer Plan (Espina et al., 2021). The need for better dissemination across Europe was identified from surveys showing that too few Europeans are well informed on how to reduce their risk of cancer (Ritchie et al., 2021). The strengthening of primary, secondary, and tertiary cancer prevention has also been achieved through the newly established Cancer Prevention Europe network, chaired by ENV, and its role in shaping the EU Cancer Mission and Europe's Beating Cancer Plan (Berns et al., 2020).

Inspired by the European Code Against Cancer, IARC called for this model to be extended to other world regions to achieve a World Code Against Cancer. In 2021, this process has begun with the preparation of the first Latin American and Caribbean Code Against Cancer, in collaboration with the Pan American Health Organization and several regional partners. In parallel, the use of more modern technologies (mHealth) to spread knowledge on cancer prevention through mobile phone messages has been explored in this region through dissemination research. The importance of, and barriers to, cancer prevention were discussed in a Special Issue of the journal *Molecular Oncology*, coordinated by guest editors in ENV (Schüz and Espina, 2021).

Recent research findings

Whether and to what extent the increasing use of pesticides contributes to the global cancer burden remains a major environmental health concern, and ENV is involved in several activities to study cancer risk in relation to pesticide

use. A study of the incidence of cancer in farmers and agricultural workers, compared with the general population, in eight countries within the AGRICOH consortium (https://agricoh.iarc.fr/) has illustrated that these occupational groups generally have reduced incidence rates, in particular for cancer types associated with unhealthy lifestyle factors such as smoking or physical inactivity (Togawa et al., 2021b); increased incidence rates were found only for skin melanoma and multiple myeloma in women, and for prostate cancer. These findings confirm the challenges of studying a factor such as exposure to pesticides in an otherwise relatively healthy population. In other pesticide-related research, there was little evidence that the exposure of parents to pesticides increases the subsequent risk of testicular cancer in their male offspring, perhaps with the exception of fungicides (Danjou et al., 2021), as seen in a large-scale case–control study in France. A systematic review confirmed concerns that the exposure of parents to pesticides increases the risk of leukaemia in their offspring (Karalexi et al., 2021).

Lung cancer is the most common occupationally related cancer type. An analysis by the ENV-coordinated SYNERGY consortium of 16 case–control studies of lung cancer confirmed that working as a painter, which is among the jobs that require respective preventive measures, was associated with a 30% increase in the risk of lung cancer (Guha et al., 2021). Using the same data source for an advanced dose–response analysis showed the critical roles of diesel motor exhaust (Ge et al., 2020a) and respirable crystalline silica (Ge et al., 2020b) in causing occupationally related lung cancers. In a different occupational cancer study, ENV determined that four well-known lung carcinogens (asbestos, respirable crystalline silica, chromium VI, and nickel) also increase the risk of laryngeal cancer (Hall et al., 2020).

Another large employment sector worldwide is the petroleum industry; a systematic review by ENV highlighted the limited scientific knowledge on cancer risks because of the lack of systematic epidemiological studies, both on a global scale (Onyije et al., 2021) and within major oil-producing countries such as the Islamic

Figure 2. Although tattoos are common, public awareness of the possible related health hazards and risks is low. In addition to the possibility of skin irritation, the potential threat from subcutaneous exposure to chemicals in the tattoo ink, which have proven to be carcinogenic by dermal or respiratory uptake, remains widely neglected. Lymphatic accumulation of such toxins could pose an unknown risk of immune-related cancers, particularly the group of non-Hodgkin lymphomas. © IARC.

Republic of Iran (Hosseini et al., 2021). In further occupational studies, valuable insights for worker protection are expected to be gained from the large-scale historical cohort study of almost 36 000 miners and millers exposed to chrysotile (asbestos) in the Russian Federation, working in the world's largest active chrysotile mine and enrichment factory; fieldwork was completed in late 2019 (Schüz et al., 2020a), and reports on measures to ensure high data quality have been published (Olsson et al., 2020; Schüz et al., 2020b). Finally, many substances used in the traditional art of tattooing, a practice that has increased substantially in popularity, are established occupational carcinogens. Therefore, an increased risk of some cancer types, in particular lymphomas, is not implausible (Figure 2), and ENV has just started the first prospective investigations with collaborators in France and Germany (Foerster et al., 2020b).

Another example of a collaborative focused research programme where fieldwork studies were needed is the case of oesophageal cancer in East

Africa and southern Africa. Through the Oesophageal Squamous Cell Carcinoma African Prevention Research (ESCCAPE) study, ENV and a network of African institutions (Figure 3) completed case–control studies in Kenya, Malawi, and the United Republic of Tanzania in 2021. The findings so far indicate the presence of multiple risk factors, notably the considerable role of tobacco use and alcohol consumption in men and of consumption of hot beverages in both sexes. Poor oral health and hygiene are also implicated, and studies of the pathways driving these associations, such as constituents of the oral microbiome, are under way. The ESCCAPE study also includes investigations of the impact of geophagia, the intentional consumption of non-food items (typically soil, a very common practice during pregnancy, potentially causing irritation to the mucosa), an example of a never-studied factor. This habit was not found to increase risk of oesophageal squamous cell cancer (Narh et al., 2021).

Protection from radiation at low doses still needs to be optimized, and data from the aftermath of nuclear accidents remain the most informative source. Therefore, ENV researchers observed with concern a lack of funding for previously developed research strategies related to the Chernobyl nuclear accident, which should have been implemented with urgency, given that the affected populations are ageing and the possibility of their participation in studies is decreasing (Ostroumova et al., 2020). Recent IARC-led research on Chernobyl showed no statistically significantly increased risk of breast cancer in association with district-averaged accumulated breast radiation dose after adjustment for age, time, and urbanicity in female populations of the most radioactively contaminated areas of Belarus (1978–2010) and Ukraine (1990–2010) (Zupunski et al., 2021) (Figure 4), but detailed analytical studies on breast cancer are warranted. The gold mine tailings in South Africa are also of concern, because of their contamination with uranium; a study of hair samples confirmed elevated levels in residents of various neighbourhoods, highlighting the need for studies of possible adverse health effects in humans.

Figure 3. Meeting of the Oesophageal Squamous Cell Carcinoma African Prevention Research (ESCCAPE) study team of collaborators from IARC, Kenya (Moi University, Eldoret), Malawi (College of Medicine, Blantyre), the United Kingdom (University of Liverpool), and the United Republic of Tanzania (Kilimanjaro Clinical Research Institute/Kilimanjaro Christian Medical Centre, Moshi), held in Blantyre, Malawi, in February 2020. © IARC.

Because mobile phone use is ubiquitous and technologies change regularly, the monitoring of potential adverse health effects associated with their use remains important. ENV has compared the incidence rates of the most common type of brain tumour – glioma – in men in the Nordic countries with projections of increased risk scenarios related to mobile phone use; the results suggest that if there is a risk, it is very small. These recent population findings are not compatible with the results of previous case–control studies, indicating that the effects have at least been overestimated. Continued monitoring is warranted, and ENV is participating in the multinational prospective cohort study of mobile phone users (Cohort Study of Mobile Phone Use and Health [COSMOS]; Tettamanti et al., 2020).

Childhood cancer remains a priority research area of ENV. In 2021, ENV coordinated a Special Issue of the journal *Cancer Epidemiology* describing the situation with respect to awareness, diagnosis, referral, and treatment of childhood cancer around the world, showing disparities between high- and low-income countries of greater magnitude than for most adult cancer types (Schüz and Roman, 2021). An assessment of the impact of the COVID-19 pandemic on paediatric oncology diagnoses in Germany in 2020 revealed a significantly higher incidence of all childhood cancers and in all childhood age ranges (Erdmann et al., 2021); the underlying reasons for this increase are not known, and close monitoring is warranted.

Figure 4. Breast cancer relative risk (RR) estimates by 5-year-lagged cumulative absorbed breast dose categories compared with the reference category (< 5.0 mGy; RR = 1.00) adjusted for attained age and urban or rural status, and stratified by 5-year intervals in (a) Belarus and (b) Ukraine. Reproduced with permission from Zupunski et al. (2021), © John Wiley & Sons.
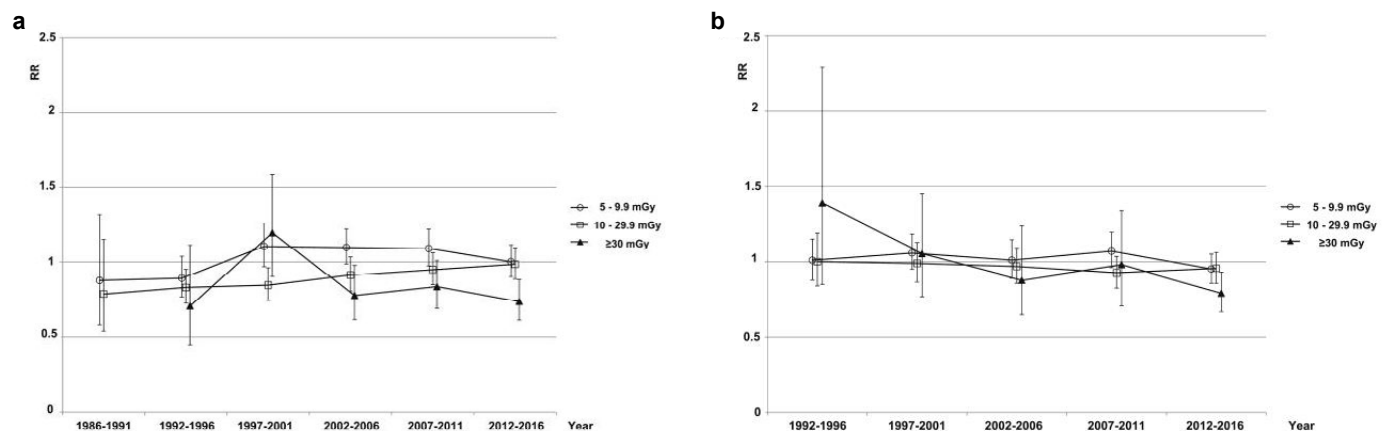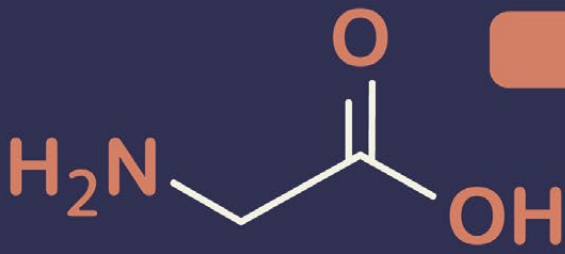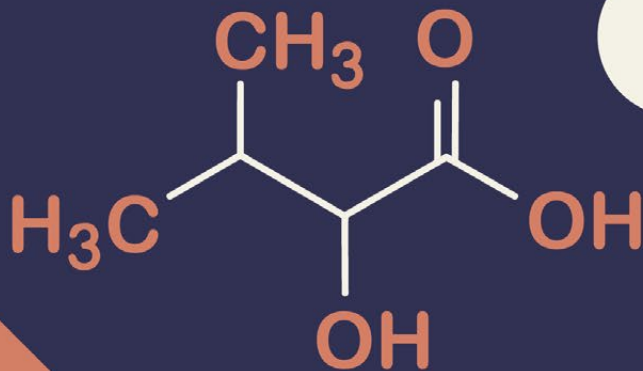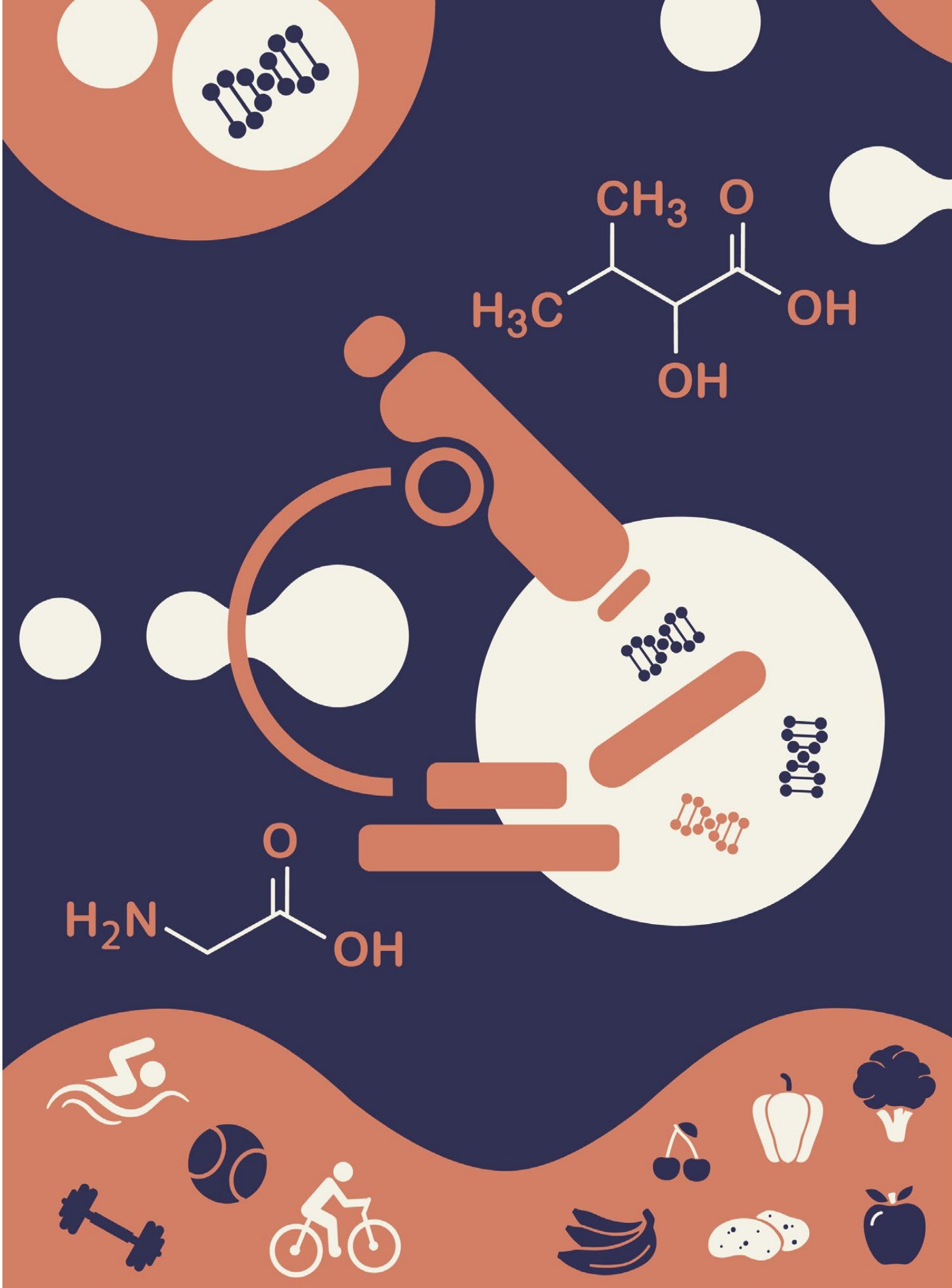
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The Section of Nutrition and Metabolism (NME) comprises three highly integrated groups: the Biomarkers Group (BMA), the Nutritional Epidemiology Group (NEP), and the Nutritional Methodology and Biostatistics Group (NMB). The Section combines large-scale 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 of 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 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.

With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, NME was renamed as the Nutrition and Metabolism Branch.

ESTABLISHING AN EPIDEMIOLOGICAL STUDY IN AFGHANISTAN: KANDAHAR OBESITY RESEARCH

As a result of rapid economic, social, and cultural changes, the prevalence of obesity in Afghanistan is increasing and dietary habits are shifting from the traditional pattern to a pattern more typical of industrialized countries, with concomitant increases in the incidence of noncommunicable diseases (NCDs).

A population-based cross-sectional study was designed in Kandahar city, and data were collected on sociodemographic characteristics, health history, anthropometry, physical activity, and diet. NME used stratified sampling to recruit an equal number of participants in the normal-weight, overweight, and obese categories. Body fat composition was analysed using bioelectric impedance analysis, and dried blood, urine, and stool samples were collected for biomarker analyses.

The study included 712 participants (411 men and 301 women); 92% lived in urban areas, 73% were married, 42% were aged 20–30 years, 51% were not formally educated, 79% were never-smokers, and 68% had central obesity. With respect to NCDs, 38% were hypertensive, 18% were diabetic, 30% had dyslipidaemia, 36% had fatty liver disease, and 50% were symptomatic for anxiety and/or depression.

This is the first study that will assess dietary patterns, lifestyle factors, and their association with obesity and metabolic health in Afghanistan. The data collected will be an invaluable resource for future studies on biomarkers or the microbiome, and could be used to train future public health scientists in Afghanistan.

Kandahar Obesity Research. © IARC.

Metabolomics reveals new biomarkers for intake of processed meat

Processed meat has been associated with a higher risk of colorectal cancer; however, identification of the etiologically relevant components of this heterogeneous food group remains challenging. The Biomarkers Group (BMA) applied an untargeted metabolomic approach to identify novel biomarkers of intake for processed meat products in a randomized cross-over dietary intervention and in 474 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Several pepper-derived alkaloids were positively associated with intake of sausage and processed meat and may be used as biomarkers to improve assessment of intake of processed meat in epidemiological studies (Figure 1) (Wedekind et al., 2021).

New data on biomarkers of exposure and their associations with disease risk collected in the Exposome-Explorer database

The Exposome-Explorer database (http://exposome-explorer.iarc.fr) provides detailed information on more than 1000 biomarkers of dietary and pollutant exposures as measured in various populations. New information on their associations with cancer risk in relevant epidemiological studies, derived from more than 300 scientific papers, has now been collated (Neveu et al., 2020).

Identification of biomarkers to explore novel etiological hypotheses in breast cancer

BMA applied targeted metabolomics to identify novel metabolites associated with breast cancer, breast density, and potential modifiable determinants.

In premenopausal Mexican women from the Mexican Teachers Cohort, sphingomyelin (SM) C16:1 and phosphatidylcholine (PC) ae C30:2 were inversely associated with percentage mammographic density and were positively associated with cholesterol and metabolic syndrome components (His et al., 2021a).

As part of the EPIC study, BMA observed novel associations between circulating concentrations of acetylcarnitine, arginine, asparagine, and PCs, and breast cancer. Correlates of these biomarkers were investigated (His et al., 2021b), and PCs were observed to be inversely associated with adiposity and positively associated with total and saturated fat intakes. PC ae C36:2 was inversely associated with alcohol consumption and positively associated with healthy lifestyle. Asparagine was inversely associated with adiposity. These findings suggest possible mechanisms for novel etiological hypotheses on breast cancer.

Obesity and endometrial cancer: disentangling underlying mechanisms

Obesity is a major risk factor for endometrial cancer, but the underlying pathways and their relative contribution are still unclear. In a study conducted as part of EPIC, pathways characterized by reduced adiponectin and increased inflammatory biomarkers, insulin, and estrogen explained about 70% of the association between endometrial cancer and obesity (Dashti et al., 2021).

Using metabolomics, BMA discovered alterations in concentrations of glycine, serine, SM C18:0, and free carnitine associated with endometrial cancer (Figure 2) (Dossus et al., 2021). BMA also identified a metabolic signature of obesity among more than 4000 EPIC participants that was more predictive of endometrial cancer risk than anthropometric measures (Kliemann et al., 2021).

Figure 1. Scaled relative intensities of pepper alkaloid metabolites in plasma samples associated with intake of several processed food products in a dietary intervention study (*n* = 12). Reproduced from Wedekind et al. (2021). © John Wiley & Sons.
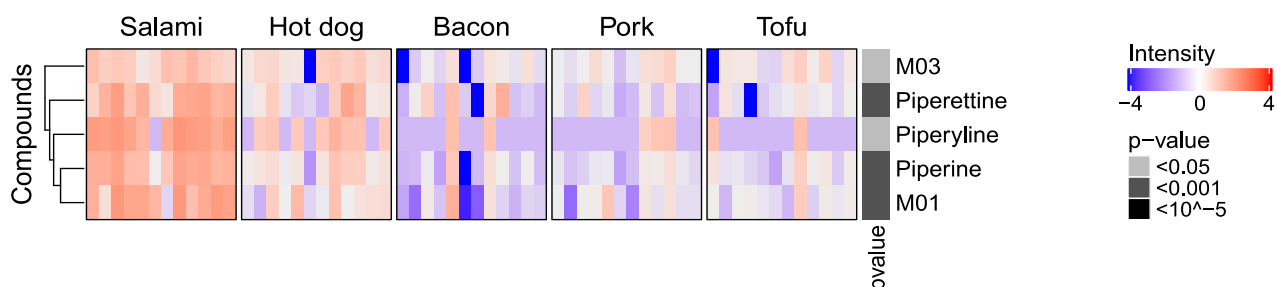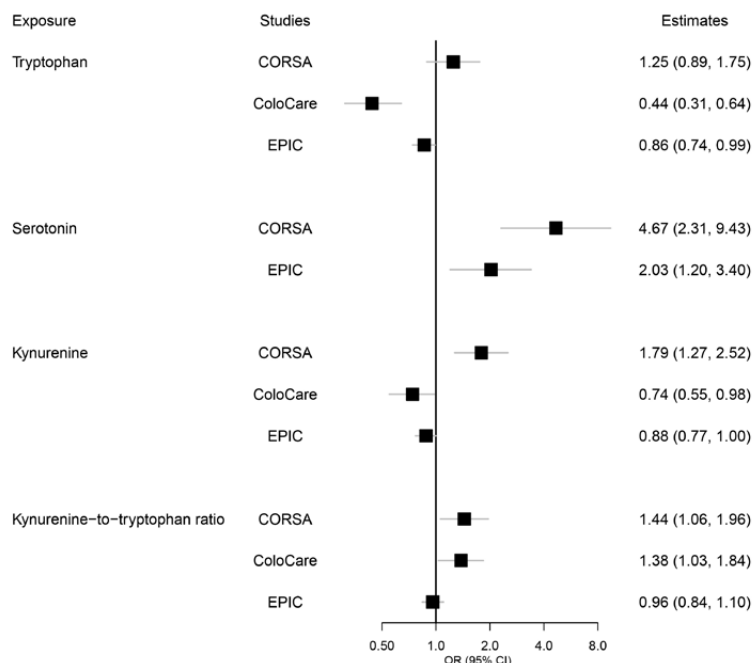
Dysregulation of tryptophan metabolism has been linked to the development of colorectal cancer, but few epidemiological studies have addressed this hypothesis. BMA studied associations between tryptophan metabolites and colon cancer risk in the ColoCare, Colorectal Cancer Study of Austria (CORSA), and EPIC cohorts (Papadimitriou et al., 2021). Tryptophan levels were inversely associated and serotonin levels positively associated with colon cancer risk (Figure 3). These results support earlier studies on the role of tryptophan metabolism in colon cancer and offer new insights into changes in the metabolic flux of tryptophan before and after diagnosis of colon cancer.

Figure 2. Odds ratios (ORs) and *P* values for the associations between metabolites and risk of endometrial cancer in models adjusted for body mass index (BMI). ORs are estimated per standard deviation (SD) increase in log-transformed metabolite concentrations, from logistic regression conditional on matching variables. The figure shows statistical significance based on *P* values (significant metabolites above the dotted line). SM, sphingomyelin. Reproduced from Dossus et al. (2021). © 2021, Published by Elsevier Inc.
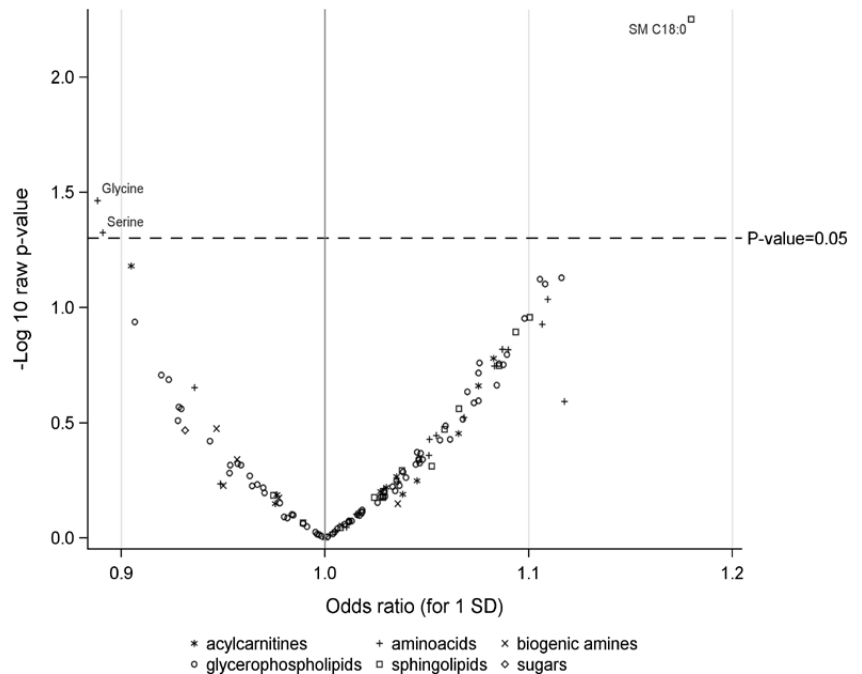
Figure 3. Associations of tryptophan, serotonin, kynurenine, and kynurenine-to-tryptophan ratio with colon cancer in the Colorectal Cancer Study of Austria (CORSA), ColoCare, and European Prospective Investigation into Cancer and Nutrition (EPIC) studies. The odds ratios (ORs) correspond to a 1 standard deviation difference in concentration levels of the biomarkers, except for serotonin where the comparison was made between detectable and undetectable concentration levels. CI, confidence interval. Reproduced with permission from Papadimitriou et al. (2021a), John Wiley & Sons.

Exposure	Studies		Estimates
Tryptophan	CORSA		1.25 (0.89, 1.75)
	ColoCare		0.44 (0.31, 0.64)
	EPIC		0.86 (0.74, 0.99)
Serotonin	CORSA		4.67 (2.31, 9.43)
	EPIC		2.03 (1.20, 3.40)
Kynurenine	CORSA		1.79 (1.27, 2.52)
	ColoCare		0.74 (0.55, 0.98)
	EPIC		0.88 (0.77, 1.00)
Kynurenine–to–tryptophan ratio	CORSA		1.44 (1.06, 1.96)
	ColoCare		1.38 (1.03, 1.84)
	EPIC		0.96 (0.84, 1.10)

Nutritional Epidemiology Group (NEP)

Insulin, insulin-like growth factors, and breast and colorectal cancers

Experimental and epidemiological evidence has implicated the insulin and insulin-like growth factor (IGF) axis in breast and colorectal cancer development, but causality of these relationships is uncertain. In observational and Mendelian randomization (MR) analyses, the Nutritional Epidemiology Group (NEP) investigated the role of circulating IGF-1 and fasting insulin in breast and colorectal cancer development. In the UK Biobank, higher IGF-1 concentrations were associated with greater breast (hazard ratio [HR] per 5 nmol/L, 1.11; 95% confidence interval [CI], 1.07–1.16) and colorectal cancer risk (HR per 1 standard deviation [SD], 1.11; 95% CI, 1.05–1.17). In MR analyses, genetically predicted IGF-1 concentrations were positively associated with breast (odds ratio [OR] per 5 nmol/L, 1.05; 95% CI, 1.01–1.10) and colorectal cancer risk (OR per 1 SD increment, 1.08; 95% CI, 1.03–1.12). Genetically predicted fasting insulin levels were positively associated with colorectal cancer risk (OR per 1 SD, 1.65; 95% CI, 1.15–2.36) (Murphy et al., 2021a). These results support probable causal relationships and suggest that targeting the insulin–IGF axis may be beneficial in preventing breast and colorectal tumorigenesis (Murphy et al., 2020a, 2020b).

Exploring the role of iron in colorectal cancer

Iron is hypothesized to play a role in colorectal tumorigenesis; however, epidemiological evidence is limited. NEP examined the association between dietary and circulating iron and colorectal cancer via genetically predicted circulating iron using MR in 58 221 cases of colorectal cancer and 67 694 controls, and dietary total, haem, and non-haem iron assessed using dietary questionnaires within the EPIC cohort (6162 cases of colorectal cancer, 450 101 non-cases). A positive association was observed for genetically predicted circulating iron and colon cancer risk (OR per SD, 1.08; 95% CI, 1.00–1.17; P value, 0.05) (Tsilidis et al., 2021). In the EPIC study, haem iron was positively associated with colorectal cancer in men (HR Q5 vs Q1, 1.13; 95% CI, 0.99–1.29) but not in women. These findings support a possible causal association between circulating iron and haem iron and the development of colorectal cancer.

Food processing and cancer risk and mortality

Global industrialization has increased the consumption of ultra-processed foods (UPFs) while reducing food biodiversity. Recent analyses by NEP as part of the EPIC cohort examined the associations between processed food consumption and cancer risk. Positive associations between UPFs and several cancer sites were found, and an inverse association was observed for minimally processed foods in relation to most of the cancer outcomes.

Evidence suggests that UPFs may increase cancer risk via their obesogenic properties and their poor nutritional value, as well as through exposure to potentially carcinogenic compounds such as certain food additives and neoformed processing contaminants. The increase in UPF consumption parallels a steady decrease in food biodiversity as a result of industrialization. The continuing studies of NEP have already demonstrated an increased risk of premature death and cancer risk with lower species diversity in the diet (Hanley-Cook et al., 2021).

Metabolic profiling and colorectal cancer

Risk of colorectal cancer can be lowered by adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines. NEP derived metabolic signatures of adherence to these guidelines and tested their associations with colorectal cancer risk as part of the EPIC cohort. Higher WCRF/AICR scores were characterized by metabolic signatures of increased odd-chain fatty acids, serine, glycine, and specific PCs. These signatures were more strongly inversely associated with colorectal cancer risk (OR, 0.62 per unit change; 95% CI, 0.50–0.78) than the WCRF/AICR score (OR, 0.93 per unit change; 95% CI, 0.86–1.00) overall. Measuring a specific panel of metabolites representative of a healthy or unhealthy lifestyle may identify strata of the population at higher risk of colorectal cancer.

BIOSTATISTICAL ACTIVITIES

The increasing availability of molecular data in large epidemiological studies requires the development and application of ad hoc statistical methodology. The Nutritional Methodology and Biostatistics Group (NMB) has implemented a new pipeline for the normalization and pooling of metabolomics data (Viallon et al., 2021). A new machine-learning method based on an extension of the lasso penalty was developed to analyse large-dimension data in (nested) case–control studies with several disease subtypes (Ballout et al., 2021). In line with recent developments in the field of causal inference, NMB applied modern causal mediation analysis to investigate the biological processes underlying the carcinogenic effect of obesity and alcohol (Assi et al., 2020; Dashti et al., 2021), and MR analysis was applied to investigate the causality of bilirubin on cancer occurrence (Seyed Khoei et al., 2020a, 2021).

LIFESTYLE AND RISK OF MULTIMORBIDITY

Improvements in longevity have increased the likelihood of an individual developing two or more diseases, referred to as multimorbidity. Cardiovascular diseases, type 2 diabetes, and cancer are the most common NCDs and represent major causes of morbidity, disability, and impaired quality of life. Limited evidence exists on how established risk factors for single NCDs are related to the clustering

Figure 4. Cumulative incidence functions (CIFs) describing the development of cancer, cardiovascular disease (CVD), and type 2 diabetes (T2D), and subsequent cancer–cardiometabolic multimorbidity (MM). Cancer refers to first malignant tumours at any site excluding non-melanoma skin cancer. CIFs are plotted for men (dotted) and women (continuous) aged 65 years for healthy lifestyle index (HLI) values of 15 (healthy, 85th percentile in green) and 5 (unhealthy, 4th percentile in red). HLI ranges from 0 to 20 units; higher scores indicate healthier lifestyles. Reproduced from Freisling et al. (2020a). © 2020, Freisling et al.
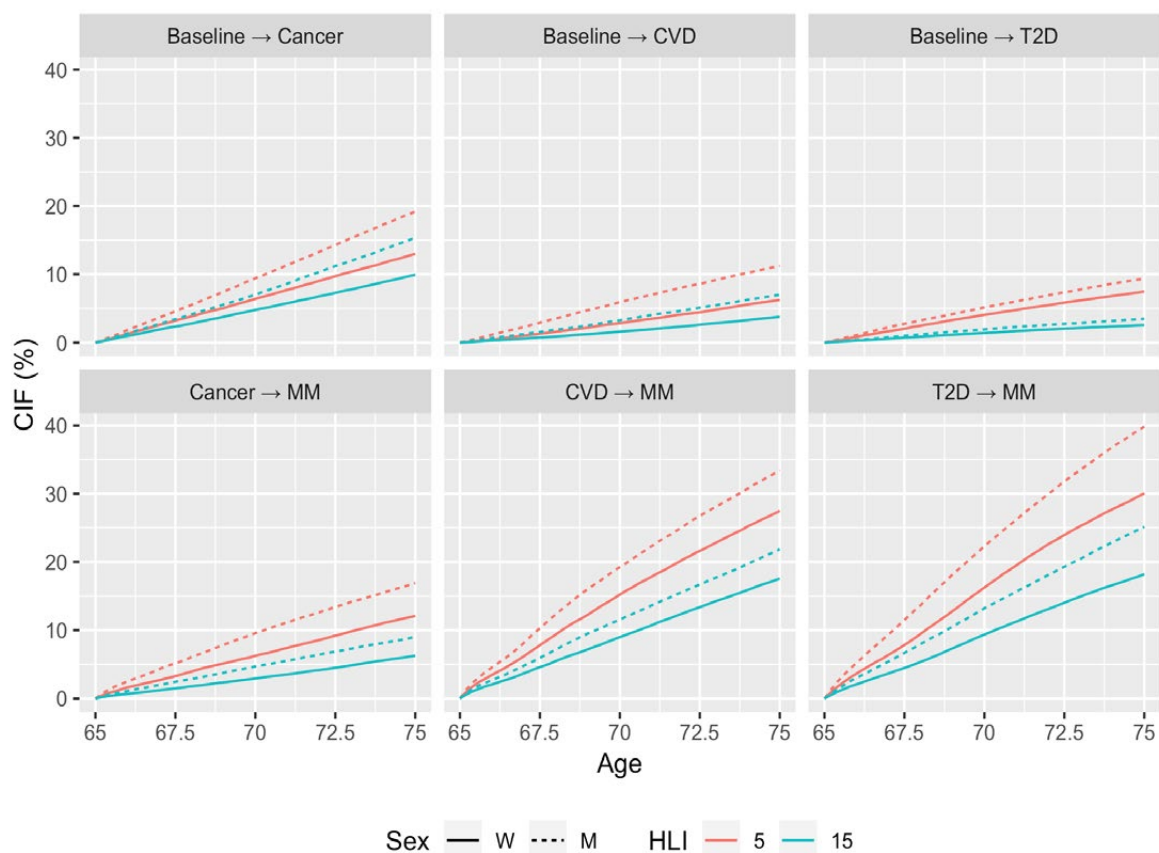
of NCDs within individuals. Within a large cohort of 300 000 participants from seven European countries, NMB showed that favourable lifestyle habits reduced the risk of incident multimorbidity from cancer and cardiometabolic diseases (Freisling et al., 2020a). In particular, NMB's absolute risk model assessed the burden of multimorbidity among participants who experienced a first disease, and quantified the preventive potential of healthy lifestyle habits with regard to multimorbidity of cancer and cardiometabolic diseases. For example, after diagnosis with type 2 diabetes, the 10-year absolute risks

of multimorbidity were 40% for men and 30% for women with an unhealthy lifestyle, and 25% for men and 18% for women with a healthy lifestyle (Figure 4) (Freisling et al., 2020a).

Alcohol and cancer

Modest associations between alcohol consumption and cancer, particularly for light and moderate intakes, may be missed as a result of measurement error in self-reported assessments. NMB identified 2-hydroxy-3-methylbutyric acid as a novel biomarker of alcohol consumption in the EPIC study and the Alpha-Tocopher-

ol, Beta-Carotene Cancer (ATBC) study (Loftfield et al., 2021). Higher levels of 2-hydroxy-3-methylbutyric acid were positively associated with risk of hepato-cellular carcinoma, pancreatic cancer, and liver disease mortality. These metabolites could help advance the study of alcohol and cancer risk in population-based studies.

In a pooled analysis of EPIC and Melbourne Cohort Collaborative Study (MCCS) data, a novel positive association between lifetime alcohol intake and risk of noncardia stomach cancer was identified (Jayasekara et al., 2021).

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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 to 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.

GEN 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. Germline genetic analysis usually comprises 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 comple-ment 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.

With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, GEN was renamed as the Genomic Epidemiology Branch, to better capture the broad range of scientific activities under way.

MUTOGRAPHS: BUILDING UP A LARGE CANCER BIOREPOSITORY ACROSS FIVE CONTINENTS

GEP, in collaboration with GCS and the Section of Environment and Radiation (ENV), the Laboratory Services and Biobank Group (LSB), and the Section of Support to Research (SSR), has devoted substantial resources to recruiting large series of cancer cases, comprising extensive questionnaire information and biological samples, as part of the Mutographs Grand Challenge project. Delays due to the COVID-19 pandemic in 2020 and 2021 had a major impact on recruitment and timelines. However, GEP has worked closely with all centres participating in the project, has adapted the recruitment and processing protocols to comply with COVID-19 restrictions, and continues to support the progress of the project locally.

Ontario Institute for Cancer Research, Toronto, Canada. Courtesy of Pancreatic Cancer Toronto, Canada.

Digestive Diseases Research Institute, Tehran, Islamic Republic of Iran. Courtesy of Digestive Diseases Research Institute, Tehran University of Medical Sciences, Islamic Republic of Iran.

Hospital Italiano de Buenos Aires, Argentina. Courtesy of Hospital Italiano de Buenos Aires, Argentina.

GENETIC EPIDEMIOLOGY GROUP (GEP)

During the 2020–2021 biennium, the Genetic Epidemiology Group (GEP) has continued research efforts on how genomics can be used to understand the causes of cancer, as well as how genomics can contribute to the early detection and outcome prediction of cancer (Ginsburg et al., 2021a). Some prominent examples of the work of the Group over the biennium are described here.

Table 1. Current progress on sample collection and processing by cancer type in the Mutographs project

Sample type	Samples and data at IARC	Samples shipped to Wellcome Sanger Institute	Whole-genome sequencing released	Target	Proportion of target achieved (%)
Oesophageal squamous cell carcinoma	1482	671	552	552	100
Renal cell carcinoma	1261	1141	594	1000	59
Colorectal cancer	1378	386	150	1000	15
Head and neck cancer	622	186	0	300	0
Pancreatic ductal adenocarcinoma	693	297	115	650	18
Oesophageal adenocarcinoma	704	262	110	650	17
Total	6140	2943	1521	3852	39

Figure 1. Average relative attributions of single-base substitution (SBS) COSMIC signatures are broadly similar between all countries. Signatures accounting for less than 5% on average (with the exception of SBS3 and SBS16) are grouped together into the "other" category. Reproduced with permission from Moody et al. (2021). © 2021, The Author, under exclusive licence to Springer Nature America, Inc.

IDENTIFYING NOVEL CAUSES OF MULTIPLE CANCER TYPES THROUGH ANALYSIS OF MUTATION SIGNATURES: THE MUTOGRAPHS STUDY

The Mutographs project aims to understand the causes of five different cancer types across five continents by generating mutational signature profiles. The initial recruitment of approximately 6000 cases has been completed, and 3000 cases have been successfully processed at IARC and sent to the Wellcome Sanger Institute for whole-genome sequencing (Table 1). GEP completed the first group of 1552 cancers sequenced in 2021, and genomic, exposure, and clinical data will be publicly available through the International Cancer Genome Consortium Accelerating Research in Genomic Oncology (ICGC ARGO) platform. The analysis of 552 cases of oesophageal cancer from eight countries with varying incidence rates showed the high prevalence of APOBEC signatures in all cases, as well as specific mutation signatures linked to opium consumption and alcohol consumption, as well as to homologous DNA repair deficiency (Figure 1) (Moody et al., 2021). Analysis of approximately 1000 kidney cancers is continuing, and preliminary results are shedding light on the contribution of environmental causes to the high risk of kidney cancer in central Europe. Most of the processing and sequencing efforts are now focused on cases of head and neck cancer, colorectal cancer, gastro-oesophageal adenocarcinoma, and pancreatic adenocarcinoma. Based on the same design and methodology as the Mutographs project, three additional side studies investigating specific geographical exposures of interest have been initiated. For example, GEP is studying the plausible sources of aristolochic acid exposure that could cause renal and urinary tract cancers in the Balkan region. The Group also aims to elucidate the role of opium consumption in the development of bladder cancer in the Kerman province of the Islamic Republic of Iran, and to

investigate the mutational profile differences in gallbladder cancer cases from regions of high and low incidence in India.

EVALUATING STRATEGIES TO IMPROVE EARLY DETECTION AND OUTCOME IN LUNG CANCER

The overall goal of GEP is to identify individuals at sufficiently high risk of developing lung cancer to justify screening and early detection. The initial approach of the Group was to develop and validate lung cancer risk prediction models using the vast information harmonized in the Lung Cancer Cohort Consortium (LC3), including lung cancer risk factors and outcomes from more than 20 cohorts around the world, representing more than 2.5 million individuals in 15 countries (Robbins et al., 2021). In addition, using the framework of the Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) study, GEP is actively investigating the potential of a wide range of biomarker types for lung cancer

risk prediction; initial studies indicate that circulating protein biomarkers have the most promising potential to improve the identification of individuals most likely to benefit from screening. The Group completed the initial discovery scan of 1200 proteins on 252 case–control pairs from two LC3 cohorts. This enabled the identification of the five most informative protein panels, which were assayed in 477 case–control pairs from four additional cohorts (Figure 2).

QUITTING SMOKING AFTER DIAGNOSIS OF LUNG CANCER IMPROVES SURVIVAL

The effect of smoking cessation in lung cancer survival was evaluated using information collected as part of the 15-year collaborative study with the N.N. Blokhin National Medical Research Centre of Oncology of the Russian Academy of Medical Sciences. GEP showed that smoking cessation after lung cancer diagnosis substantially improved overall and progression-free survival among current smokers with early-stage lung

cancer; similar effects were observed among mild to moderate smokers and heavy smokers, and among patients with earlier-stage and later-stage tumours (Figure 3) (Sheikh et al., 2021).

PROGRESS INVESTIGATING ETIOLOGICAL AND PROGNOSTIC FACTORS IN HEAD AND NECK CANCERS

Two main collaborative projects have showed important evidence of the role of human papillomavirus (HPV) infection in the development of oropharyngeal cancer. Recent evidence from the work in the HPV Cancer Cohort Consortium (HPVC3) has shown that HPV16 E6 is easily detectable in blood and is highly sensitive (> 90%) and specific (> 99%), and that seropositivity can occur decades before cancer is detectable. As part of the VOYAGER study, GEP conducted the largest genome-wide association study analysis with a focus on oropharyngeal cancer. After stratifying by HPV status, a protective effect was shown for one human leukocyte antigen

Figure 3. Association between quitting smoking after diagnosis of lung cancer and the probability of overall survival (left) and progression-free survival (right). © IARC.
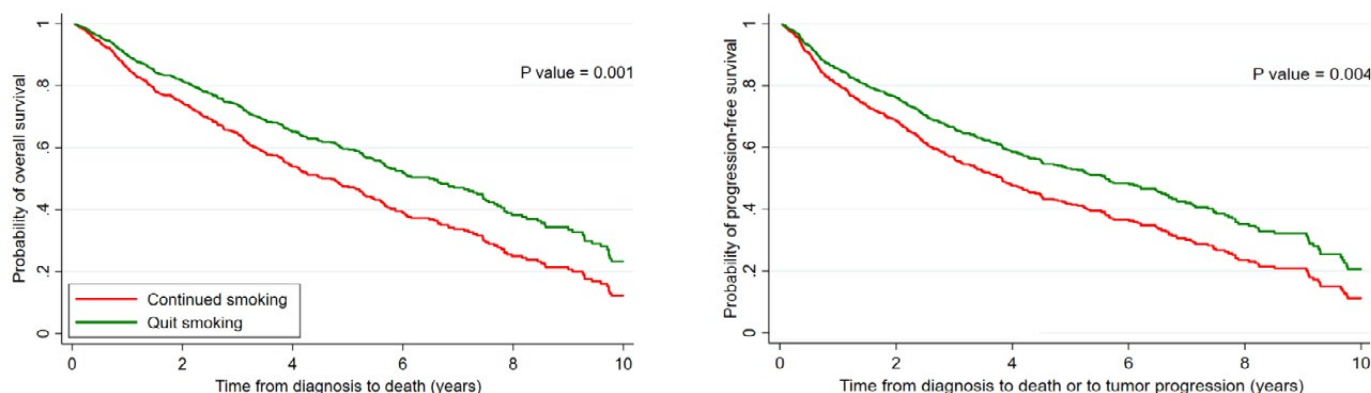
locus (rs4713462) against HPV-positive oropharyngeal cancer, which also correlated with low antibody levels against HPV16 E6 (Ferreiro-Iglesias et al., 2021). Furthermore, the first survival analysis in 1463 patients with head and neck cancer in South America after completion of a 3-year follow-up confirmed that survival was better for HPV-related than for HPV-unrelated oropharyngeal cancer, as well as the negative prognostic effect of advanced clinical stage and alcohol consumption (Abrahão et al., 2020).

GENETIC CANCER SUSCEPTIBILITY GROUP (GCS)

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

In the context of early biomarkers, GCS has explored highly recurrent telomerase reverse transcriptase (*TERT*) gene promoter mutations as biomarkers for the early detection of urothelial cancer, and developed assays for the detection of low-abundance *TERT* promoter mutations (Zvereva et al., 2020a). This assay was used in a nested case–control study within a longitudinal population-based prospective cohort of 50 000 individuals in the Islamic Republic of Iran, and demonstrated that *TERT* mutations could be detected in urine samples obtained up to 10 years before the primary diagnosis of bladder cancer, and were not detected in matched controls (100% specificity and 46.6% sensitivity) (Figure 4) (Hosen et al., 2020a). The study demonstrated the presence of these mutations in urine in asymptomatic individuals who later developed bladder cancer, highlighting the potential of urinary *TERT* promoter mutations to be used as a simple, inexpensive, and non-invasive early detection biomarker. These results received broad coverage by international media, including the United Nations News, France Info, the La Chaîne Info news channel, and the *Daily Mail* (in the United Kingdom), as well as science magazines and specific urology websites.

The Rare Cancers Genomics initiative aims at the molecular characterization of rare cancers (http://rarecancersgenomics.com/), including malignant pleural mesothelioma (MESOMICS) and lung neuroendocrine neoplasms (lungNENomics). In the MESOMICS project, GCS has contributed to the comprehensive molecular and pathological evaluation of transitional mesothelioma assisted by a deep learning approach (Galateau Salle et al., 2020) and provided an overview of molecular advances in the classification of pleural mesotheliomas (Fernandez-Cuesta et al., 2021). In the lungNENomics project, GCS generated

Figure 4. Association between *TERT* promoter mutation mutant allelic fractions (MAFs, %) and the time interval from urine collection to clinical diagnosis of bladder cancer. The MAFs of the mutations detected by the UroMuTERT assay (next-generation sequencing-based assay) in the 14 urine samples of the asymptomatic subjects from the Golestan Cohort Study are plotted against the time in years from urine collection to diagnosis of bladder cancer. Reproduced from Hosen et al. (2020a). © 2020 Published by Elsevier B.V.
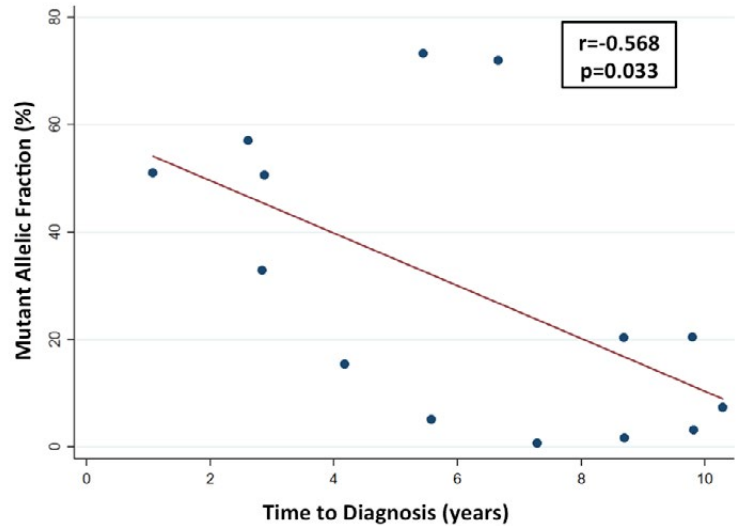
Figure 5. Schematic representation of the different classifications of malignant pleural mesothelioma and their key molecular features. The front face of the pyramid represents the current WHO classifications (top) and the different discrete (middle) and continuous (bottom) molecular classifications that have been proposed. For discrete molecular classifications, the proposed molecular clusters are reported. For Blum et al., a gradient between the epithelioid score (E-score) and the sarcomatoid score (S-score) is depicted. For Alcala et al., the association between the first dimension of the molecular classification and the WHO histological type is shown. The side face of the pyramid represents features and subtypes mentioned in each study that have not been reported to be significantly correlated with the histological types; for Alcala et al., the second molecular dimension is represented, which was shown to summarize features independent of the WHO classification. Colours represent the association between features and the different types: red, sarcomatoid or sarcomatoid-like profiles; orange, biphasic or biphasic-like profiles; green, epithelioid or epithelioid-like profiles; and grey, no proven association with the WHO classification. Reprinted by permission from Fernandez-Cuesta et al. (2021), © 2021.
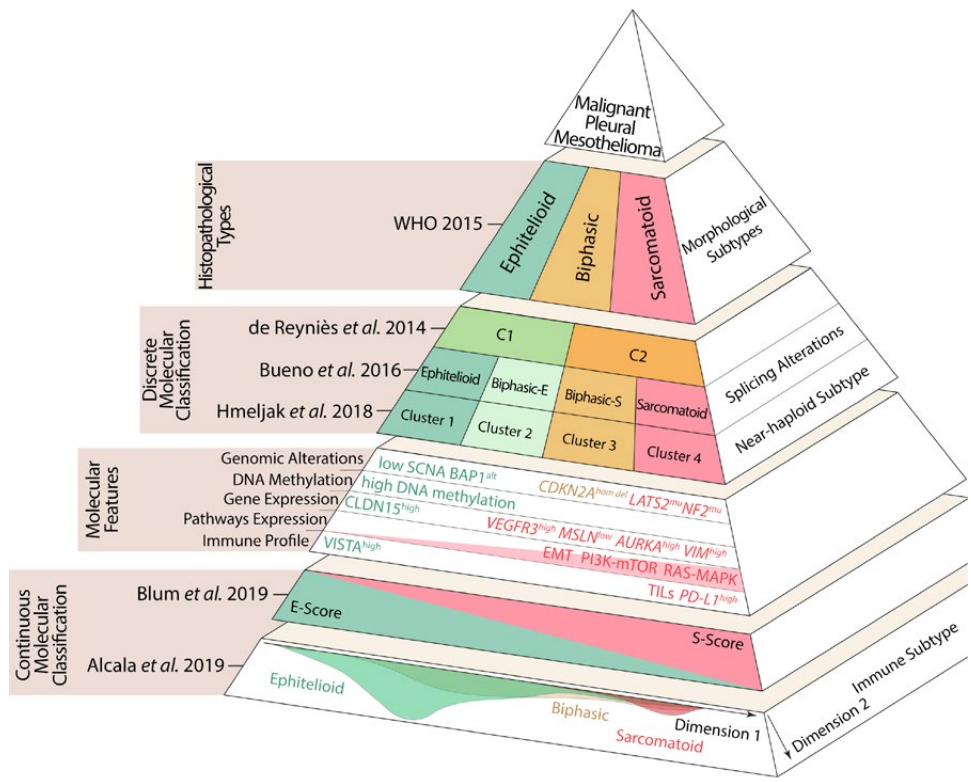
the first molecular map of lung neuroendocrine neoplasms (Gabriel et al., 2020), led (Foll and Fernandez-Cuesta, 2020) and contributed (Lantuejoul et al., 2020) to reviews in the field of lung neuroendocrine neoplasms, and contributed (Dr Fernandez-Cuesta) to the 2021 fifth edition of the WHO Classification of Tumours of the lung, pleura, thymus, and heart. The Rare Cancers Genomics initiative has a strong computational biology component, particularly for the analysis and integration of –omics data (including whole-genome and/or transcriptome sequencing and methylation arrays), interpretation of histopathological images with deep learning algorithms, and modelling of evolutionary processes associated with tumour progression. GCS actively shares these tools as open-source packages (https://github. com/IARCbioinfo) and maximizes their reuse potential by providing reproducible analyses and online training, ultimately building capacity for cancer genomics (Figure 5).

In the context of how germline variation influences cancer susceptibility, GCS has worked within the International Lung Cancer Consortium (ILCCO) to identify a lung cancer susceptibility variant in the DNA repair gene *ATM*. This variant is a missense variant in *ATM* and has an important genetic effect, with allele carriers having an up to 3–4-fold increase in the risk of lung cancer relative to non-carriers. It also appears to be most relevant to lung cancer in women and lung adenocarcinomas in never-smokers; although it is very rare in most parts of the world, it approaches frequencies of 3% in Ashkenazi Jewish populations (Ji et al., 2020a).

GCS leads the pathology workflow for the Mutographs of Cancers project, a continuing large-scale international study that aims to unveil the carcinogenic role of environmental exposures by analysing the mutational signatures through whole-genome sequencing (https://www.mutographs.org/). GCS also investigated the morphological features of 1000 non-tumoral renal tissues from patients with renal cell carcinoma, and found that the frequency of chronic renal parenchymal changes with the predominance of chronic interstitial nephritis pattern in patients with renal cell carcinoma varies by country; these changes are more frequent in Romania and Serbia (Table 2) (Abedi-Ardekani et al., 2021).

Table 2. Odds ratios and 95% confidence intervals (CIs) for association between country and observation of moderate to severe chronic renal parenchymal changes in non-neoplastic kidney tissues of patients with renal cell carcinoma

Recruiting country	Odds ratio (95% CI)			
	Unadjusted	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Russian Federation	Reference	Reference	Reference	Reference
United Kingdom	0.84 (0.25–2.76)	0.64 (0.19–2.16)	0.59 (0.17–2.01)	0.39 (0.10–1.49)
Czechia	1.79 (0.82–3.92)	1.34 (0.59–3.00)	1.54 (0.67–3.57)	1.28 (0.56–2.91)
Romania	3.40 (1.41–8.18)	3.12 (1.26–7.74)	3.16 (1.24–8.03)	2.67 (1.07–6.67)
Serbia	4.63 (1.33–16.08)	5.06 (1.39–18.44)	6.27 (1.40–28.02)	4.37 (1.20–15.96)
Romania and Serbia	3.62 (1.57–8.32)	3.42 (1.44–8.12)	3.53 (1.45–8.58)	2.96 (1.24–7.03)

[a] Adjusted for age, sex, and percentage of medulla.
[b] Adjusted for age, sex, percentage of medulla, stage, and tumour size.
[c] Adjusted for age, sex, diabetes, hypertension, and use of non-steroidal anti-inflammatory drugs (NSAIDs).
Source: Reproduced from Abedi-Ardekani et al. (2021). Copyright © 2021, Abedi-Ardekani et al.

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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). With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, EDP became part of the newly created Early Detection, Prevention, and Infections Branch.

One of the principles that continue to guide EDP's work is the search for simplified, affordable technology adaptable to 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 carries out implementation and health economics research. In addition, EDP develops educational materials and conducts training activities for cancer control. EDP has established extensive networks involving highly skilled clinicians, epidemiologists, and other

personnel. These networks facilitate the transfer of research technology to the local researchers and often their students, who participate actively in study design and conduct, and data analysis. An important part of the work of EDP is the dissemination of the scientific evidence base and the provision of technical assistance to governments and policy-makers in countries developing cancer control programmes.

The multicentre and multidisciplinary studies of EDP are conducted within two separate Groups: the Prevention and Implementation Group (PRI) and the Screening Group (SCR).

Training of Trainers in CELAC within CanScreen5

The objective of the Screening Group project "Reduction of inequalities in cancer screening: a case study in the Community of Latin American and Caribbean States (CELAC)" is to examine policies in CELAC aimed at reducing inequalities in effective participation of the eligible population in cancer screening. The project, implemented in collaboration with the Centre for Global Health Inequalities Research (CHAIN) in Norway (supported by the Research Council of Norway) and the Pan American Health Organization (PAHO), also aims to enhance the capacity of the cancer screening programme managers in CELAC to implement quality-assured screening programmes. This has become an integral part of the IARC project Cancer Screening in Five Continents (CanScreen5) (https://canscreen5.iarc.fr).

This Training of Trainers programme is a package of e-learning modules and live sessions. E-learning modules cover principles of cancer screening, planning and implementing screening programmes, and ensuring quality. Live sessions include keynote lectures and group discussions. Among other topics, lectures cover cancer control in the region, indicators in cervical cancer screening, social inequalities, and implementation science.

Countries contributing to the Cancer Screening in Five Continents (CanScreen5) initiative, with their stage in the process indicated. © IARC.

The first phase of Training of Trainers in CELAC has been carried out and involved 65 participants from 22 countries. After the training, participants reported that their knowledge had been increased by more than 50%, and this learning will be reinforced during face-to-face workshops. Using the CanScreen5 self-paced learning programme, participants will be able to train colleagues in their respective countries.

"Keep holding our hand" (quote from a Training of Trainers participant from Honduras). © IARC.
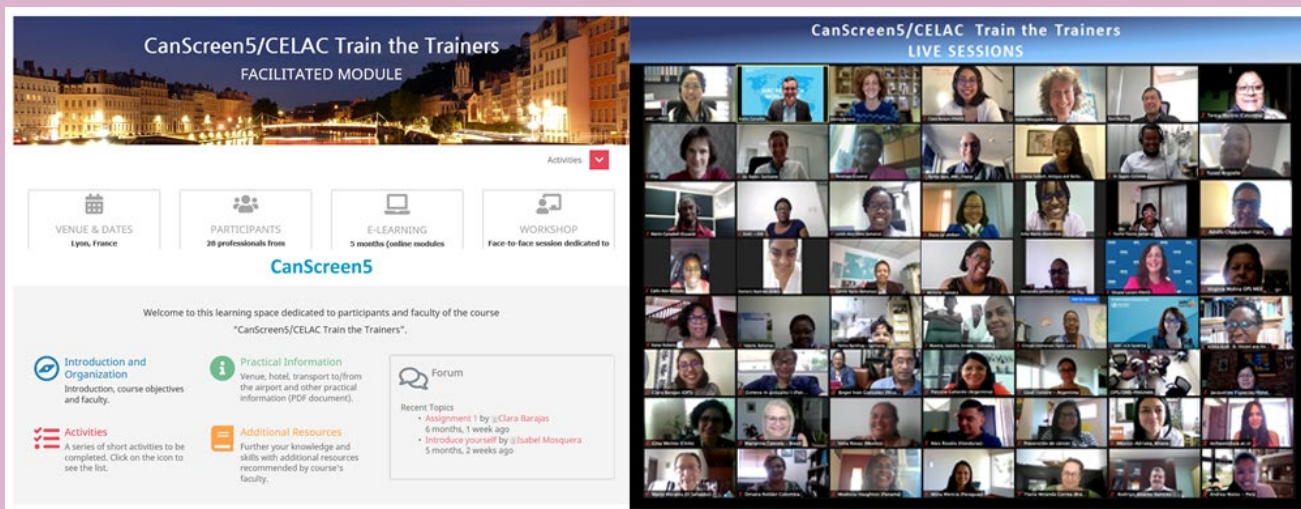
Prevention and Implementation Group (PRI)

HPV vaccine efficacy

In collaboration with the United States National Cancer Institute, the ESCUDDO randomized trial comparing one dose versus two doses of the bivalent and nonavalent human papillomavirus (HPV) vaccines among 20 000 adolescent girls (aged 12–16 years) is continuing in Costa Rica. Recruitment has been completed, and follow-up has been extended to 5 years to account for the possible impact of the COVID-19 pandemic, which may change exposure to HPV through changes in social interactions. In the Costa Rica HPV vaccine trial (CVT) study, the Prevention and Implementation Group (PRI) has demonstrated that one dose is still highly protective and immunogenic 11 years after vaccination (Kreimer et al., 2020a) and that three doses are protective against high-grade lesions during long-term follow-up (Porras et al., 2020).

Cervical screening in Latin America

Despite steady reductions in cervical cancer incidence and mortality in Latin America over the past decades, the incidence rates are still above the elimination threshold (age-standardized incidence rate of 4 cases per 100 000 women per year) (Figure 1) (Pilleron et al., 2020), highlighting the need for effective strategies to achieve the elimination goals.

The ASCUS-COL trial in Colombia investigated the efficacy to prevent precancerous cervical lesions of HPV testing compared with the usual care (immediate colposcopy and repeat Pap smear) in 2661 women with atypical squamous cells of undetermined significance (ASCUS) Pap results. HPV testing was found to reduce the burden of cervical lesions by 65% and colposcopy referral by 41% (Baena et al.,

2020). No differences in health-related quality of life were observed by HPV positivity status (Urrea Cosme et al., 2020). When collected samples were used, the performance of the recently developed S5-methylation test (United Kingdom) to triage HPV-positive women (with ASCUS Pap results) highlighted the potential role of S5-methylation in HPV-based cervical screening (Ramirez et al., 2021).

The ESTAMPA study investigates cervical cancer screening and triage techniques in women (aged 30–64 years) in nine countries in Latin America. HPV-positive women receive colposcopy, biopsy, and treatment and a second screen after 18 months as needed. The main outcome is advanced cancer precursors (Almonte et al., 2020). More than 42 000 women have been recruited, and a high adherence to the screening process has been reported; 95% of

Figure 1. Distribution of age-standardized incidence rates of cervical cancer per 100 000 women per year in 2018 by country and subregion, compared with the elimination threshold defined by WHO of 4 per 100 000 women per year. Reproduced with permission from Pilleron et al. (2020), © John Wiley and Sons.
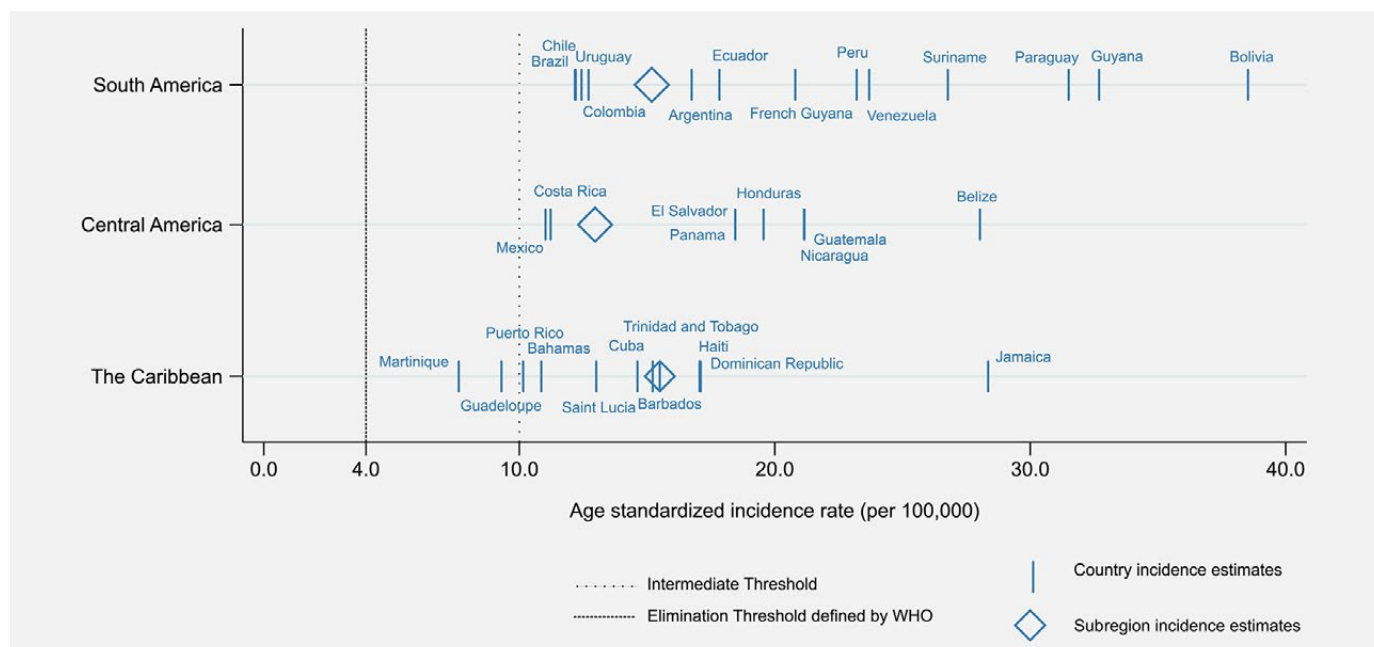
Figure 2. Progress of the ESTAMPA study as at July 2021. * Percentage computed after excluding 270 women who withdrew from the study. ** Percentage computed among women eligible to attend the 18-month visit (i.e. without cervical intraepithelial neoplasia grade 2 [CIN2] and in the study for at least 18 months). HPV, human papillomavirus. © IARC.
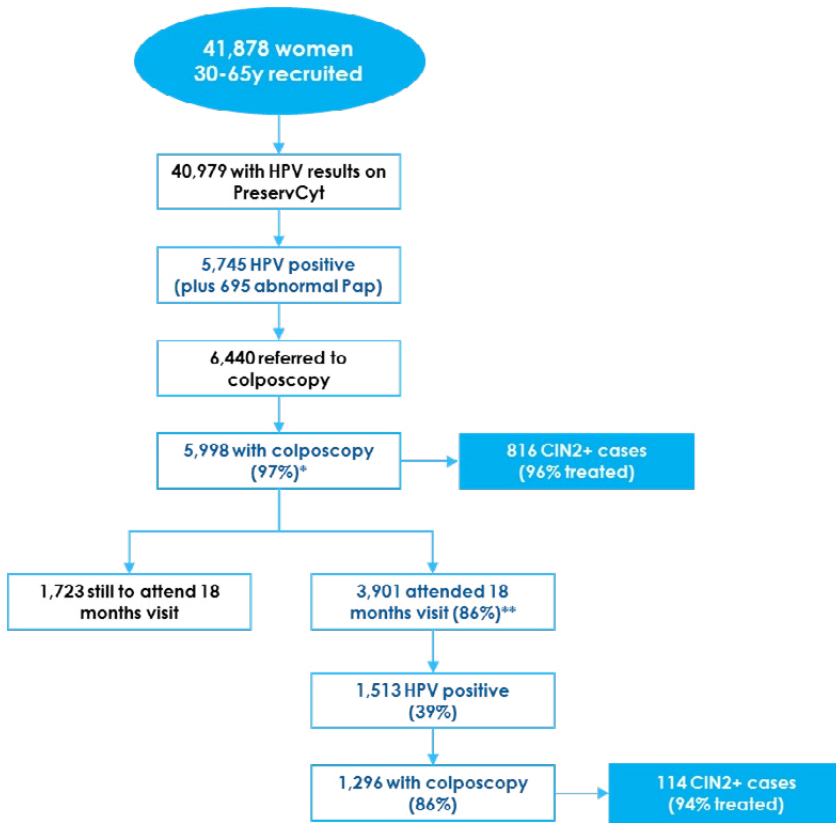
high-grade lesions detected have been treated (Figure 2). Results are supported by a study network promoting the sharing of experiences among more than 200 multidisciplinary professionals (Figure 3). In addition, the Psycho-ESTAMPA tool to assess the psychosocial impact of an HPV-positive screening result was developed and validated and will be used to measure the impact of various methods of communicating HPV test results (Arrossi et al., 2020).

To further support the implementation of HPV screening in the region, PRI is also conducting formative research on barriers to and facilitators of adoption of the WHO cervical screening guidelines, in the GUIDES project.

Cervical screening and treatment in Africa

The CESTA study compares the efficacy of cervical screening by (i) HPV detection with visual inspection with acetic acid (VIA) triage of HPV-positive women and ablative treatment of women who are both HPV-positive and VIA-positive, with (ii) HPV detection followed by ablative treatment of HPV-positive women. In Senegal, 18% of 350 HIV-negative women (aged 30–54 years) were HPV-positive, compared with 62% of 400 women living with HIV (aged 25–54 years) in South Africa; an additional 1200 women living with HIV are being recruited in South Africa to enable the evaluation of other, more suitable screening techniques.

A collaborative randomized trial in women living with HIV in Kenya previously reported that recurrent high-grade cervical disease (cervical intraepithelial neoplasia grade 2 or worse [CIN2+]) was lower after treatment by the loop electrosurgical excision procedure (LEEP) than after cryotherapy. Secondary data analyses demonstrated that endocervical curettage does not increase detection of CIN2+ (Chung et al., 2021a) and that the reduction in recurrence was associated with a decrease in HPV persistence in LEEP-treated women (Chung et al., 2021b).

Helicobacter pylori infection and gastric cancer

The HELPER study, a continuing collaboration with the National Cancer Center of Korea, has enrolled 11 799 participants, and 5269 participants who tested positive for *H. pylori* were randomized to eradication or placebo to investigate the reduction in the incidence of gastric cancer. All participants are being endoscopically followed up within the Korean National Cancer Screening Program.

The GISTAR study, a collaboration with the University of Latvia, is investigating whether *H. pylori* test-and-treat and endoscopic follow-up of subjects with serological evidence of atrophic gastritis reduces gastric cancer mortality. Recruitment is continuing, with more than 10 000 participants included and followed up so far.

The prevalence of *H. pylori* and gastric lesions in low-risk and high-risk areas for gastric cancer is being investigated in the ENIGMA studies. In ENIGMA-Chile, the prevalence of serologically determined atrophic gastritis was significantly higher in the high-risk area, although comparable *H. pylori* prevalence is observed in both areas (Herrero et al., 2020).

Breast cancer screening in Belarus

Within the joint European Union and United Nations project BELMED (Preventing noncommunicable diseases, promoting healthy lifestyle, and support to modernization of the health system in Belarus), PRI supported the breast mammography screening component, particularly by ensuring the quality of the programme through training of health-care professionals and the establishment of monitoring processes. The final report of the BELMED screening component is expected in early 2022.
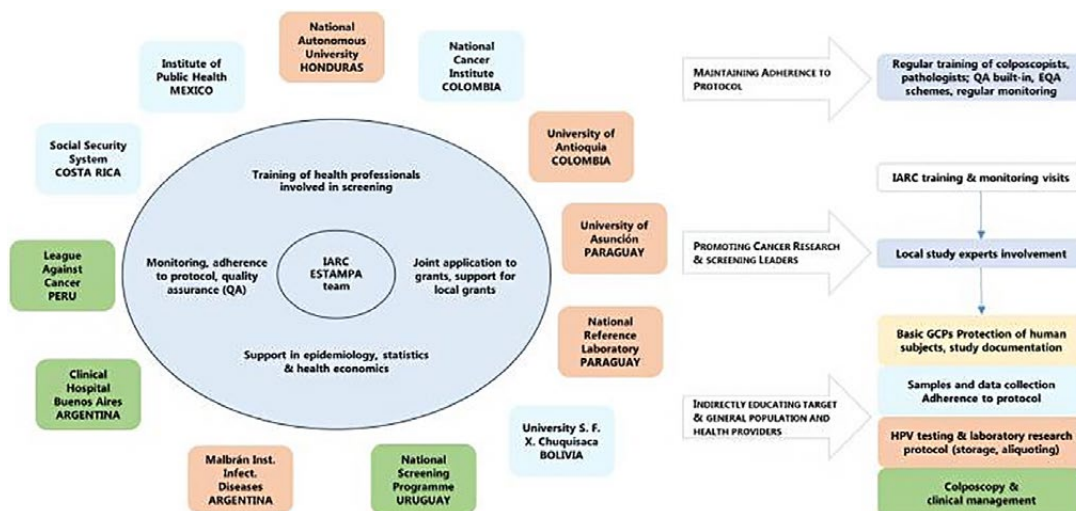
Screening Group (SCR)

Studies led by the Screening Group (SCR) during the 2020–2021 biennium have generated valuable evidence to support the development of resource-appropriate policies to deliver effective cancer prevention and early detection services in the following domains.

Evaluation of HPV vaccine

The SCR study under way in India recently reported that the vaccine efficacy of a single dose of quadrivalent HPV vaccine was as high as that of two doses and three doses at a median follow-up of 9.0 years. Vaccine efficacy against persistent HPV16/18 infection was 95.4% in recipients of a single dose, 93.1% in recipients of two doses, and 93.3% in recipients of three doses (Table 1) (Basu et al., 2021c).

SCR evaluated a new quadrivalent HPV vaccine produced by the Serum Institute of India (SII) in a phase II randomized trial that included female and male participants in two age cohorts: 9–14 years (*n* = 300) and 15–26 years (*n* = 300). The participants received either Gardasil or the SII vaccine (CTRI/2018/06/014601). Neutralizing antibody titre against vaccine-targeted genotypes (HPV6, HPV11, HPV16, and HPV18) was very high 7 months after vaccination, with 100% seroconversion irrespective of the vaccine type, indicating that the new vaccine is as immunogenic as Gardasil. A recommendation of a single dose and the use of a locally manufactured vaccine will significantly improve the affordability of vaccination programmes against HPV.

Cervical cancer screening and management of precancers

In a study in rural China, 9526 women (aged 30–65 years) were screened for cervical cancer on self-collected vaginal samples using the *care*HPV test (a signal amplification test) and a locally developed polymerase chain reaction (PCR)-based HPV test. The PCR-based test had significantly higher sensitivity in detecting high-grade precancers and/ or cancers compared with the *care*HPV test (96.7% vs 72.5%) but lower specificity (82.1% vs 86.0%). Triaging with HPV16/18 genotyping considerably improved the specificity (97.0%), with some reduction in sensitivity (73.6%) (Zhao et al., 2020a).

In a study in Zambia aiming to evaluate thermal ablation for treatment of cervical precancer, 2456 VIA-positive women were randomized to be treated with thermal ablation, cryotherapy, or loop excision. Treatment success rates were similar for the three techniques, although they were significantly lower in HIV-positive women than in HIV-negative women (49% vs 83%). Data from the studies were shared with WHO for guideline development.

Oral cancer screening

SCR assessed a risk prediction model for oral cancer screening. The model showed that screening with visual examination of ever-users of tobacco and/or alcohol with no additional risk stratification would achieve a reduction of 23.3% in oral cancer mortality. Screening would be highly efficient, and the model indicated that screening of only 50% of ever-

Table 1. Efficacy of a single dose of quadrivalent human papillomavirus (HPV) vaccine compared with that of two doses and three doses (all vaccines given at age 10–18 years) for the prevention of incident and persistent HPV infections; 10-year follow-up data from IARC HPV vaccine study in India

	Unvaccinated	Single dose	Two doses (days 1 and ≥ 180)	Three doses (days 1, 60, and ≥ 180)
HPV incidence				
Number of women assessed	1479	2858	2166	2019
Incident HPV16 and/or HPV18 infections				
Observed events	138	92	59	59
Adjusted vaccine efficacy[a] (%) (95% CI)		63.5 (51.2 to 73.1)	67.7 (55.2 to 77.2)	66.4 (53.6 to 76.3)
Incident HPV31, HPV33, and/or HPV45 infections				
Observed events	148	136	89	86
Adjusted vaccine efficacy[a] (%) (95% CI)		43.5 (25.4 to 56.5)	54.0 (38.5 to 66.5)	54.6 (38.3 to 66.6)
HPV persistence				
Number of women assessed	1260	2135	1452	1460
Persistent HPV16 and/or HPV18 infections				
Observed events	32	1	1	1
Adjusted vaccine efficacy[a] (%) (95% CI)		95.4 (85.0 to 99.9)	93.1 (77.3 to 99.8)	93.3 (77.5 to 99.7)
Persistent HPV31, HPV33 and/or HPV45 infections				
Observed events	14	14	11	7
Adjusted vaccine efficacy[a] (%) (95% CI)		8.8 (−230.8 to 62.6)	8.4 (−239.3 to 65.7)	38.8 (−124.4 to 80.2)

CI, confidence interval; HPV, human papillomavirus.

[a] Adjusted through direct standardization on the five strata created from the disease risk score estimates.

Source: Reprinted from Basu P et al. (2021c). © 2021. World Health Organization. Licensee Elsevier.

users of tobacco and/or alcohol would lead to a similar reduction in mortality (19.7%) (Cheung et al., 2021).

SCREENING AND EARLY DIAGNOSIS OF BREAST CANCER

To investigate the variability in the performance of screening mammography across the European Union, SCR estimated breast cancer detection rates adjusted by age, screening interval, and positive predictive value. For women aged 50–69 years, the detection rate of invasive cancers ranged between 3.8 and 7.4 per 1000 and that of ductal carcinoma in situ ranged between 0.7 and 2.7 per 1000 across countries (Armaroli et al., 2020). The remarkable heterogeneity was due to different background risk and differences in the quality and organization of programmes.

The SCR patterns-of-care study, involving 2120 patients with breast cancer registered during 2008–2017 at two publicly funded oncology centres in Morocco, reported a median delay of 6 months between symptom onset and physician consultation (Mrabti et al., 2021). A total of 45% of the patients presented with stage III or IV cancer. The median delay between registration at an oncology centre and the initiation of treatment was 1.5 months. Disparities in the quality of care between the two oncology centres resulted in a 25% difference in 5-year disease-free survival for early-stage breast cancers.

COLORECTAL CANCER SCREENING

SCR published comparative data on the performance of colorectal cancer screening programmes across the European Union. The participation rate was higher in countries that have adopted faecal immunochemical testing (FIT) (range, 22.8–71.3%) than in those using guaiac faecal occult blood testing (gFOBT) (range, 4.5–66.6%). Large variations in screening performance were observed. Compliance with referral for colonoscopy ranged between 64% and 92%. The detection rates of advanced adenomas and colorectal cancer were higher with FIT than with gFOBT, and higher in men than in women.

SCR implemented a demonstration project in Morocco to screen 9763 men and women for colorectal cancer using FIT through routine primary-care facilities. Of the 4.7% of participants who tested positive, only 62.6% underwent colonoscopy, highlighting the challenges of implementing colorectal cancer screening in the country. The detection rate of colorectal cancer was low (0.7 per 1000).

IMPACT OF COVID-19 ON CANCER DETECTION

SCR published a commentary on best practices to continue with cancer screening during the advancing and receding COVID-19 pandemic. SCR has also conducted studies to assess the impact of the pandemic on cancer screening programmes, especially in LMICs (Figure 4) (Basu et al., 2021a; Villain et al., 2021). These studies have also highlighted how some LMICs have leveraged the vertical investments made to mitigate the COVID-19 pandemic to improve the quality and reach of cancer screening programmes (Basu et al., 2021b).

Figure 4. IARC evaluated the impact of the COVID-19 pandemic on cancer screening programmes in several countries. The figure shows the significant decrease in the number of women screened for cervical cancer per month in Bangladesh in 2020 compared with previous years. The figure also shows how the programme recovered from the impact of lockdown within a few months as a result of planned measures. The bars indicate the number of COVID-19 cases detected by months in 2020. VIA, visual inspection with acetic acid. Reprinted from Basu et al. (2021b), © 2021, with permission from Elsevier.
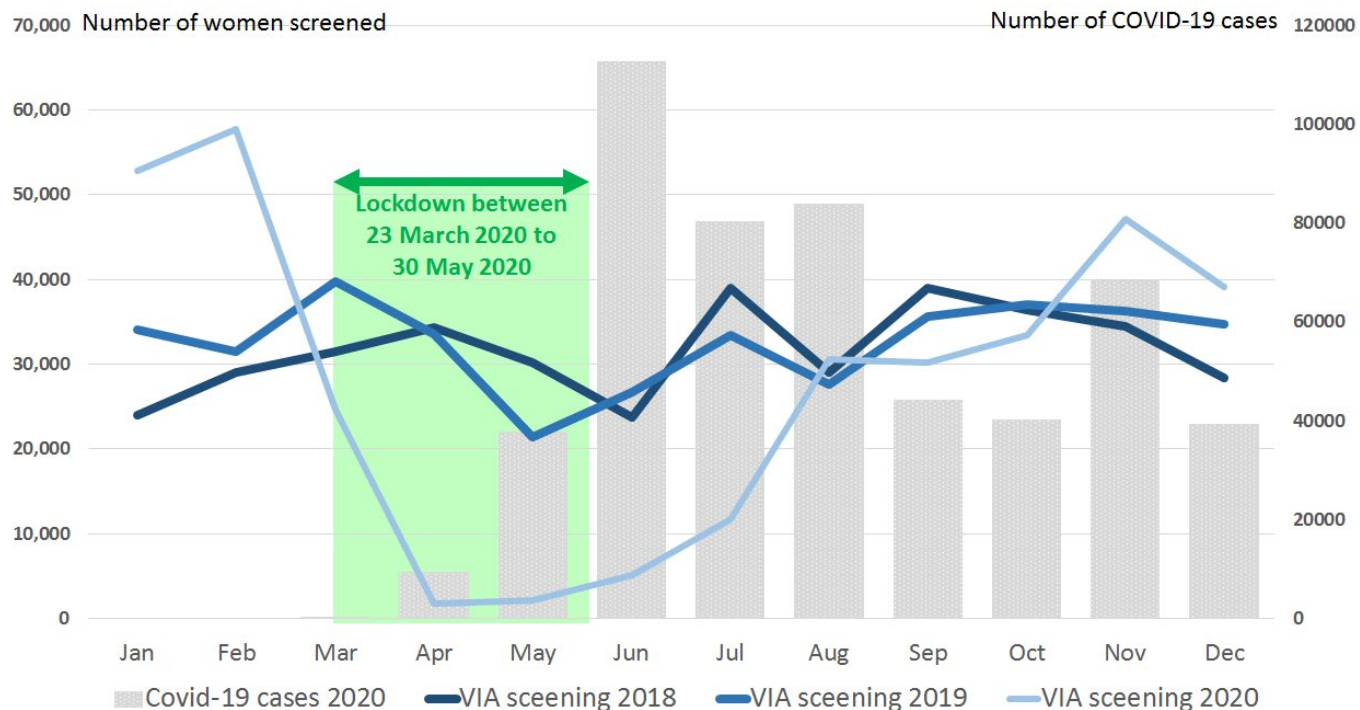
Office of the Director

Director
Dr Elisabete Weiderpass

Director's Office team

Programme officer
Dr Véronique Chajès

Bioethics and compliance officer
Dr Chiara Scoccianti

Strategic Engagement and External Relations (SEE)

Strategic engagement and resource mobilization officer
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Communications officer
Ms Véronique Terrasse
(from January 2021)

Information assistants
Mr Nicholas O'Connor
(from January 2021)
Ms Morena Sarzo
(from January 2021)

Executive assistant to the Director
Ms Nadia Akel

Secretaries
Ms Laurence Marnat
Ms Sylvie Nouveau
(from January 2021)

Consultants
Ms Laure Bernou (until May 2021)
Mr Olivier Exertier
Ms Beatrix Lahoupe
(until November 2020)

Trainees
Ms Houda Bouabdallah
Mr Tarek Eleiwy (until July 2020)
Ms Camille Mebarkia
(until March 2021)

The Office of the Director is composed of a team that provides scientific and administrative support to the Agency, specialist knowledge in strategic engagement, resource mobilization, and external relations, and expertise in bioethics and compliance. The bioethics and compliance team is an integral part of the Director's Office, to ensure its independence in the evaluation of the Agency's scientific work.

The team in the Director's Office supports the IARC Director in the implementation of the Agency's strategic priorities, as described in the IARC Medium-Term Strategy 2021–2025. This strategic roadmap was formulated by a Working Group including members of the IARC Scientific Council and Governing Council, and WHO, and was fully endorsed by the IARC Scientific Council and Governing Council in 2021. The guiding objective of IARC – the promotion of international collaboration in cancer research – has remained unchanged since 1965, but the focus has been shifted to ensure the greatest public health impact of the Agency's work. IARC continues to address its fundamental priorities and will gradually strengthen its engagement in three emerging priorities, notably implementation research. Progress in the implementation of the IARC Medium-Term Strategy 2021–2025 will be assessed within an evaluation framework composed of pertinent key performance indicators (KPIs).

The organizational structure of IARC was revised during the biennium to promote collaboration across the Agency. The former Sections and Groups have been replaced by scientific Branches. The new structure is complemented by the conceptual idea of four scientific Pillars, representing IARC's four fundamental research priorities. A Nordic Research Leadership Training course was offered to senior scientific personnel to strengthen the Agency's strategic and scientific leadership.

In 2021, the Senior Leadership Team (SLT) was reviewed and replaced by a Senior Advisory Team on Management (SAT), whose purpose is to provide senior advisory support to the Director on

strategic, management, and operational policy matters for decision-making.

Strategic scientific discussions now take place within the IARC Science Forum and Open Forum to stimulate new and exciting scientific and creative ideas. The IARC Cross-Cutting Working Group on Cancer Prevention Knowledge Translation and Transfer was created to accelerate the adoption and implementation of evidence-based cancer prevention and control strategies among stakeholders.

The Director's Office team is also responsible for strengthening and expanding the Agency's network of Participating States, governmental and nongovernmental partners, funding agencies, and collaborators.

The Agency signed five Memoranda of Understanding (MoU), with the Beijing Genomics Institute at Shenzhen/China National GeneBank in China, the Sociedade Beneficente Israelita Brasileira Albert Einstein in Brazil, the National Center for Disease Control and Public Health in Georgia, the Trustees of Columbia University in the City of New York in the USA, and the National Cancer Registry operated by the National Institute of Oncology in Hungary. IARC also renewed its MoU with the National Cancer Center Japan.

IARC and WHO re-engaged in a structured dialogue to develop a joint action plan to identify areas of cooperation. The plan will help bring to fruition the implementation of key global cancer initiatives towards better public health.

During the 2020–2021 biennium, the Director's Office had some important achievements. In May 2021, China joined IARC, bringing the total number of Participating States to 27. IARC is in contact with partners in Lyon to increase awareness of the fundraising campaign for the Nouveau Centre building. The Agency has strengthened its collaboration with Centre Léon Bérard and is already engaging with more than 50 local actors. This engagement is very important, not only for IARC's relationship with local authorities but also to boost local participation in the Nouveau Centre campaign.

Strategic Engagement and External Relations (SEE)

The IARC Resource Mobilization strategy relies on four focus areas, as shown in the diagram. During the 2020–2021 biennium, important milestones have been achieved in each of these areas.

At the Sixty-third Session of the Governing Council in May 2021, IARC welcomed a new Participating State: China. The Secretariat has also engaged very closely with other potential new Participating States, including Portugal and Saudi Arabia, and is on track to meet the target of welcoming one new Participating State per biennium.

The Agency continued to be successful in attracting funding through research grants, with an average success rate of 27%

on 2019 applications. In 2020, 236 new grant applications and funding requests were submitted and the Agency signed extrabudgetary contracts amounting to a total value of €20.07 million, of which €12.34 million was attributed to IARC. Novel funding sources are being systematically identified and funding opportunities are closely monitored by a dedicated team, which continuously screens more than 130 funders; in 2020, more than 340 funding opportunities were posted on the intranet Resource Mobilization pages for IARC colleagues to consider.

IARC has been officially recognized by the Organisation for Economic Co-operation and Development (OECD) as an international organization eligible to receive official development assistance (ODA), with a coefficient of 51%. This means that 51% of Participating States' assessed contributions to IARC can be reported by them to the OECD as ODA. In addition, because IARC has a strong focus on cancer prevention research in low- and middle-income countries (LMICs), the Secretariat has developed a set of projects that are 100% ODA-compliant; this is often an advantage when seeking funding from development agencies and/or philanthropic organizations. The Secretariat is currently discussing such projects with different potential donors to substantially enlarge the direct funding component received by the Agency.

The Secretariat was able to attract funding from non-state actors during this biennium. For example, the European Society for Medical Oncology (ESMO) provided the funding to create and maintain the *World Cancer Report* Updates learning platform. Children with Cancer UK and the Terry Fox Foundation have funded fellowships for postdoctoral scientists from LMICs and thus helped to fulfil the capacity-building mission of IARC. Thanks to the support of the Sociedade Beneficente Israelita Brasileira Albert Einstein, IARC has started the development of a Latin America Code Against Cancer, similar to the European Code Against Cancer.
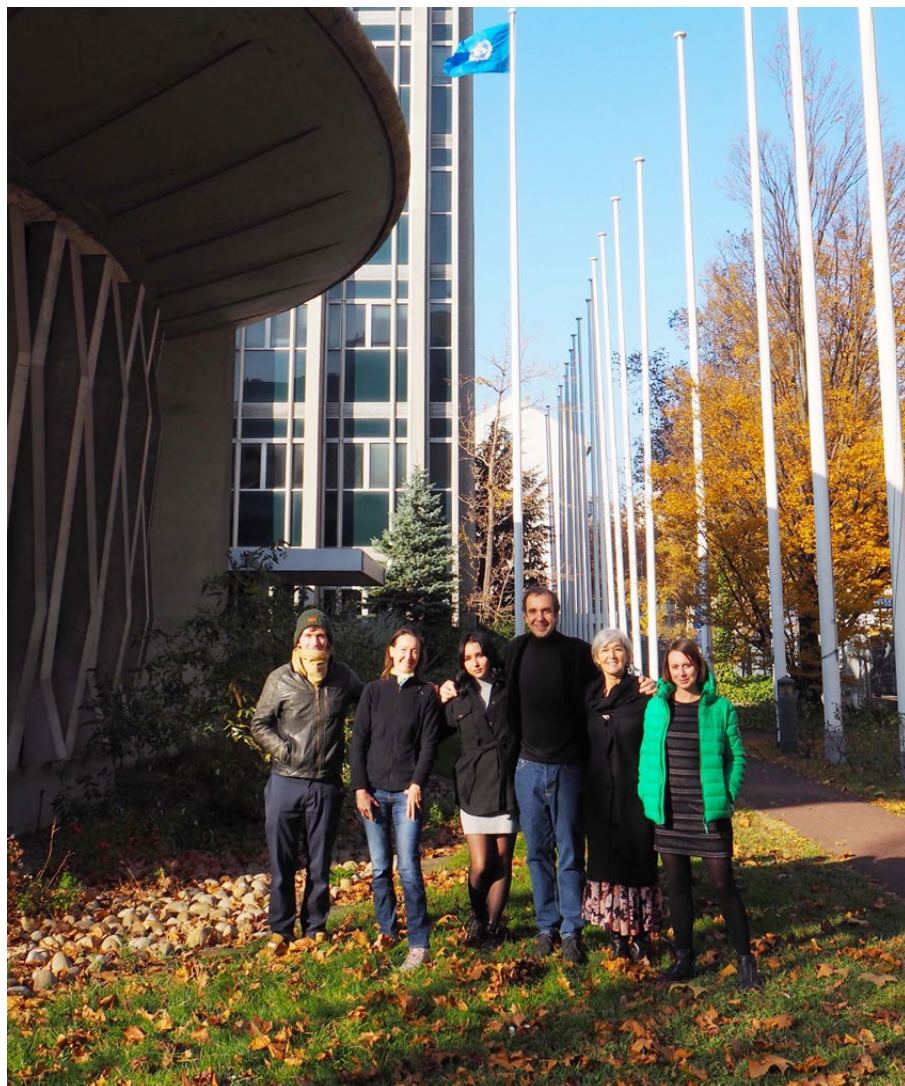
IARC has launched a three-pronged fundraising campaign for the Nouveau Centre building. This campaign focuses on attracting large gifts from ultra-high-net-worth individuals (during this biennium, the Secretariat was able to secure a gift of €1 million from Mr Alain Mérieux) and obtaining in-kind donations of equipment for the Nouveau Centre (IARC has signed in-kind donation agreements with several companies, including Office Concept, Froilabo, and Comadequat). The Secretariat also launched a crowdfunding campaign during the Sixty-third Session of the Governing Council. Through a web-based platform (https://isupport.iarc.fr/), IARC supporters can have their name, or that of a loved one, inscribed on the glass doors of the Nouveau Centre building in exchange for an affordable donation.

In January 2021, a new unit was created that includes both Strategic Engagement and External Relations (SEE). SEE will ensure that IARC's communications reach a wider and more diverse audience, promoting the concept of open science as advocated by the Director. By reaching out to a very diverse range of potential partners and audiences, SEE will ensure that IARC's brand recognition improves and that, as a result, IARC becomes more attractive to potential partners.

New IARC Initiatives

IARC Equity and Diversity Advisory Group (EDAG)

The IARC Equity and Diversity Advisory Group (EDAG) was formed in November 2018. It was originally known as the Women in Science Advisory Group (WiSA). One year later, it was decided to expand the scope of the group to cover equity and diversity in general, and hence the name was changed. The EDAG currently has eight members, who represent all the different types of IARC personnel, including professional staff, administrative staff, early career scientists, and visiting scientists.

The aim of the EDAG, which advises the Director, is to ensure that individuals or groups of individuals within the Agency are not treated differently or less favourably on the basis of race, sex, disability, religion or belief, sexual orientation, or age.

The members of the Equity and Diversity Advisory Group.

Equity and diversity are promoted by:
• treating all IARC personnel fairly;
• enabling all IARC personnel to develop to their full potential;
• creating an inclusive culture;
• ensuring equal access to opportunities for learning and career development;
• ensuring that IARC/WHO policies, procedures, and processes do not result in discrimination; and
• equipping personnel to recognize and challenge inequality and discrimination in the workplace.

Recent EDAG initiatives include a virtual happy hour for LGBTQ+ personnel and friends, the creation of an award scheme for prominent female scientists, and a workshop followed by discussions on implicit bias.

IARC Cross-Cutting Working Group on Cancer Prevention Knowledge Translation and Transfer (KTT WG)

The IARC Cross-Cutting Working Group on Cancer Prevention Knowledge Translation and Transfer (KTT WG) was created in 2020. The vision of the KTT WG is to build bridges and create links so that the scientific knowledge produced by IARC and its collaborators reaches important decision-makers in cancer prevention. The aim of the KTT WG is to translate and transfer high-quality evidence on cancer prevention to stakeholders for their benefit and use, by connecting researchers and research users.

The KTT WG is composed of a dynamic interdisciplinary group of scientists and experts in strategy and communication, who catalyse efforts and stimulate cross-Agency synergies to deliver the latest scientific results to the target audience: stakeholders, decision-makers, and policy-makers from public health institutions, ministries of health, civil society organizations, noncommunicable disease networks, health professionals' societies, and philanthropic organizations. The immediate goals of the KTT WG are to develop a set of targeted resources in the form of comprehensive packages on selected topics, by summarizing the outcomes of projects that can have an impact on recommendations, actions, and policies, and also to raise awareness.

In the first year of its existence, the KTT WG has established the IARC Evidence Summary Brief series, which has received much media attention, and launched a website dedicated to this series. It is anticipated that the Evidence Summary Briefs will help to accelerate the adoption and implementation of evidence-based strategies, while also creating new opportunities for capacity-building and research. The KTT WG is currently conducting a pilot survey and interviews of key stakeholders to obtain advice on broad dissemination strategies and on evaluation of the impact of such strategies.

The dedicated webpage of the IARC Evidence Summary Briefs series (https://iarc.fr/evidence-summary-briefs-series/) shows the first two Briefs to be launched: "Breast Cancer Outcomes in Sub-Saharan Africa" and "The Nutri-Score: A Science-Based Front-of-Pack Nutrition Label".

Communications Group (COM)

Group head
Dr Nicolas Gaudin (until March 2020)
Dr Tamás Landesz
(acting, until December 2020)
Ms Teresa Lee
(acting, until September 2020)

Secretary
Ms Sylvie Nouveau
(until December 2020)

Knowledge manager
Ms Teresa Lee

Managing editor
Dr Karen Müller

Scientific editor
Dr Heidi Mattock
(until December 2020)

Technical editor
Ms Jessica Cox
(until December 2020)

Communications officer
Ms Véronique Terrasse
(until December 2020)

Institutional webmaster
Ms Maria de la Trinidad Valdivieso
Gonzalez

Web architect
Mr Danil Kister (until April 2020)

Information assistants
Ms Latifa Bouanzi
Ms Meaghan Fortune
(until December 2020)
Ms Fiona Gould (until January 2020)
Ms Sylvia Lesage
Mr Nicholas O'Connor
(until December 2020)
Ms Solène Quennehen
(until December 2020)
Ms Morena Sarzo
(until December 2020)
Mr Othman Yaqoubi

The Communications Group (COM) has been an integral part of the Director's Office, aiming to present a clear and cohesive image of IARC and its work to the scientific community, the media, and the general public. The role of COM has also encompassed information- and publication-related services to the research Sections, and the work of the COM Group Head as the External Relations Officer and Liaison with WHO headquarters. COM was restructured in January 2021 as part of the broader reorganization of the Agency. Publishing, library, and web services became part of the Services to Science and Research Branch (SSR), whereas media and external communications remained in the Director's Office as part of the Strategic Engagement and External Relations team.

Digital strategy and dissemination

Stewarding the IARC e-bookshop, and in particular the WHO Classification of Tumours Online annual subscription, which was launched in September 2019, was the focus of the 2020–2021 biennium. The digital subscription website currently offers the complete contents of the 11 most recent volumes of this renowned series, along with whole slide images. The number of subscriptions has grown steadily throughout the biennium, complementing the sale of print books by WHO Press. The current total of digital subscriptions stands at 4200. Hospital libraries, pathology units, and other institutional subscribers are offered a bulk discount model.

The 2020–2021 biennium was also a period of intense behind-the-scenes work to make the Agency's publications compliant with the technical standards of the United States National Library of Medicine (NLM), whose Bookshelf database serves as a repository and additional dissemination channel for many IARC titles.

Corporate visual identity

COM spearheaded the commissioning of a new corporate visual identity that expresses the principles and values crystalized in the IARC Medium-Term Strategy 2021–2025. The new visual identity, comprising a graphic charter and templates for a wide variety of communications materials, was announced in September 2021. Implementation will be carried out in stages, with the goal of full cohesion in the Agency's visual branding.

Publications key performance indicators and bibliometrics

The IARC Medium-Term Strategy 2021–2025 prompted a revision of COM's key performance indicators (KPIs) reporting on publications. Moving away from metrics predominantly driven by impact factor, COM strives for a more complete and well-rounded view of the impact of the Agency's scientific publishing by considering the *h*-index, altmetrics, and collaboration with countries.

Information services

The provision of information services to IARC personnel and external visitors via the Agency's library is less publicly visible but serves an important function. 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 IARC personnel. Instructional sessions on PubMed, in-depth searching for systematic reviews, copyright, and publishing issues were successfully conducted online during the biennium.

Although the COVID-19 pandemic has led to an even greater emphasis on digital formats and access, for the IARC library this biennium also prompted a review of its legacy print collection in anticipation of the Agency's move to the Nouveau Centre building, where shelving capacity will be significantly reduced. Deselection of materials has been conducted in consultation with IARC scientists and will result in a leaner and refreshed physical collection.

Open Access

In terms of the broader Open Access landscape, this biennium witnessed the January 2021 launch of Plan S, an Open Access initiative supported by an international consortium of research funders. Open Access compliance with funding authorities, including Plan S members, is a priority for the Agency, and an information session for IARC scientists was co-presented with a WHO Press staff member in December 2020.

The IARC Governing Council Special Fund for Open Access, which earmarks €50 000 per annum for journal article processing charges, supported 25 articles in 2020 and 21 articles to date in 2021.

During the 2020–2021 biennium, IARC published the following reference publications:

WHO Classification of Tumours

- WHO Classification of Soft Tissue and Bone Tumours, 5th edition (print)
- WHO Classification of Female Genital Tumours, 5th edition (print)
- WHO Classification of Thoracic Tumours, 5th edition (print)

IARC Monographs

- Volume 120, Benzene (print)
- Volume 121, Styrene, Styrene-7,8-Oxide, and Quinoline (print)
- Volume 122, Isobutyl Nitrite, β-Picoline, and Some Acrylates (print)
- Volume 123, Some Nitrobenzenes and Other Industrial Chemicals (PDF and print)
- Volume 124, Night Shift Work (PDF and print)
- Volume 125, Some Industrial Chemical Intermediates and Solvents (PDF and print)
- Volume 126, Opium Consumption (PDF)
- Volume 127, Some Aromatic Amines and Related Compounds (PDF)
- Volume 128, Acrolein, Crotonaldehyde, and Arecoline (PDF)

IARC Scientific Publications

- Cancer Incidence in Five Continents, Volume XI, IARC Scientific Publication No. 166 (PDF and print)

Biennial Report

- Biennial Report 2018–2019 (print)
- Rapport biennal 2018–2019 (PDF)

Non-series publications

- World Cancer Report: Cancer Research for Cancer Prevention (PDF and print)
- A Checklist for Dad (print)
- Patterns of Care for Women with Breast Cancer in Morocco: An Assessment of Breast Cancer Diagnosis, Management, and Survival in Two Leading Oncology Centres (PDF)

Electronic resources

- Atlas of Visual Inspection of the Cervix with Acetic Acid for Screening, Triage, and Assessment for Treatment, IARC CancerBase No. 16

Editing, layout, translation, and language services

The COM Editing and Layout team is responsible for the editing and layout of established IARC Publications series and non-series publications. The team helps to maintain the reputation and image of the Agency by ensuring high corporate standards. COM also helps to produce various promotional materials about the Agency and its publications.

In addition, COM presents training on writing and publishing and provides English editing services for various materials for the IARC website, as well as articles for submission to peer-reviewed journals, book chapters, and other manuscripts. COM provides translation services for short documents and coordinates external translation services for longer documents. COM also organizes 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 scientists, researchers, and the cancer community, as well as among policy-makers, the media, and the general public.

From January 2020 to September 2021, efforts to design and develop a wide range of visuals led to an increase in activities on IARC's social media platforms. During this period, 534 tweets were posted to the IARC Twitter account and 41 new videos were published on the IARC YouTube channel. This increase in activity was reflected by an increase in the audience: the IARC Twitter account gained more than 3500 followers, surpassing 10 000 followers in May 2021, and the IARC YouTube channel gained 1245 subscribers, about three quarters of the total number who have subscribed to date.

Full communications packages were systematically developed to mark key events such as World Cancer Day, Cervical Cancer Awareness Month, World Cancer Research Day, and Breast Cancer Awareness Month. These packages included videos, Q&As, interviews, news items, infographics, and animations. Specific themes were regularly developed as Featured News topics on the IARC website. From January 2020 to August 2021, almost 250 news items were published on the IARC website.

Media activities continued to grow, with regular interactions with journalists. Interviews with IARC scientists appeared in a wide range of media. Much of this media coverage arose from one of the 23 press releases published to highlight IARC's scientific results. For example, IARC Press Release No. 299 on alcohol and cancer was covered by the BBC, *The Guardian*, Sky News, *Le Monde*, *El País*, and other top-tier international media outlets.

In 2020–2021, communications activities also supported the Agency's resource mobilization efforts and, in particular, the progress of the construction of the Nouveau Centre building, in order to increase IARC's visibility among the public and the Agency's partners at the local level in Lyon. To this end, a press conference was held in July 2021 and marketing materials were disseminated with the support of local communications companies.

Several activities and events, including webinars, were organized with key partners in Lyon to highlight IARC's role as a core player in cancer research, not only at the international level but also at the local and national levels.

Finally, interactions with international partners increased significantly throughout this biennium, including regular communications and coordination meetings with WHO teams at the headquarters and regional levels, active participation by IARC in various major communication events and campaigns with the Union for International Cancer Control (UICC), and IARC's driving role in the promotion and design of the World Cancer Research Day campaign.

Web services

The key aim of the Web services team is to harness web technology to ensure the timely dissemination of the Agency's scientific activities (cancer statistics, publications, meetings, courses, fellowships, etc.) and the complete integration of this information across IARC's newly developed communication channels.

To further the Agency's Internet presence, the Web services team in collaboration with Information Technology Services (ITS) and an external contractor focused on enhancing the look and feel of the IARC website and adding specific features. These included, for example, the implementation of vertical scrolling on the IARC homepage (https://www.iarc.who.int/) as well as the creation of Research Branch webpages (https://www.iarc.who.int/branches/) that reflect the new IARC organizational structure, which took effect in January 2021. In addition, and in close collaboration with the Office of the Director of Administration and Finance (DAF) and the Resource Mobilization Office, specific webpages were created in support of resource mobilization activities (https://www.iarc.who.int/about-iarc-newbuilding/, https://www.iarc.who.int/donations-nc/).

As part of the broader goal of promoting IARC's research, the Web services team in collaboration with ITS and an external contractor coordinated the development of a new look and feel for IARC's Research Project websites in a new content management system (CMS), and migrated 35 existing websites into the CMS in a cloud-based solution.

In addition, during the biennium the Web services team developed or validated and launched nine websites:
- International Collaboration for Cancer Classification and Research (IC³R): https://ic3r.iarc.who.int
- Cancer Risk in Childhood Cancer Survivors (CRICCS): https://criccs.iarc.who.int/
- NORDCAN 2.0: Comparable cancer statistics: https://nordcan.iarc.fr/en
- Human Exposome Assessment Platform (HEAP): https://heap-exposome.eu/
- *World Cancer Report* Updates learning platform: https://learning.iarc.fr/wcr/
- Cancer Prevention Europe Learning Centre: https://cancerpreventioneurope.iarc.fr/learning-centre/
- Cancers Attributable to Alcohol: https://gco.iarc.fr/causes/alcohol/home
- IARC Cervical Cancer Image Bank: https://screening.iarc.fr/cervicalimagebank.php
- Cancer Over Time: https://gco.iarc.fr/overtime

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

Key achievements of IARC's education and training programme during 2020–2021 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.

With the start of the new IARC Medium-Term Strategy 2021–2025 and the new organizational structure as of 1 January 2021, ETR was renamed as the Learning and Capacity-Building Branch.

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 receive training at IARC by participating in collaborative research projects. These Early Career and Visiting Scientists are supported either by project funds from IARC Groups or by IARC Fellowships. A total of 254 Early Career and Visiting Scientists from 58 different countries worked at IARC during the biennium. This represents a 13.9% decrease compared with the previous biennium, which is directly related to reduced mobility resulting from the travel restrictions imposed during the COVID-19 pandemic.

Hosting environment and career growth

The internal programme of generic skills courses, jointly managed by ETR and the Human Resources Office, offered 30 courses to Early Career and Visiting Scientists in 2020–2021 (Table 1), which were attended by more than 200 people. Because of the COVID-19 pandemic, the courses offered were reduced to high-priority events and were held online. In addition, Early Career and Visiting Scientists accessed 97 learning resources from the WHO ilearn learning platform. An IARC Mentoring Programme was developed with a group of volunteers from across the Agency as part of the IARC Quality of Work Life initiative (Figure 1).

ETR continued to work closely with the Early Career Scientists Association (ECSA). Among other activities, ECSA successfully held online events, including a Career Day, featuring a career panel and a seminar on working efficiently from home, and a Scientific Week, enabling the presentation of work to peers from IARC, the Cancéropôle Lyon Auvergne Rhône-Alpes, the United States National Cancer Institute, and the German Cancer Research Center.

Postdoctoral Fellowships

The Agency awarded seven IARC Postdoctoral Fellowships to candidates from low- and middle-income countries (LMICs) for projects in line with IARC's emerging priorities or on the relationship between cancer and COVID-19. In addition, as part of efforts to identify complementary sources of funding for the programme, negotiations with Children with Cancer UK led to a call for IARC Postdoctoral Fellowships for scientists wishing to carry out research on paediatric cancers or cancer in teenagers and young adults. Two such fellowships were awarded.

Three return grants were awarded, to assist former IARC Postdoctoral Fellows in the establishment of research activities in their home countries.

Table 1. Generic courses for Early Career Scientists, 2020 and 2021

Research skill development	Writing skills
Multivariate analysis for -omics data integration: principles and applications	Copyright issues (twice)
Tidyverse fundamentals with R	Effective scientific posters
	Publications catch-all/catch-up
	Publishing in scientific journals
	PubMed workshop: search efficiently
	Systematic reviews search methodology

IT skills	Communication skills
Electronic Laboratory Notebook	Effective interpersonal communication techniques (four times)
REDCap for data collection	Social media
REDCap for surveys	

Career management and development	Leadership and management
Career Compass webinar	Efficient communication between team member and supervisor: being on the same page
Career Compass follow-up webinar	Research leadership training course (twice)
Confident career conversations	Task management
Creating and maintaining high performance	Teamwork and collaboration
Giving and receiving feedback (twice)	
Motivation and focus (twice)	

Figure 1. Flyer to promote the concept of the IARC Mentoring Programme. © IARC.

Figure 2. Cancer Screening in Five Continents (CanScreen5) Train the Trainers live session. © IARC.

Short-term fellowships

In collaboration with the Union for International Cancer Control (UICC), the UICC-IARC Development Fellowship enables a selected number of IARC Summer School participants from LMICs to visit IARC for a period of 1 month for further training and collaboration. Seven UICC-IARC Development Fellowships were awarded.

Courses Programme

The courses programme is designed to enhance the capacity of the global research community, in particular in LMICs, through lifelong learning in the areas of the Agency's expertise.

Learning events

The Agency organized 37 courses or webinars targeting researchers and health professionals from many countries, in particular LMICs (Table 2). Because of the COVID-19 pandemic, courses were offered online, were redesigned to combine live sessions with facilitated self-learning, and lasted from a period of a few days, for example the

cancer staging course, to several months, for example the IARC Summer School 2021, the ChildGICR Masterclass, and the Cancer Screening in Five Continents (CanScreen5) Train the Trainers course (Figure 2). More than 2700 scientists and health professionals benefited from these learning events during the biennium.

Self-learning resources

As a key complement to live events, IARC continued to produce self-learning resources. A new self-paced learning programme on cancer screening and early diagnosis was launched in the framework of the CanScreen5 project. This resource was translated into Russian and will soon be available in Spanish (https://learning.iarc.fr/edp/resources/pgm-cancer-screening/).

As part of the Cancer Prevention Europe consortium, self-learning modules on the fourth edition of the European Code Against Cancer were produced and were translated into French, Hungarian, Polish, and Spanish (https://learning.iarc.fr/edp/cpe/) (Figure 3).

Learning portal

Launched in 2019, the IARC Learning portal (https://learning.iarc.fr) enables access to several thematic learning platforms (Biobanking, Cancer Prevention and Early Detection, and *World Cancer Report* Updates). It also provides access to IARC WebTV, including the IARC Summer School video channel, as well as to the websites of other IARC-led projects with learning materials on cancer surveillance and on the exposome (the Human Exposome Assessment Platform). The IARC Learning portal continues to attract an increasing audience. Since November 2019, 1554 people (1423 during 2020–2021) have created an account on the portal to freely access learning resources.

Table 2. Learning events, 2020 and 2021

Course title	Location	Number of participants	External collaborations
Cancer surveillance			
Cancer registration: basic principles and methods for the Organisation of Eastern Caribbean States (OECS)	Online	46	IARC Caribbean Hub for Cancer Registration – Martinique Cancer Registry – OECS Health Unit Joint Virtual Caribbean Course
GICR Childhood cancer	Online	25	St. Jude Children's Research Hospital
GICR-WHO EMRO Basic cancer registration course	Online	45	WHO Regional Office for the Eastern Mediterranean
GICR-WHO EMRO Data quality course	Online	20	WHO Regional Office for the Eastern Mediterranean
GICR Staging and Essential TNM course	Online	15	Union for International Cancer Control (UICC)
IARC-National Cancer Center Korea Joint Summer School on Cancer Registration: Principles and Methods	Online	32	GICR, National Cancer Center of the Republic of Korea and its Graduate School of Cancer Science and Policy (NCC-GCSP)
Cancer prevention and early detection			
CanScreen5 – Train the Trainers – African region	Online	32	American Cancer Society (ACS), Medical Research Council (United Kingdom)
CanScreen5 – Train the Trainers – Pan American Health Organization – Community of Caribbean and Latin American States (CELAC) countries (3 sessions)	Online	79	American Cancer Society (ACS), Centre for Global Health Inequalities Research (CHAIN) of Norway
IARC-Centre Léon Bérard Série d'échanges – Bouger contre le cancer (in French)	Online	220	Centre Léon Bérard, Lyon, France
IARC-Centre Léon Bérard Série d'échanges – Mieux manger pour ma santé (in French)	Online	121	Centre Léon Bérard, Lyon, France
IARC Summer School: Implementing Cancer Prevention and Early Detection	Online	34	Union for International Cancer Control (UICC)
Precision oncology	Online	40	European Scientific Institute, University of Grenoble
Prevention and screening to control chronic diseases: an illustration with cancer – Master of Public Health: Epidemiology of Chronic Diseases	Online	15	French National School of Public Health
Projet Care4Afrique – Benin – IVA et thermo-coagulation (in French)	Online	17	
Running 8-HPV type OncoE6/E7 Cervical Test for ESTAMPA (2 series)	Online	8	
Stakeholder analysis of barriers to cancer screening	Online	25	Pan American Health Organization
The contribution of the Innovative Partnership for Action Against Cancer (iPAAC) Joint Action to building capacity for cancer prevention	Online	87	Cancer Society of Finland, Association of European Cancer Leagues
World Cancer Report webinar series – HPV vaccination	Online	288	European Society for Medical Oncology (ESMO)
World Cancer Report webinar series – Obesity and cancer	Online	351	European Society for Medical Oncology (ESMO)
World Cancer Report webinar series – Social inequalities and cancer	Online	282	European Society for Medical Oncology (ESMO)
World Cancer Report webinar series – COVID-19 and cancer screening	Online	391	European Society for Medical Oncology (ESMO)

Table 2. Learning events, 2020 and 2021 (continued)

Course title	Location	Number of participants	External collaborations
World Cancer Report webinar series – Challenges and opportunities for primary cancer prevention	Online	261	European Society for Medical Oncology (ESMO)
Cancer research infrastructure and methods			
Biobank ethics and governance, for BCNet members (2 webinars)	Online	27	National Cancer Institute (NCI) Center for Global Health (CGH)
Human exposome "Bring your own data workshop" for HEAP consortium	Online	20	Human Exposome Assessment Platform (HEAP) consortium members
IARC Summer School: Introduction to Cancer Epidemiology	Online	39	Union for International Cancer Control (UICC)
Multivariate analysis for -omics data integration: principles and applications	IARC, Lyon	30	Swiss Institute of Biostatistics
Safe handling of biological samples, for BCNet members (4 webinars)	Online	55	National Cancer Institute (NCI) Center for Global Health (CGH)
Scientific writing for peer-reviewed publications, for scientists from African and Latin American countries	Online	16	
UiT Winter School on Cancer Epidemiology	Norway and online	43 + 40	The Arctic University of Norway (UiT)
Leadership and management			
Research Leadership Training Programme (2 series)	Online	15	Mobilize Strategy Consulting

Figure 3. Self-paced e-learning module for the European Code Against Cancer, fourth edition. © IARC.

As part of the IARC Learning portal, and with the support of and in collaboration with the European Society for Medical Oncology (ESMO), IARC launched the *World Cancer Report* Updates learning platform (https://learning.iarc.fr/wcr/) (Figure 4). This provides learning resources and opportunities related to selected content from the 2020 *World Cancer Report*, as well as on developments in cancer research for cancer prevention. Five live webinars provided the opportunity to 2008 researchers and health professionals from 140 countries to interact with international experts. Four e-learning modules were created from the webinar recordings, including short video teasers, quizzes, questions and answers, and certificates of completion.

Key Partnerships

Relationships between IARC and academic institutions continued to be strengthened during the 2020–2021 biennium. For example, an agreement was reached with the Italian Istituto Superiore di Sanità for the joint supervision and hosting of three PhD students. IARC was also invited to partner with the German Cancer Research Center for the development of a Cancer Prevention Graduate School. In addition, ETR collaborated with the Karolinska Institutet and other European institutions in the Human Exposome Assessment Platform consortium, funded by the European Union.

IARC has been involved in the development of the WHO Academy at several levels. As well as contributing to governance and infrastructure aspects, two IARC learning programmes were selected as part of the development of the first courses of the Academy: the Comprehensive Learning Programme on Screening, Diagnosis, and Management of Cervical Precancer; and the Managing Infrastructure for Medical Research Learning Programme.

Figure 4. The *World Cancer Report* Updates learning platform. © IARC.
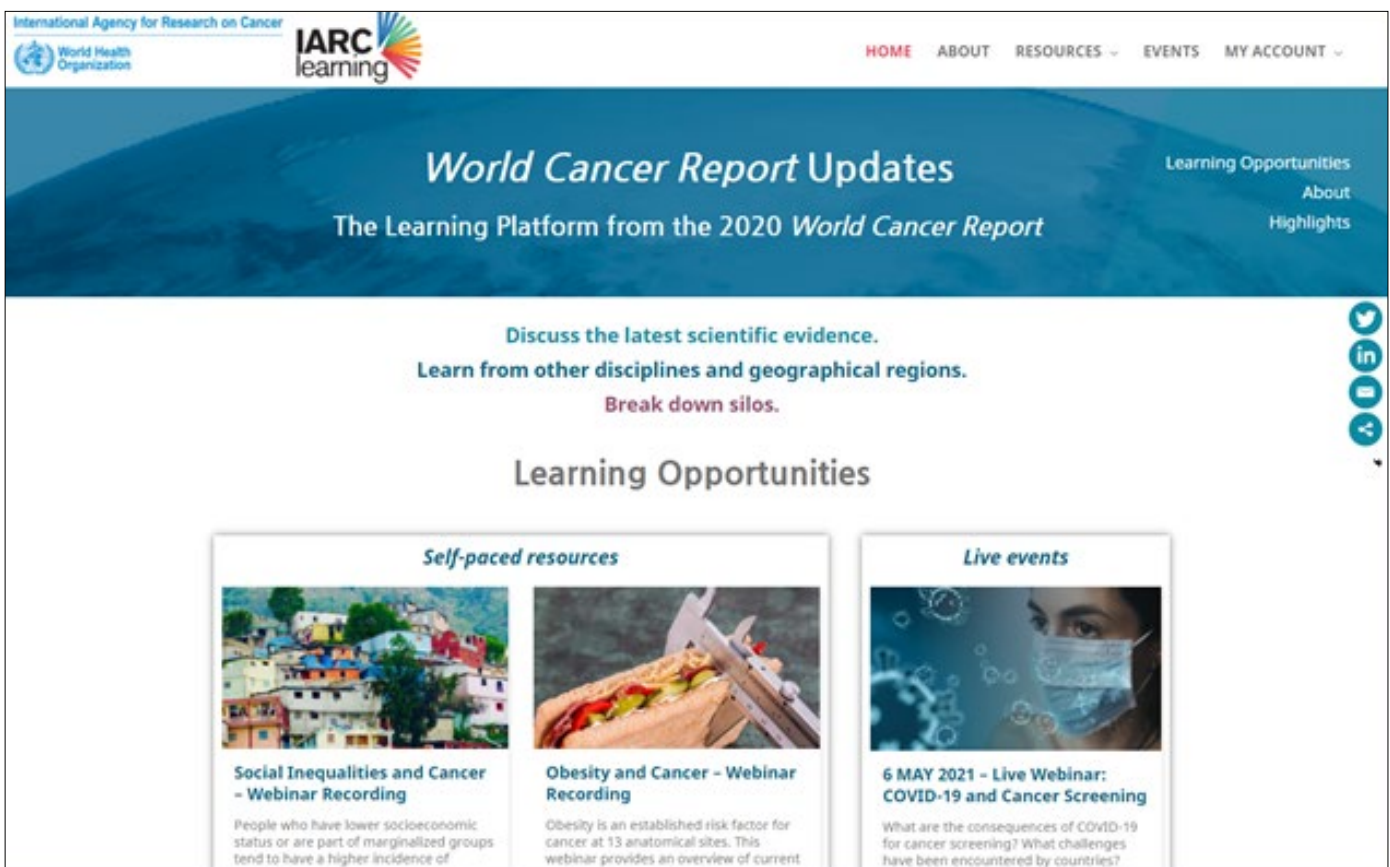
IARC Summer School in Cancer Epidemiology 2021

The IARC Summer School in Cancer Epidemiology aims to improve the methodological and practical skills of cancer researchers and health professionals. Because of the COVID-19 pandemic, the 2021 course was redesigned and conducted entirely online, while maintaining the features that make the course unique: the fostering of international collaboration, the provision of multiple opportunities for interaction, and the delivery of high-quality multidisciplinary lectures and practical activities to facilitate the learning process of participants.

Two modules were offered: Introduction to Cancer Epidemiology, and Implementing Cancer Prevention and Early Detection. A blended learning approach was adopted for both modules, including 4 weeks of self-paced activities (recorded lectures and assignments, punctuated by two or three live sessions and networking events), followed by 2 weeks of daily live sessions and group work activities. A total of 73 cancer researchers and health professionals from more than 45 countries (the vast majority of which were LMICs) participated in the two modules.

All the resources used to deliver the 2021 Summer School are available from the IARC Learning portal (https://learning.iarc.fr).

Participants were invited to report their impressions and experience of the 2021 Summer School. The recorded testimonials perfectly illustrate the spirit of the IARC Summer School: the shared learning, sharing of experiences, and the international networking for cancer prevention across countries. The feedback from participants and the assessment of the course directors will be taken into consideration in the design of future IARC Summer Schools and other similar events, to ensure that, when on-site events are again permitted, potential on-site components of courses will be even more focused on the practical and networking aspects.

IARC tweet with IARC Summer School 2021 participants. © IARC.

IARC @IARCWHO · Jun 28

The **#IARCSummerschool** Prevention module is starting the second part of its programme with 2 weeks of daily live sessions and intensive group work activity across borders!

Want to follow IARC Summer School 🎓📚 content? Take a look 👀 here learning.iarc.fr

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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. LSB also leads national and international research projects on biobanking and medical research infrastructure. In addition, LSB provides technical and safety advice to the Nouveau Centre project for the future laboratories and biobank, in alignment with the IARC Medium-Term Strategy 2021–2025.

Within the new organizational structure as of 1 January 2021, LSB was renamed as Laboratory Support, Biobanking, and Services.

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

Laboratory services

LSB ensures that optimal laboratory services are available, including a laboratory store that provides consumables, glass-washing facilities, mycoplasma testing and quarantine for cell cultures, pipette checking, and the freezing and/or retrieval of cell lines in nitrogen gas. In conjunction with the Laboratory Steering Committee (LSC), LSB oversees the common laboratory platforms and ensures that 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.

Health and safety

Health and safety issues are managed in collaboration with the Occupational Health and Safety Committee (OHSC). The IARC safety manual, a key document, is now available online; it is updated regularly and is aligned with the latest national and international guidelines. The first section of the manual describes the role of all personnel and 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, including risks related to the handling of carcinogens, liquid nitrogen, and laboratory waste.

IARC authorizations for the restricted use of genetically modified organisms (GMOs) are handled by LSB. Radionuclide experimentation has ceased entirely, and the relevant authorizations have not been renewed. LSB initiated the declaration of the biological collections stored at IARC and the authorization to import and/or export biological samples in accordance with CODECOH; this authorization is valid until 2025.

During the biennium, LSB provided 124 safety briefings for newcomers and 28 training sessions for newcomers working in laboratories. LSB made more than 10 presentations to 93 laboratory personnel, covering new guidelines linked to COVID-19 constraints; working with liquid nitrogen, with carcinogens, and with the Fusion FX system; working in the L3 or L2+ laboratories; and completing the Electronic Laboratory Notebook. LSB also published a report on biosafety, describing gaps in current knowledge (Roux et al., 2021).

LSB plays many important roles in the preparation for the move to the Nouveau Centre building, including participating in the laboratory working group, the biobank working group, and the transfer and move working group; several calls for tender; the donation campaign; and the implementation of new procedures.

Biobank services

The IARC Biobank maintains biological sample collections from international studies and operates a service platform for sample retrieval, inventory, aliquoting, DNA extraction and quantification, and reception or shipment of biological material worldwide.

The IARC sample management database (SAMI) stores information on more than 6 million biological specimens. During the biennium, more than 363 000 new samples were imported into SAMI and more than 65 000 samples were accessed for collaborators. SAMI is continuously being upgraded, and version 2.0 was launched in 2020.

The standard procedures that govern sample transfer to and from the Agency and the management of samples were updated (e.g. the new sample disposal policy). During the biennium, 106 Material Transfer Agreements for incoming and outgoing samples were technically validated. LSB supervised the replacement of obsolete equipment and the purchase of 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 validated and installed on cold storage equipment, anticipating the move to and expansion within the Nouveau Centre building.

The Biobank continues to provide preanalytical services on a cost-recovery basis. During the biennium, 18 projects were serviced, all of which related to requests from international institutions. This resulted in more than 12 000 sample retrievals from liquid nitrogen, 5133 DNA extractions, 7162 DNA aliquots, 5034 plasma and serum aliquots, and 205 receptions or shipments of samples from or to 23 countries worldwide. The Biobank inventoried more than 67 000 individual samples and provided support across the continuum, from reception to data upload into SAMI (Figure 2).

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

Figure 2. An overview of the services provided by the IARC Biobank as at September 2021. © IARC.
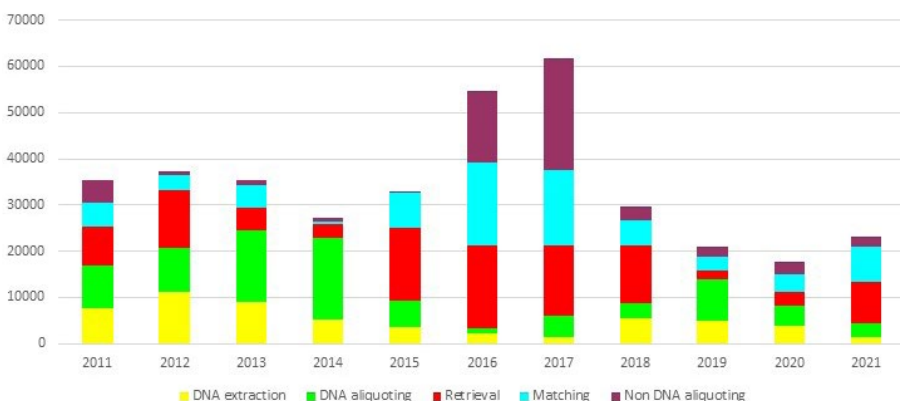
BCNet

LSB participates in several research programmes, in line with IARC's mission of cancer research for cancer prevention. To address the underrepresentation of biological resources in low- and middle-income countries (LMICs) in research, the LMICs Biobank and Cohort Building Network (BCNet; https://bcnet.iarc.fr/) was established by IARC in 2013. Currently, 42 institutions in 23 countries are members of BCNet (Figure 3). During the biennium, BCNet delivered four presentations to external collaborators (in Nigeria, Kenya, the Philippines, and Macao Special Administrative Region, China) and published several seminal articles (Henderson et al., 2020; Kozlakidis, 2020; Vodosin et al., 2021).

BCNet direct funding is provided by the Center for Global Health, National Cancer Institute, National Institutes of Health, USA. LSB gratefully acknowledges all the members of BCNet and their active discussions and exchanges, which have enriched our scientific world as well as our contextual understanding of global research.

Collaborations

With regard to infrastructure research, LSB represents IARC at the International Organization for Standardization (ISO; https://www.iso.org/) and at the Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium (BBMRI-ERIC; https://www.bbmri-eric.eu/) (Figure 4). LSB participated in infrastructure research from the perspective of operational readiness and responsiveness (Henderson and Kozlakidis, 2020; Aisyah et al., 2021; Wei et al., 2021b). LSB also contributed to the development of further recommendations and guidelines (Jazieh and

Figure 3. Map of BCNet member countries as at September 2021. © IARC.

Figure 4. The Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium (BBMRI-ERIC), together with IARC, launched an initiative on better understanding the landscape of paediatric biobanking (https://iarc.who.int/news-events/call-for-participation-and-resource-landscaping-on-elsi-issues-for-biobanking-with-children/). © Adobe Stock.

Kozlakidis, 2020; Vandenberg et al., 2020; Cree et al., 2021a), with a particular emphasis on data and artificial intelligence (Eklund et al., 2020; Kozlakidis, 2020; Kozlakidis and Nigam, 2020), and to the development of a future WHO Academy course.

During the biennium, LSB investigated the impact of the COVID-19 pandemic on infrastructures and cancer patients (Allocca et al., 2020a, 2020b; Di Lorenzo et al., 2020a, 2020b; Aisyah et al., 2021). This research will continue as part of the regional project "Impact of COVID-19 on Cancer" (IMCOCA), a *Projet Structurant* funded by Cancéropôle Lyon Auvergne Rhône-Alpes (CLARA; https://www.canceropole-clara.com/),

awarded jointly to Centre Léon Bérard (CLB; https://www.centreleonberard.fr/en) and LSB (Figure 5).

LSB participates in projects funded by the European Commission: the Human Exposome Assessment Platform (HEAP) project (grant no. 874662) (https://heap-exposome.eu/) and the Twinning for the Armenian Research Infrastructure on Cancer Research (ARICE) project (grant no. 952417) (https://www.arice.am/). Funding is provided by BBMRI-ERIC for the European Paediatric Translational Research Infrastructure (https://eptri.eu/) and the Center of Excellence in Biobanking and Biomedical Research at the University of Cyprus (https://biobank.cy/).

Figure 5. The "Impact of COVID-19 on Cancer" (IMCOCA) *Projet Structurant* **is funded by Cancéropôle Lyon Auvergne Rhône-Alpes (CLARA) and was awarded jointly to Centre Léon Bérard (CLB) and LSB. Courtesy of CLARA.**

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The main role of the Section of Support to Research (SSR) is to ensure the smooth operations of IARC and to enable the achievement of the Agency's scientific objectives. With the start of the new IARC Medium-Term Strategy 2021–2025 and the new IARC organizational structure as of 1 January 2021, SSR was renamed as the Services to Science and Research Branch.

SSR is made up of six specialized operational units, which provide services intrinsic to the successful implementation of the Agency's scientific programmes: (i) Office of the Director of Administration and Finance, including legal support and data protection; (ii) Budget and Finance Office, including supporting resource mobilization activities; (iii) Human Resources Office, including staff training and capacity-building; (iv) Administrative Services Office, including procurement, conference services, building management, and security; (v) Information Technology Services, including telecommuni-

cations; and (vi) Publishing, Library, and Web Services, including publications production and copyright management (which became part of SSR in January 2021 as part of the restructuring). SSR ensures that the Agency's activities meet the highest sector standards of resource management, operational efficiency, and accountability in the use of the funding made available by its Participating States and donors.

In addition to the regular provision of daily operational services, during 2020–2021 the following achievements of SSR contributed substantively to maintaining IARC's leadership status in the ever-changing international research environment.

SSR continued to spearhead the review of IARC's core values, which represent the Agency's DNA, and helped embed these values in every aspect of the Agency's work. During the biennium the Quality of Work Life initiative was launched;

this is an important programme that aims to ultimately improve the quality of science at IARC. Based on broad consultation with IARC personnel, multiple working groups, involving volunteers from across the Agency, have been set up in four target areas: (i) working in a respectful and harmonious environment, (ii) opportunities for growth, training, and development, (iii) well-being and work–life balance, and (iv) team and performance management.

Notable progress has been made, in close cooperation with our host country, in the construction of a new state-of-the-art IARC headquarters in Lyon: the Nouveau Centre building. The First Stone Ceremony was held in February 2020 with the participation of the IARC Scientific Council and local dignitaries. Work on the building has progressed well since then, despite the challenges created by the COVID-19 pandemic. The new building is scheduled to be finished in time to enable its occupation

by the end of 2022. As well as working towards the construction of IARC's future premises, SSR has continued to ensure that the Agency's scientific activities are not significantly interrupted by the continued technical failures experienced in the current premises.

As a result of the COVID-19 pandemic, SSR activated the Agency's Business Continuity Management Team to guide IARC personnel through the various periods of lockdown, applying a phased approach. SSR adapted the current premises to be compliant with WHO and host country health and safety measures as well as health protocols, while ensuring that daily operations and scientific work can continue uninterrupted. Effective teleworking was enabled through the use of the latest cloud-based communications, collaboration, and productivity platforms, and the expansion of the virtual private network (VPN) technology to all IARC personnel. Several additional services for virtual meetings, electronic workflows, and electronic signatures made it possible for work to continue seamlessly.

The IARC Specific Guide on Engagement with Non-State Actors was updated and further simplified to provide clear operational guidance, complementing the WHO Framework of Engagement with Non-State Actors (FENSA).

SSR supported the Director in efforts to mobilize additional external financial resources to deliver the approved programme of work, in developing an IARC Investment Case to help resource mobilization efforts, and in launching the new IARC Medium-Term Strategy 2021–2025.

SSR continued 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. The Agency continued to receive unqualified (or fully compliant) audit opinions from the External Auditors throughout the biennium. In 2021, for the first time, IARC received no recommendations from the External Auditors and managed to close all prior year recommendations successfully.

Enable and support continuous Learning and Development (L&D)

L&D Framework
- Equip all personnel with knowledge, skills, and competencies
- Support development, career, and learning pathways
- Foster a working environment that supports a culture of collaboration, innovation, and excellence

Supervisory, Managerial, and Leadership Training Plan
Encourage all IARC personnel to participate in different learning activities that strengthen and develop skills in: (1) Performance management, (2) Team and group management, and (3) Leadership

QWL Work Plan
Quality of Work Life (QWL) Work Plan Part 2: Opportunities for growth, training, and development

In addition, SSR continued to put in place measures aimed at maximizing the professional and personal potential of personnel, and fostering a work environment that supports collaboration and excellence. Because of constraints resulting from the COVID-19 pandemic, face-to-face training sessions were replaced by online courses and novel group-based learning methods.

An innovative scientific leadership programme comprising various modules was launched in 2021. The first cohort of students included senior and mid-level scientific managers at IARC. The second cohort also included external scientists from low- and middle-income countries as well as scientists nominated by IARC Participating States.

SSR remains committed to the principle of continuous quality improvement, striving to further enhance the Agency's processes and support services by, among others, collecting feedback through regular service surveys. Five impact areas devised by SSR to enable IARC to fulfil the IARC Medium-Term Strategy 2021–2025 and to help build a learning and adaptive organization fit for the 21st century are (i) faster delivery of results, (ii) pooling of resources, (iii) technological innovation and advancement, (iv) fit for Open Science, and (v) culture shift and personal growth. SSR holds monthly Administrative Town Hall meetings to communicate SSR objectives and planned activities and to explain new operational policies and administrative procedures of general interest.

SSR beyond 2020
Our key principles

1 FACILITATE
Making things happen for science, professional and effective support

User centric approach, placing scientists and scientific outcomes at the centre of what we do

2 INNOVATE
Enabling continuous improvements and innovation through best practice methods and a fit for purpose operational structure

3 COLLABORATE
Close collaborative partnership with scientific pillars

More cross-functional collaboration within SSR using a systemic approach

COMMITTEES

Laboratory research is essential for IARC to conduct studies on the causes and mechanisms of cancer, to support cancer prevention. Research laboratories are embedded within five Branches within the new IARC organizational structure (Genomic Epidemiology; Nutrition and Metabolism; Epigenomics and Mechanisms; Early Detection, Prevention, and Infections; and Evidence Synthesis and Classification), and LSB provides global laboratory services, including biobanking. 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 during the 2020–2021 biennium, conducted in close collaboration with LSB and ASO, have concerned the establishment of rules for laboratory activities under COVID-19 constraints, the coordination of the acquisition of new equipment for the histopathology laboratory (one automated slide staining system [Histostainer], one cryostat, and an upgrade of the digital scanner), the creation (with the Director's Office) of a decision-making framework for in-house laboratory capacity versus outsourcing, the overall maintenance of laboratory equipment, the contribution to the IARC donation campaign for laboratory equipment, the logistical preparation for the move to the Nouveau Centre building, and the organization of seminars on new laboratory technologies.

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.

During the 2020–2021 biennium, the BSC renewed its membership, welcomed a new chairperson, and completed the acquisition of a semi-automated liquid nitrogen storage platform dedicated to cell line preservation. Other tasks during the biennium include the expansion of remote temperature monitoring capabilities for freezers, a review of operations under COVID-19 constraints, the creation of an Agency policy for the disposal of samples, operational alignment to the updated CODECOH regulations, the contribution to the IARC donation campaign for laboratory equipment, and visits to the Nouveau Centre construction site.

The BSC has initiated planning for the move of the IARC Biobank to the Nouveau Centre building (in close collaboration with ASO) and has identified sample collections to be disposed of before the move.

COMPUTATIONAL BIOLOGY, BIOINFORMATICS, AND BIOSTATISTICS COMMITTEE (C3B)

The IARC Computational Biology, Bioinformatics, and Biostatistics Committee (C3B) has continued to oversee the Agency's activities in these areas.

The overall structure of the C3B was changed, with the creation of the roles of responsible officers in bioinformatics, biostatistics, and scientific information technology (IT), carried out by Dr Matthieu Foll (GCS), Dr Vivian Viallon (NMB), and Mr Christopher Jack (ITS), respectively. These individuals take the primary responsibility for these activities across IARC.

The main activity of the C3B during the 2020–2021 biennium was the creation of the IARC Scientific IT platform, which provides access to shared centralized computing and storage resources. This shared and centralized approach has several advantages: the data are stored in a secure environment on the IARC premises, the platform facilitates collaborative work, it is cost-effective, and it helps data owners to comply with best practices required to store sensitive or personal data. This system has also been crucial during the COVID-19 pandemic, to enable IARC personnel to work remotely. Scientific opportunities will be associated with further developments; in particular, IARC will become a data hub for some projects, with external collaborators able to use the platform remotely.

The C3B acknowledges the departure of Mr Christopher Jack (ITS) to pursue professional opportunities elsewhere. Mr Jack was instrumental in scientific computing at the Agency, and the C3B sincerely thanks him for his efforts and wishes him well in his future post.

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 2020–2021 biennium, the IEC was composed of 11 senior individuals from diverse backgrounds and nationalities. The IEC is chaired by Professor Samar Al-Homoud, supported by Dr Hans Storm (vice-chair from February 2020 to February 2021) and Dr Angeliki Kerasidou (vice-chair in January 2020 and since February 2021) 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 biennium (up to June 2021), the IEC evaluated 69 new projects and 52 resubmissions of projects previously reviewed by the IEC. During the COVID-19 lockdowns in 2020, the IEC strongly supported the IARC principal investigators with its procedure for expedited review between official meetings, clearing 40% more projects than in 2019. The IEC updated its rules and procedures (RAPs) and standard operating procedures (SOPs) with changes to the procedures for regular submission and expedited review, to further facilitate clearance between IEC meetings by the IEC chairs with the support of the secretary. The IEC questionnaire and annual report template were also updated.

OCCUPATIONAL HEALTH AND SAFETY COMMITTEE (OHSC)

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

Some of the main activities of the OHSC during the 2020–2021 biennium included the replacement of old laboratory chairs, to improve working conditions in the laboratories, and the implementation of a fall detection sensor system in isolated areas of the IARC premises. In addition, the OHSC was involved in reviewing guidelines prepared by LSB for the reception of biological samples potentially contaminated with SARS-CoV-2, and was part of a working group on the prevention and treatment of psychosocial risks, as part of the Quality of Work Life initiative. The OHSC also organized first aid training for personnel, to complement the role of the IARC Safety Team and help create a safer working environment.

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 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 2022–2023 biennium was approved in May 2021 at a level of €45 371 329.

Participating States and Representatives at IARC Governing Council's Sixty-Second Session, 11–12 May 2020 (Held Remotely)

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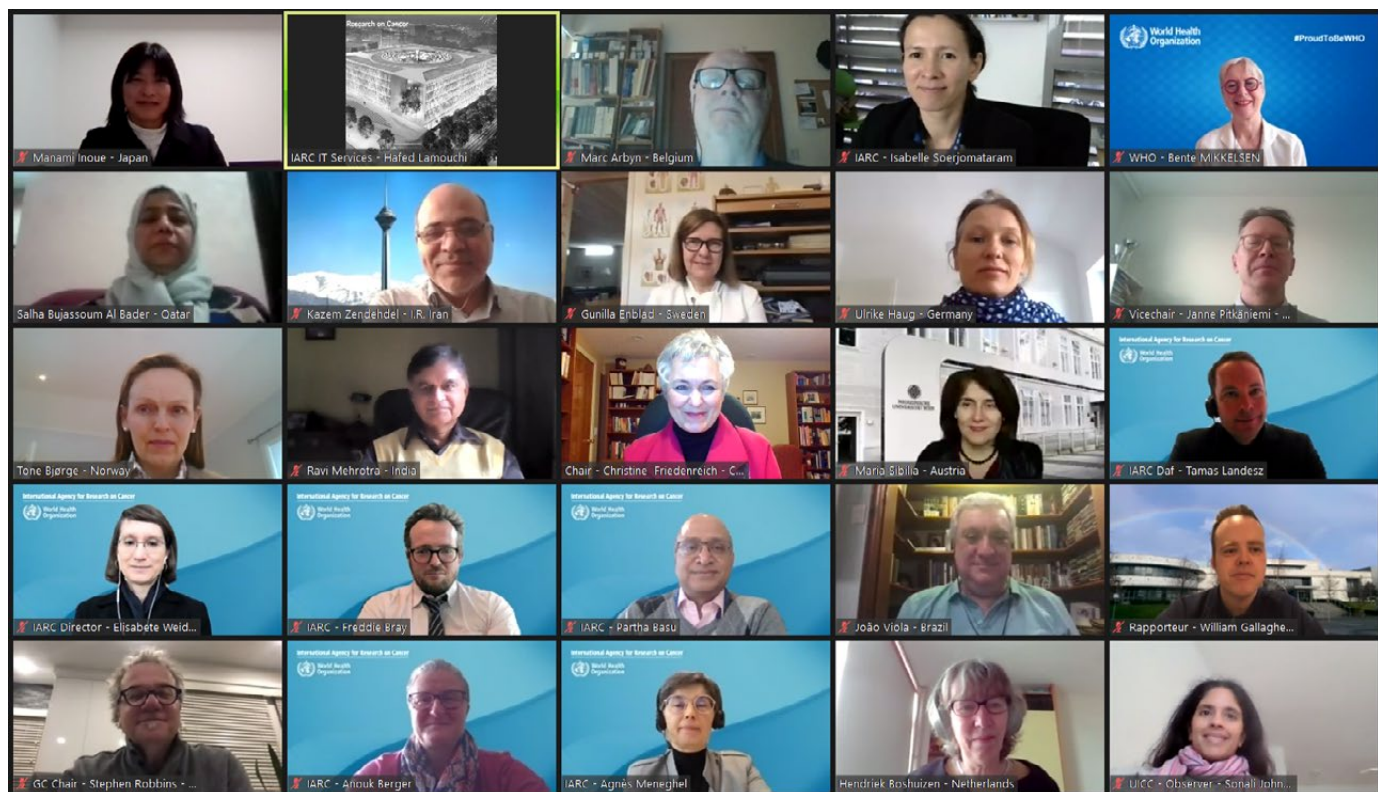
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As at 14 December 2021

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