Director's Report

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Scientific Council, 59th Session, *Lyon 8-10 February 2023, by Web conference*

International Agency for Research on Cancer

World Health Organization

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World Health Organization

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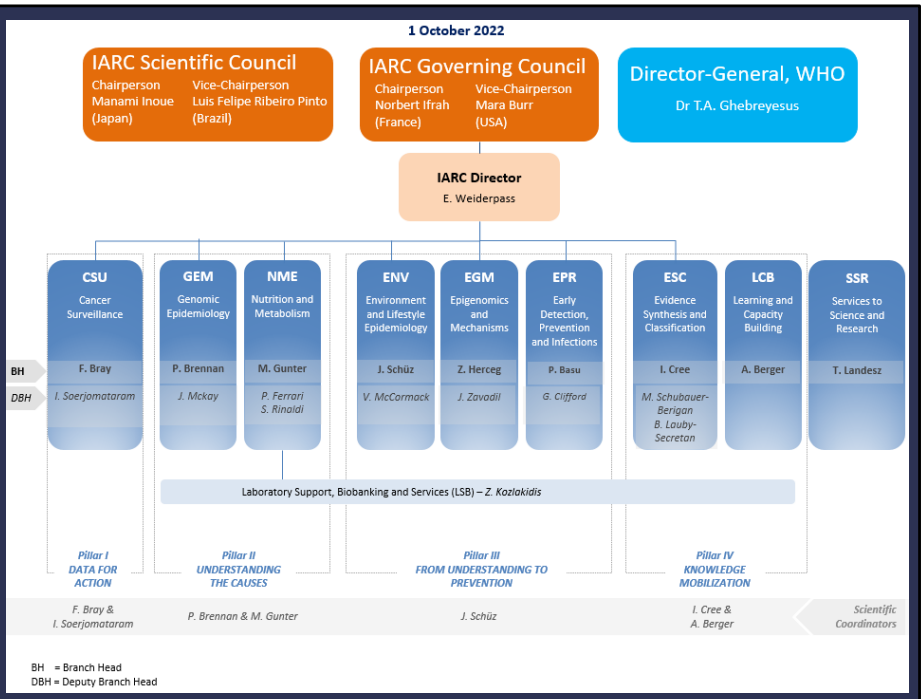
Death of Dr Paul Kleihues, IARC Director Emeritus

IARC expressed its deep regret at the death of Dr Kleihues in March 2022 at the age of 85, and its gratitude for his role in enhancing the reputation of the Agency, with major contributions to international collaboration, the consolidation of the WHO Classification of Tumours series and the initiation of the World Cancer Report series, during his directorship, from 1994 to 2003.

Death of Dr Peter Boyle, IARC Director

IARC expressed its deep regret at the death of Dr Peter Boyle in July 2022 at the age of 71 and its gratitude for his role in enhancing the reputation of the Agency during his directorship, from 2004 to 2008.

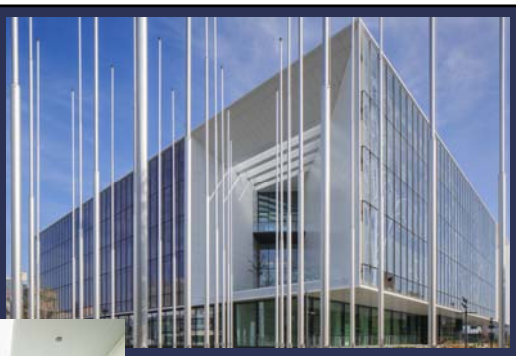
Introduction
Organigram as of 1 October 2022



The slide shows IARC organigram as of 1 October 2022
The four pillars reflect IARC's fundamental activities:
Pillar 1: data for action
Pillar 2: understanding the causes
Pillar 3: from understanding to prevention
Pillar 4: knowledge mobilization

IARC is moving to the

Nouveau Centre



Photographer: Kevin Buy

IARC is embarking in a new phase in its history: we are now moving in our new home, the Nouveau Centre.

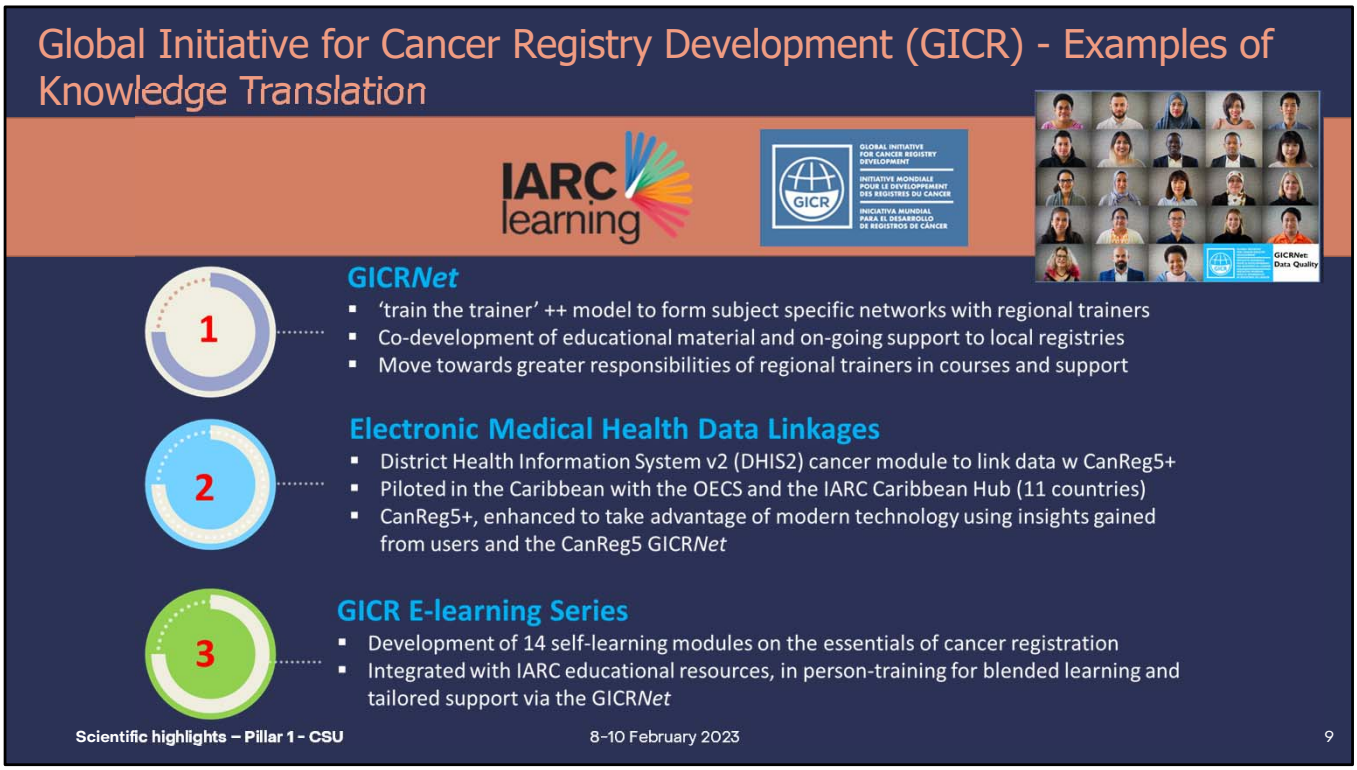
Scientific highlights

Cancer Surveillance

Pillar 1:

Data for action

The following slides present some scientific highlights for **Pillar 1: Data for action**, composed of the Cancer Surveillance (CSU) Branch.



The **Global Initiative for Cancer Registry Development** (GICR) programme has a focus action that will help develop greater capacity in cancer registration among low- and middle-income countries (LMICs). Working together with partners, the mechanisms to accelerate the uptake of cancer registration by sharing knowledge and creating local networks of support are being rolled out.

Established methods for **knowledge transfer** (KT) and professional learning are used as the basis for designing GICR training courses, reference material and modalities to reach previously underserved countries.

Three examples of KT:

- **GICRNet**

To expand the reach and sustain assistance for those who need it, the GICR has implemented new ways to deliver coordinated support for strengthening in-country cancer surveillance capacity. Networks of GICR*Net* trainers have been established covering five specific topics: CanReg5; Data quality; Coding and staging; Data analysis and Childhood cancer. To maintain the networks of already existing GICR*Net* trainers, periodic calls are held and relevant information transmitted to the group. Regional trainers are encouraged to contribute to the

development of new educational material, including translating standard presentations into other languages.

- **District Health Information System v2** (DHIS2)

Over the past decades, rapid technology advancements have offered the potential for leapfrog solutions in LMICs. Registries are often faced with pressures to demonstrate efficiencies and move away from paper-based methods. As a direct response to the technology challenge, we have launched, in collaboration with several key partners, the *Electronic Innovations in Cancer Registration* (*E-novate*) project. The aim of *E-novate* is to explore ways to share electronic data with PBCRs. A global tool is being created that supports data transfer between the *District Health Information Software 2* (DHIS2), the world's largest Health Management Information System (HIMS), and *CanReg5*, a free and open-sourced cancer registry software developed by IARC that is used worldwide. The potential uptake and benefit of the outputs of *E-novate* are expected to be far reaching, with considerable interest anticipated from Ministries of Health given its direct application to automated data collection for cancer, as a leading noncommunicable disease.

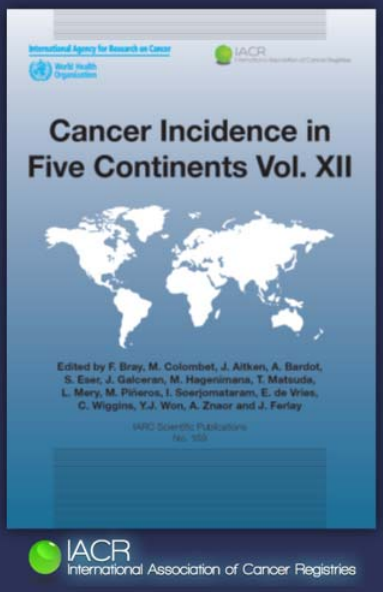
- **E-learning**

To increase opportunities for learning, a series of 15 e-learning modules covering all aspects of population-based cancer registration and use are being made available to all on a secured platform. The project was conceived to create a complete training course in cancer registration, which would permit a formal accreditation of cancer registrars through the GICR programme.

CI5-XII data submissions by region (September 2022)
(submissions relative to CI5-XI)

	Registries	Countries
Africa	30 (-)	18 (-3)
C&S America	41 (-4)	15 (+3)
N America	72 (-1)	3 (-)
Asia	389 (+207)	29 (+8)
Europe	133 (-10)	32 (+1)
Oceania	10 (+2)	4 (+2)
World	675 (+192)	101 (+11)

- Individual registry evaluation in process
- Book online in Spring 2023
- Basis for GLOBOCAN estimates



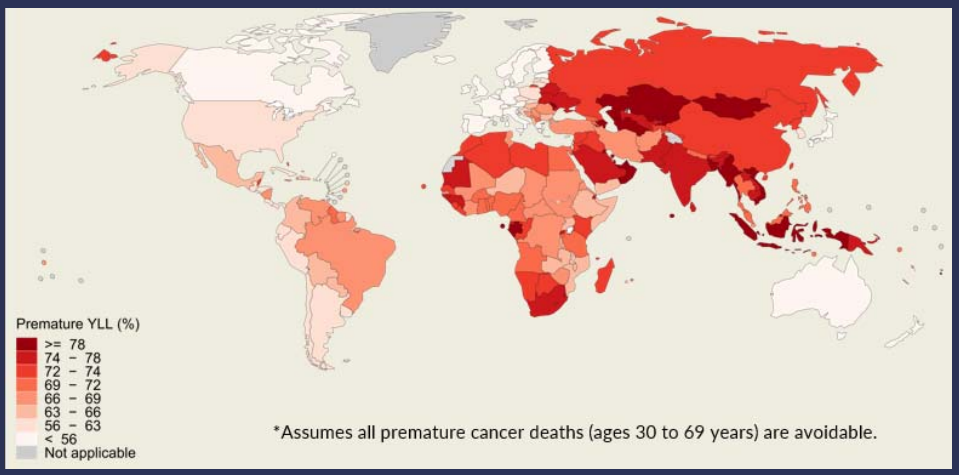
CI5-XII Editorial Board comprises: Joanne Aitken, Sultan Eser, Jaume Galceran, Marc Hagenimana, Tomohiro Matsuda, Esther de Vries, Young-Joo Won and Charles Wiggins (External Editors); Freddie Bray, Murielle Colombet, Aude Bardot, Les Mery, Marion Piñeros, Isabelle Soerjomataram, Ariana Znaor and Jacques Ferlay (+ Maria Fernan, IARC Secretariat)

The compilation of comparable quality-assured cancer incidence data across diverse registry populations worldwide is now in its 12th Volume. Cancer Incidence in Five Continents (CI5) is a flagship programme and publication from IARC, undertaken jointly with the IACR. While the underlying processes of collection and evaluation have remained relatively unchanged in 60 years, the CI5 project enables the direct engagement with individual registries, providing CSU with the necessary data to support our core programmes. In return, registries obtain a reliable and consistent evaluation of the quality of their submitted data; increasingly these reviews are linked to targeted support to specific registries in need of assistance, within the GICR programme.

How many cancer deaths are avoidable* through prevention and treatment?

- 5.3 million premature cancer deaths globally in 2020 (53% of all cancer deaths)
- 183 million avoidable Years of Life Lost (YLLs) in 2020 (69% of all YLLs)

- High income countries had low % of premature mortality
- Several LMICs had highest % of YLLs in premature age groups
- 124 million YLLs in 2020 were preventable (68% of all avoidable YLLs)
- 59 million YLLs were treatable (32% of all avoidable YLLs)



CSU continues to innovate in the provision of global cancer estimates to inform cancer prevention strategies. In this study, the proportion of cancer that can be avoided through primary, secondary and tertiary prevention is being estimated.

As a first step premature mortality as defined by the WHO is calculated, and the years of life lost that can be avoided is presented in the map.

Overall, we found that half of the global cancer deaths occurred prematurely, which represent 183 millions of life years lost that could have been avoided. The inequality across countries is evident within high income countries having much lower premature mortality and therefore reduced years of life lost, as indicated in the lightest color in the map.
In terms of priorities, most of the deaths can be prevented through primary prevention (68% of all avoidable life years lost) with the remaining 1/3 through improved access to high quality treatment.

Prevalence of childhood cancer survivors in Europe: developments in the Cancer Risk in Childhood Cancer Survivors (CRICCS) study

Objectives:

1. Estimating prevalence of childhood cancer survivors in Europe
2. Quantifying risk of second primary neoplasms (SPN) in survivors in Europe
3. Assessing determinants of risk of SPN
4. Recommendations for registries

Expected impact:

1. To quantify cancer burden in survivors
2. To support prevention and promote registry-based research

Funding: Children with Cancer UK

European estimates (work in progress):

- Using the existing data collected for the Automated Childhood Cancer Information System (ACCIS),[1] with cancer registry data available from 23 European countries
- Missing data on cancer incidence, cancer survival, and population mortality were estimated with models using data from other sources[2]

Results:

All childhood cancers survivors diagnosed at age 0–14 years[3]	10-year prevalence in 2011 No. (%)	Per million
Based on data collected from cancer registries		
23 European countries in ACCIS	83,202 (71%)	178
Including estimates based on data from UN databases		
Total WHO European region	117,068 (100%)	160
Eastern Europe	37,048 (31.7%)	127
Northern Europe and British Isles	17,254 (14.7%)	175
Southern Europe	27,596 (23.6%)	181
Western Europe	35,170 (30.0%)	187

Notes:
[1] Steliarova-Foucher E et al. Lancet Oncol. 2018;19(9):1159-69. [2] Human Mortality Database; UN inter-agency group for child mortality estimation; United Nations World Population Prospects; and WHO Mortality Database portal. [3] non-malignant tumours were excluded.

Scientific highlights – Pillar 1 - CSU 8-10 February 2023 12

Survivors of childhood cancer are exposed to a larger risk of a new cancer than the general population. The objectives of the Cancer Risk in Childhood Cancer Survivors study (CRICCS), supported by Children with Cancer UK, are to:

- Compute prevalence of childhood cancer survivors
- Estimate the risk of second cancers
- Determine the causes of this risk
- Develop guidelines for cancer registries

Reaching these objectives will help us to assess the cancer burden in survivors, support prevention, and promote registry-based research.

The preliminary results show prevalence of childhood cancer survivors in Europe, which were computed using data for 23 European countries, available in the database of the project Automated Childhood Cancer Information System. The overall 10-year limited duration prevalence in these countries was 178 per million in Europe in 2011.

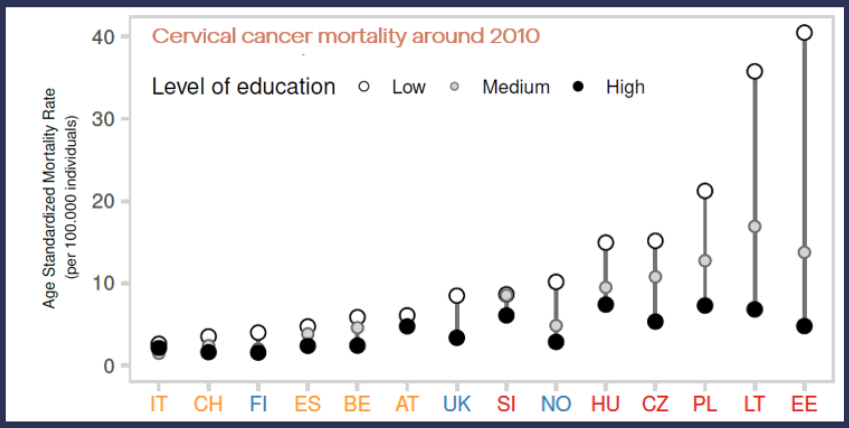
For other countries in the WHO European Region we used other data sources

and statistical models to estimate the required parameters. The 10-year prevalence of childhood cancer survivors in the whole WHO European region was 160 per million and varied from 127 in Eastern Europe to 187 in Western Europe.

Inequalities in cancer mortality between and within European countries

DEMETRIQ / LIFEPATH:

- A harmonized dataset on cancer mortality data by **education level.**
- Entire national population for **18 countries.**
- Census-based mortality follow-up studies



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CSU has sought to identify programmes of work prioritized in the **IARC Medium-Term Strategy** (MTS), including the "societal impact of cancer".

This study represents a collaboration between Erasmus MC and IARC through the DEMETRIQ and LIFEPATH projects, and involves a comprehensive comparative assessment of the magnitude and temporal trends of socioeconomic inequalities in cancer in Europe. Cancer-specific mortality data by socioeconomic status, as measured by educational level, were collected and harmonized across 18 countries in Europe and for multiple points in time over the period 1990-2015.

The variability in age-adjusted mortality from cervical cancer, as seen in the plot, is relatively narrow among higher-education groups, with much of the variability in between-country inequalities confined to differences among lower-education groups. This primarily reflects inequalities in the availability, access and uptake of effective screening programmes, which can detect and remove precancerous lesions and thus reduce incidence (the impact of HPV vaccination is not yet visible in the present data).

Scientific highlights

Genomic Epidemiology

Nutrition and Metabolism

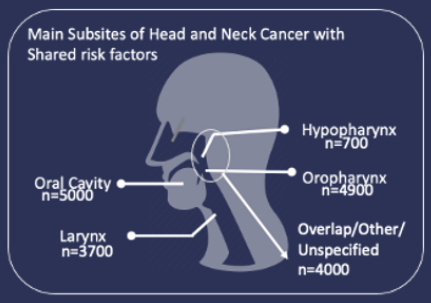
Laboratory support, Biobanking, and services

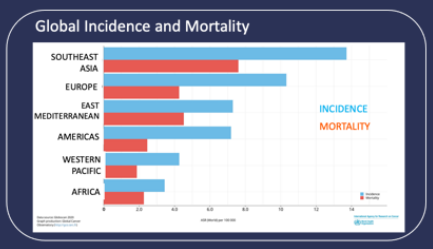
Pillar 2:

Understanding the causes

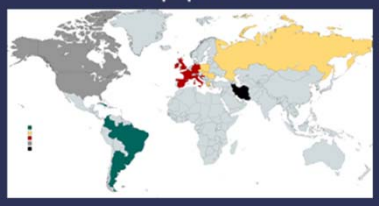
The following slides present some scientific highlights for **Pillar 2 – understanding the causes**, that includes the Genomic Epidemiology (GEM) Branch, the Nutrition and Metabolism (NME) Branch (under Review this year), and the Laboratory support, Biobanking and services (LSB).

Head and Neck cancer: Risk Susceptibility Loci across diverse populations using 18000 cases and 45000 controls

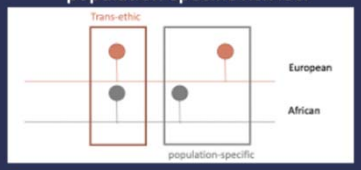




Genetic prediction tools (trait-associated genetic instruments, polygenic risk scores) require robust data from GWA studies across diverse populations



Natural variation in genetic architecture of diverse ancestries enables identification of trans-ethnic and population-specific risk loci



This is the largest GWAS on Head and Neck Cancer to date.

Contributions:

- incorporates newly generated and existing genetic data
- includes populations from 25 countries

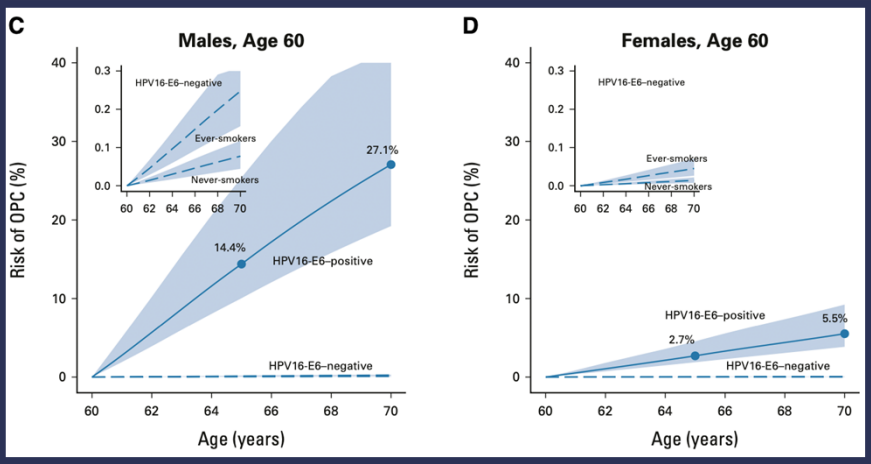
  Argentina, Brazil, Colombia, Cuba, Uruguay, Czech Republic, Poland, Russia, Greece, Romania, Slovakia, Hungary, Poland, Germany, France, UK, Ireland, Spain, Italy, Croatia, Canada, USA, Iran
- includes larynx, an understudied subsite

This is the largest GWAS study on head and neck cancer to date, including 18000 cases and 45000 controls. This large study includes populations from 25 countries, as reported in the slide. Main subsites of Head and Neck cancers include hypopharynx, oropharynx, oral cavity and larynx, an understudied subsite. This study incorporates newly generated and existing genetic data. Natural variation in genetic architecture of diverse ancestries enables identification of trans-ethnic and population-specific risk loci.

Absolute risk of oropharyngeal cancer following an HPV16-E6 test: Results from the HPV Cancer Cohort Consortium (HPVC3)

We estimated the 10-year risk of oropharyngeal cancer after a positive HPV16-E6 serology test as 27% for men and 6% for women at age 60. This warrants development of surveillance protocols.

HPVC3 includes 9 cohorts from the USA, Europe, and Australia and is coordinated by GEM.



Absolute Risk of Oropharyngeal Cancer After an HPV16-E6 Serology Test and Potential Implications for Screening: Results From the Human Papillomavirus Cancer Cohort Consortium

Robbins et al., *J Clin Oncol* 2022

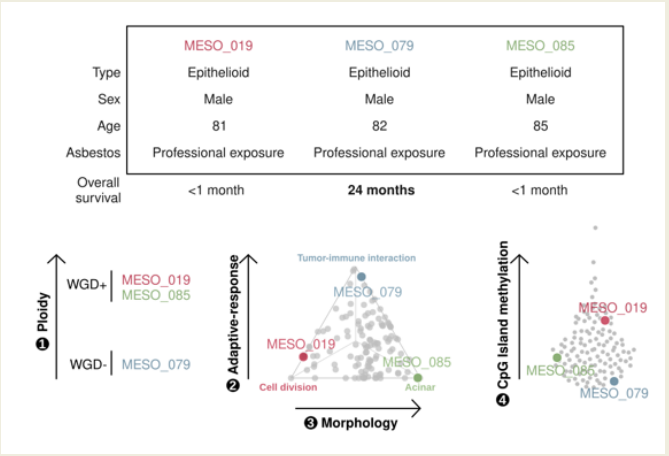
The absolute risk of oropharyngeal cancer was assessed following an HPV16-E6 serology test within the HPV Cancer Cohort Consortium (HPVC3), including 9 cohorts form the USA, Europe, and Australia coordinated by the GEM Branch. IARC scientists estimated the 10-year risk of oropharyngeal cancer after a positive HPV16-E6 serology test as 27% for men and 6% for women at age 60. This study underlines the need to develop surveillance protocols. Findings were published in 2022 in *J Clin Oncol*.

The MESOMICS project: uncovering the hidden inter-patient heterogeneity in malignant pleural mesothelioma

- Malignant Pleural Mesothelioma is a deadly disease with limited therapeutic options

Q: Why do patients with the same clinical characteristics have vastly **different tumour progressions**?

- We propose a **4-dimensional morpho-molecular classification** that explains most inter-patient differences



RARE CANCERS GENOMICS MESOMICS

Mangiante*, Alcala*, Sexton-Oates*, Di Genova* *et al*. Accepted *Nat Genet*

Scientific highlights – Pillar 2 - GEM 8-10 February 2023 17

MESOMICS is a project from the rare cancers genomics team of the GEM Branch, that aims to **uncover the hidden inter-patient heterogeneity in malignant pleural mesothelioma.**

Malignant Pleural Mesothelioma is a deadly disease with limited therapeutic options. The current IARC/WHO classification consists of three types, **but many patients with the same tumour type and**
the same clinical characteristics have vastly different tumour progressions.

As an illustration, on the top right, you can see a table presenting 3 patients from the MESOMICS cohort. The patients had the same age, sex, and the same professional exposure to asbestos, the main known carcinogen for mesothelioma. These patients also developed tumours that currently fall into the same category of the IARC/WHO Blue Books and would thus currently receive the same prognosis and treatment recommendation. Yet two of them had a very fast progression with less than 1 month survival while patient 79 experienced a slower tumour progression and survived for 2 years.

Can molecular data explain this hidden inter-patient heterogeneity?

The MESOMICS study proposes a novel classification system based on four dimensions combining morphological characteristics and molecular data.

On the bottom right, you can see that the 3 patients that had the same clinical characteristics actually have vastly different profiles based on this novel 4-dimensional classification.

Dimension 1 corresponds to the ploidy of the tumour cells and separates the longest survivor patient 79, who has a normal ploidy (WGD-), from the two short survivors which tumours underwent a whole genome duplication (WGD+).

Dimension 2 corresponds to the strength of the adaptive immune response, as measured by the amount of lymphocytes infiltrating the tumour; the longer survivor patient 79 here has the largest level of infiltration.

Dimension 3 corresponds to the cell morphology, which is correlated with the current IARC/WHO classification. Here interestingly, although the 3 patients fall into the same histological type, their molecular profiles indicate different morphologies, which shows that molecular data can provide more precise classifications.

Finally, dimension 4 corresponds to the level of DNA methylation in specific genomic locations called CpG islands, which has been shown to be associated with prognosis and used in molecular classifications in other cancers. Here the longer survivor patient 79 again stands out with a low methylation level.

To conclude, this novel classification allows a more accurate stratification of patients that could inform diagnosis and future treatments.

Mutational signatures in clear cell renal cell carcinoma from 11 countries

CANCER RESEARCH UK | GRAND CHALLENGE MUTOGRAPHS

964 renal cancer whole genomes (Fig 1)

3 main findings :

- **Aristolochic Acid signatures** present in all cases in Romania and majority in Serbia, largely absent elsewhere
- **A novel signature in Japan**, potentially linked to an unknown exposure (Fig 2)

Fig 1

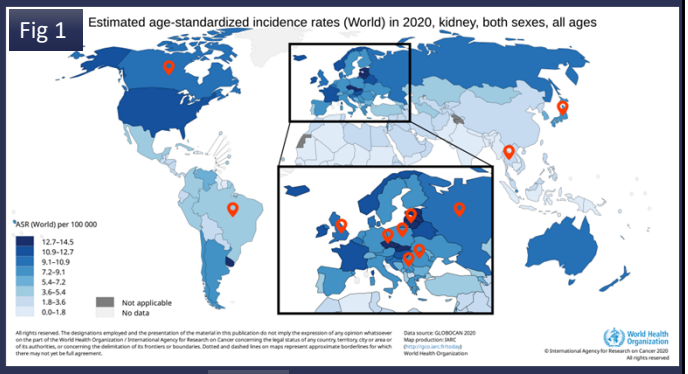
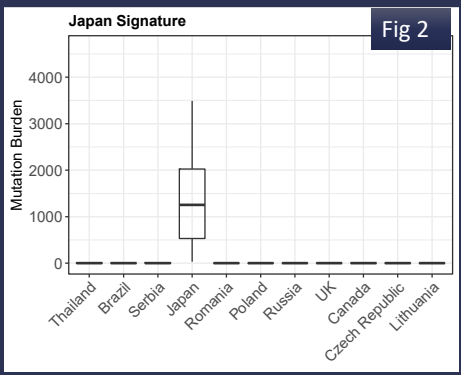
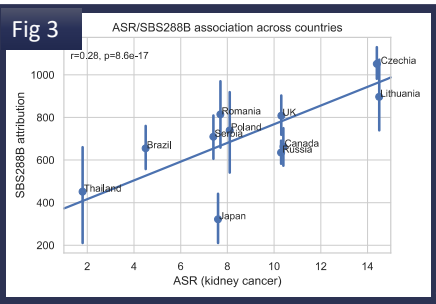


Fig 2



- **One signature** found to be significantly associated with renal cancer incidence (Fig 3)

Fig 3



Sergey Senkin, Paul Brennan on behalf of the Mutographs team

Scientific highlights – Pillar 2 – GEM

8-10 February 2023

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The Cancer Research UK Grand Challenge project **Mutographs** aims to identify mutation signatures for 5 different cancers, as well as large scale genome-wide and Mendelian randomization studies. This new study aimed to identify mutational signatures in clear cell carcinoma.

Scientists from the GEM Branch found that aristolochic acid are present in all cases in Romania and majority in Serbia, while largely absent elsewhere. A novel signature, potentially linked to an unknown exposure, was identified in Japan (Fig 2). One signature was found to be associated with renal cancer incidence, as shown in Fig 3.

PROMINENT: Discovering the molecular signatures of cancer PROMotion to INform prevENTion

Recently Awarded Cancer Grand Challenges grant **co-lead by Paul Brennan**, head of the **GEM Branch** at IARC.

9 partners from **6 institutions** in **4 countries** - France, US, Spain and Sweden.

The team received **a total of $25m** to take on the **Normal Phenotypes challenge** for **the next 5 years**.

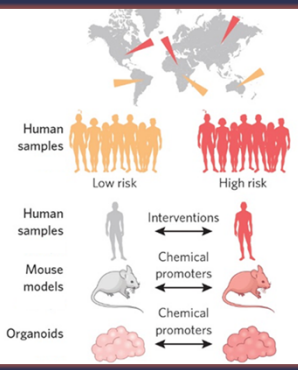
CANCER GRAND CHALLENGES

Team: PROMINENT

Funded by

CANCER RESEARCH UK | NIH NATIONAL CANCER INSTITUTE | asociación española contra el cáncer

Challenge: How can environmental, lifestyle or endogenous risk factors promote cancer through non-mutagenic processes across 8 cancer sites.



PROMINENT will analyse **normal tissue samples** to identify the main drivers and mechanisms of tumour promotion in:

- **>2,000 individuals** with different levels of exposure to **suspected promotors**
- **intervention studies** (chemotherapy, bariatric surgery, smoking cessation)
- sophisticated **mouse models**
- **human-derived organoids**

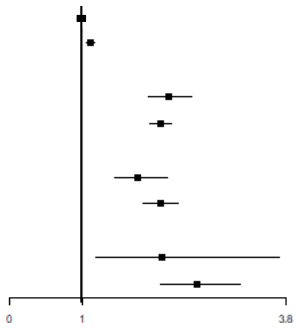
The recently awarded Grand Challenge study PROMINENT will explore molecular signatures of cancer promotion and how these can inform prevention. The objectives of this study are indicated in the slide.

Body mass index, cardiometabolic diseases, and cancer risk

- In a cohort study of electronic health records from Catalonia, Spain, we investigated among 1,774,904 individuals the joint associations of overweight/obesity (BMI ≥ 25 kg/m^2) and type 2 diabetes (T2D) and cardiovascular (CVD) diseases with obesity-related cancer risk.

- **Results suggest that individuals living with CVD or CVD & T2D may benefit most from weight management for reducing cancer risk.**

Group	n(at risk)	n(event)	HR (95%CI)
No comorbidity			
BMI <25kg/m2	606,249	12,861	Ref
BMI >=25m/kg2	1,168,655	25,221	1.11 (1.06-1.16)
T2D			
BMI <25kg/m2	10,345	262	2.18 (1.91-2.50)
BMI >=25m/kg2	54,655	1,257	2.07 (1.93-2.22)
CVD			
BMI <25kg/m2	17,056	310	1.76 (1.44-2.16)
BMI >=25m/kg2	39,517	830	2.07 (1.84-2.32)
CVD & T2D			
BMI <25kg/m2	1,206	20	2.09 (1.18-3.71)
BMI >=25m/kg2	5,091	104	2.57 (2.08-3.17)



Recalde M., Pistillo A., Fontvieille E., Duarte-Salles T., Freisling H. Under revision in *Nature Communications*.

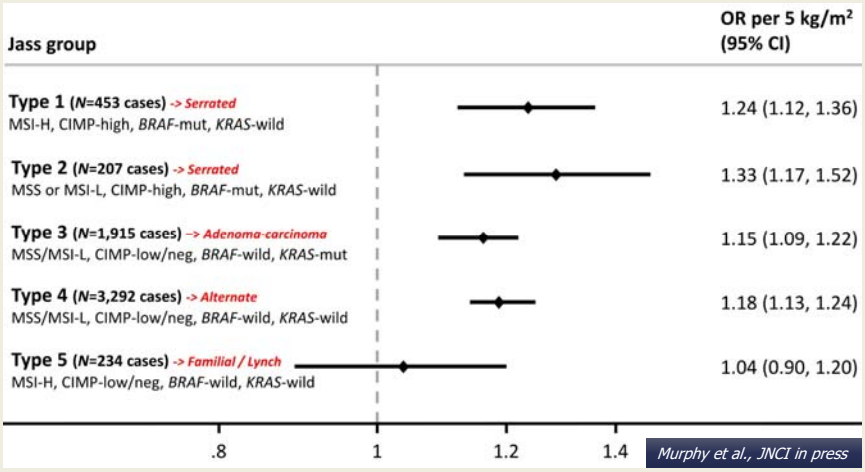
In a cohort study of electronic heath records from Catalonia, Pain, scientists from the NME Branch investigated among 1,774,904 individuals the joint associations of overweight/obesity (BMI ≥ 25 kg/m$^{2)}$ and type-2 diabetes (T2D) and cardiovascular diseases (CVD) with obesity-related cancer risk. As shown in the figure, they found higher HR associated with BMI, T2D, CVD, the stronger risk being found associated with CVD and T2D.

Results suggest that individuals living with CVD or CVD & T2D may benefit most from weight management for reducing cancer risk.

These findings are under revision in *Nature Communications*.

Body Mass Index and Molecular Subtypes of Colorectal Cancer

Pooled analysis of 11,872 cases and 11,013 controls from 11 observational studies that examined the associations between BMI and colorectal cancer by tumour molecular subtypes (Jass types)



Results suggest that obesity influences all major pathways of colorectal carcinogenesis with the exception of Jass type-5 (Lynch syndrome)

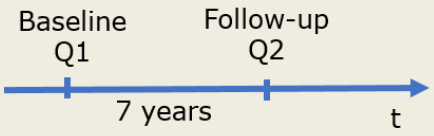
Obesity is an established risk factor for colorectal cancer (CRC); but the evidence for the association is inconsistent across molecular subtypes of the disease.

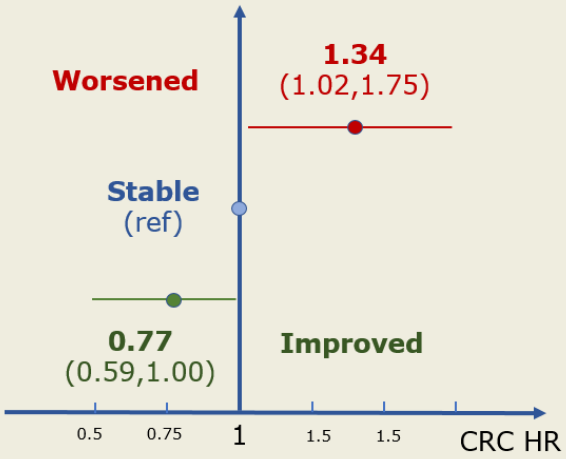
We pooled data on BMI, tumour microsatellite instability (MSI) status, CpG island methylator phenotype (CIMP) status, *BRAF* and *KRAS* mutations for 11,872 CRC cases and 11,013 controls to examine associations between BMI and CRC by tumour molecular subtypes (Jass types).

In contrast to previous reports with fewer study participants, we found limited evidence of heterogeneity for the association between BMI and CRC risk according to molecular subtype, suggesting that obesity influences nearly all major pathways involved in colorectal carcinogenesis. The null association observed for the Jass type 5 suggests that BMI is not a risk factor for the development of CRC for individuals with Lynch syndrome.

Lifestyle changes and colorectal cancer risk

- Modifiable factors assessed at baseline and during follow-up (7 years later)
- Change in the adherence to a Healthy Lifestyle Index (HLI) score: smoking, alcohol, obesity and physical activity
- Related to colorectal cancer (CRC) risk (n_{cases}=2,800) in the EPIC study (n=300k participants)
- These results **support recommendations for healthy lifestyle changes and healthy lifestyle maintenance for CRC prevention**





Botteri E., …, Ferrari P. *American J Gastroenterology*, 2022

Scientific highlights – Pillar 2 - NME 8-10 February 2023 22

The impact of changing lifestyle habits on the risk of developing colorectal cancer (CRC) was investigated in the EPIC study.

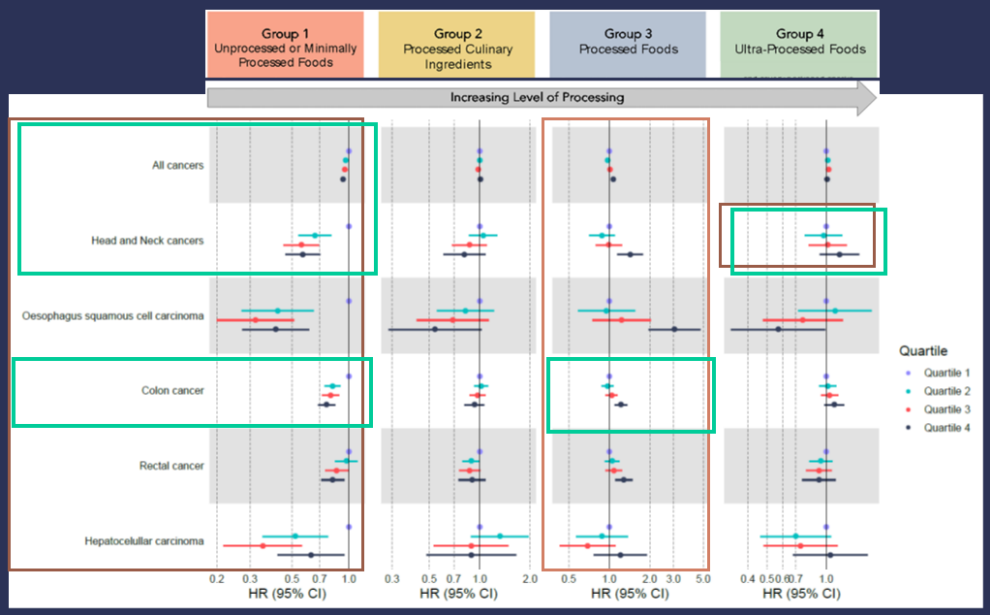
Baseline and follow-up questionnaire data, taken on average 7 years apart, were used.

A healthy lifestyle index (HLI) score based on smoking status, alcohol consumption, body mass index and physical activity was calculated and compared (among 300,000 participants, whom 2,799 colorectal cancer cases).

Compared to participants who did not change lifestyle habits between follow-up and baseline, participants who improved them had a lower risk of developing CRC, and participants who worsened them had higher CRC risk.

These results support recommendations for healthy lifestyle changes and healthy lifestyle maintenance for CRC prevention.

Food processing and cancer risk in EPIC



Conclusion:

Higher consumption of **(ultra-)processed foods** was associated with higher risk of several cancers. Consumption of **fresh foods** was inversely related with cancer risk.

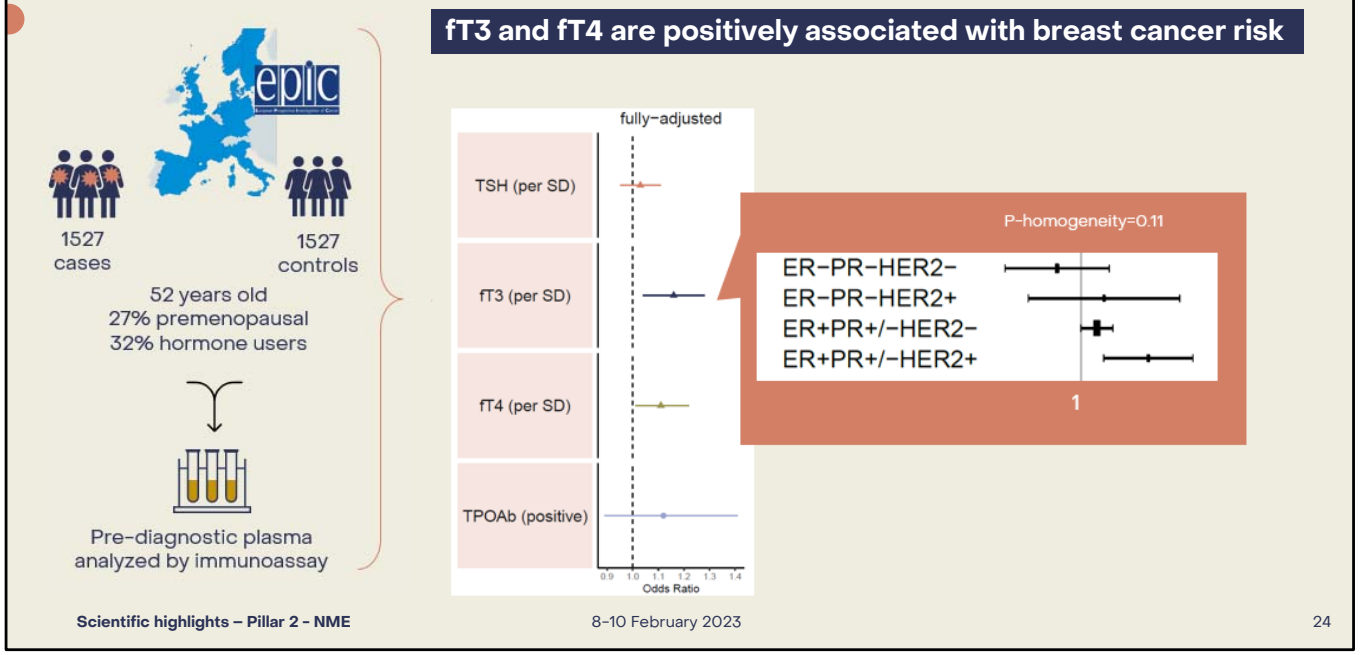
Model 1 is adjusted for sex, smoking, education, physical activity, height and diabetes.

Model 2 is further adjusted for dietary intake and quality, alcohol intake and body size factors.

Scientific highlights – Pillar 2 – NME 8-10 February 2023 **Kliemann et al. (*under review*)** 23

This study conducted by NME investigated the association between food processing and cancer risk in the European Prospective Investigation into Cancer and nutrition (EPIC) study. Based on two different models (as indicated in the slide), they found that higher consumption of processed foods is associated with increased risk of several cancers (head and neck, oesophagus squamous cell carcinoma, colon, rectal), while consumption of fresh foods was associated with lower risk of cancer.
These findings are *under review*.

Circulating thyroid hormones and breast cancer risk



A nested case control study was carried out in the EPIC cohort to investigate the associations between circulating levels of thyroid stimulating hormone TSH, free triiodothyronine fT3, free thyroxine fT4, and antibodies anti-peroxidase (antiTPO) antibodies and breast cancer risk.

1527 women diagnosed with primary invasive breast cancer during follow-up, at least 2 years after blood collection and on average 8 yeas after, were included as cases.

For each case, a control participant free of cancer was matched on age, centre, fasting status, time at blood donation, exogenous hormone use, menopausal status, and in pre-menopausal women, phase of menstrual cycle.

Women were on average 52 years old, 27% were premenopausal at blood collection, and 32% were hormones users.

Thyroid biomarkers were measured on plasma samples from cases and controls using validated immunoassays, at IARC.

We observed a positive association between fT3 and fT4 and breast cancer risk, but no significant associations with TSH nor anti-TPO antibodies. Results are from models adjusted for known breast cancer risk factors.

More specifically, regarding fT3, associations were significant only in ER-positive tumours.

Odds ratio (OR) were also greater in women not-using hormones (p-homogeneity=0.08), and those diagnosed more than 8 years after blood collection (p-homogeneity=0.08). For fT4, no heterogeneity was observed.

We plan to evaluate correlations between thyroid hormones and other biomarkers which have been linked to breast cancer risk.

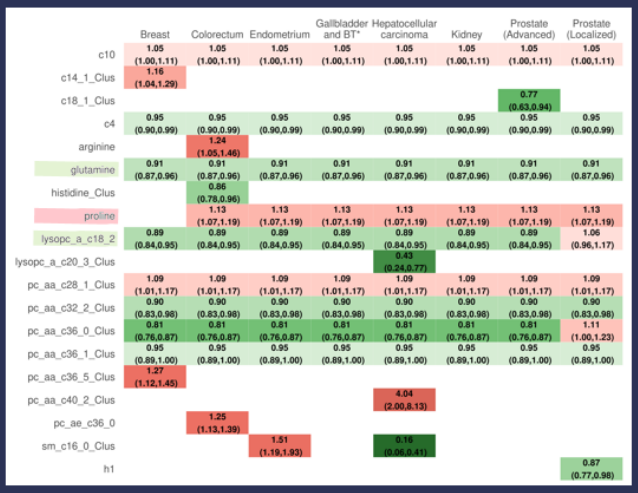
This is the largest study on this topic so far. Confirming these associations is important as they could potentially impact screening strategies for women diagnosed with thyroid disorders.

Pan-cancer analysis of pre-diagnostic metabolite blood levels in EPIC

- New machine learning method (data shared lasso)
- Targeted metabolomics studies of **8 cancer types** in EPIC to assess potential common pathways

- Several type-specific associations
- But also **9 metabolites with consistent associations across most cancer types**, including
  - glutamine, lysoPC a C18:2 (inverse)
  - proline (positive)

- Suggestive of **shared metabolic pathways** involved in cancer development across multiple cancer types



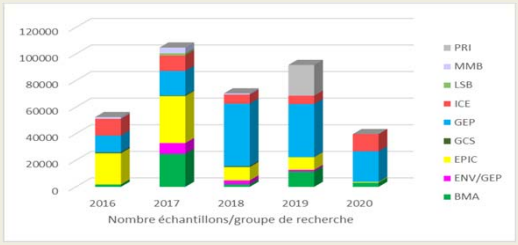
Breeur et al., 2022, *BMC Med*

A new machine learning method was applied to perform a pan-cancer analysis of pre-diagnostic metabolite blood levels in the EPIC cohort.
It used pooled data from targeted metabolomics studies of 8 cancer types to assess potential common pathways.
Several type-specific associations were observed, but this analysis also identified 9 metabolites with consistent associations across the studied cancers. For example, consistent inverse associations were observed for both glutamine and lyso-phosphatidylcholine a C18:2, whereas a consistent positive association with proline was observed.
Overall, these results suggested that shared metabolic pathways might be involved in cancer development across multiple cancer types.

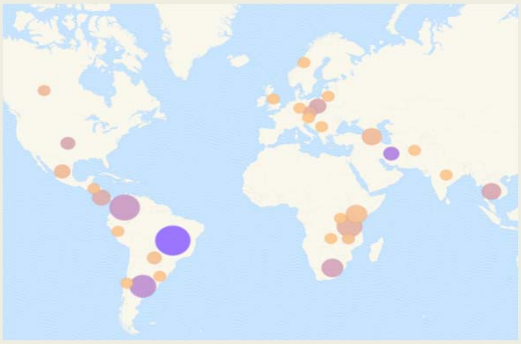
Laboratory Services and Biobank

The LSB unit operates a Sample Management System (SAMI) developed in-house and launched in 2010.

- SAMI2.0 based on Oracle APEX was launched in 2019.
- The Physical storage needs were addressed in 2021 ahead of the move to the Nouveau Centre.
- The data storage needs and data centralization remain outstanding and will be the next area of focus.



IARC importation of biological samples (2016-2020), Distribution per group (above) and by geography (below)



Total number of samples registered:	6,030,521
Total number of sample movements:	1,810,389
Total number of projects registered:	392
Total number of providing countries:	87

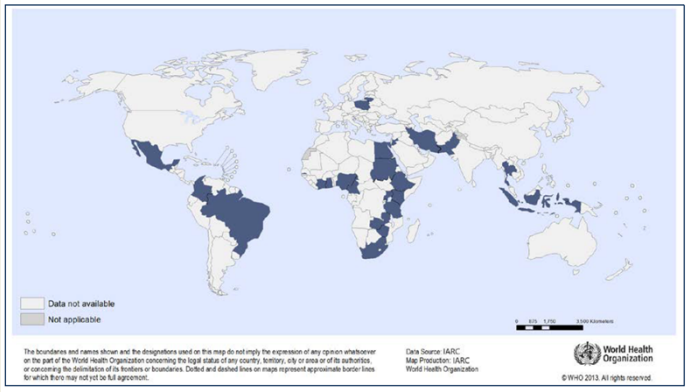
These graphs demonstrate that the IARC LSB interacts with most research Branches (though there can be significant variation year on year depending on specific project needs); and it receives (and sends) biological samples for research purposes from many countries globally (received samples from 87 countries in the last 5 years).

There has been a significant investment on the laboratory equipment ahead of the move to the Nouveau Centre; the next step would be to centralize and focus on the data needs, linking to existing efforts by ITS at the Agency.

The total number of samples currently in the IARC biobank is just over 6m; about 2m of these have been accessed for research (as most original samples have resulted to remainder samples, the total number is not affected by the use).

IARC BCNet members

- Institutional membership
- Commit to conduct collaborative studies in areas of common interest
- Agree to share expertise
- Develop common standards/protocols for LMICs
- When possible, will host other members and collaborators for training
- **24 countries, 39 institutions**



BRAZIL: Banco de Células do Rio de Janeiro; Barretos Cancer Hospital; Instituto do Câncer do Estado de São Paulo/Fundação Faculdade de Medicina CAMEROON: Faculty of Medicine and Biomedical Sciences, Université de Yaoundé; Université des Montagnes; COLOMBIA: Clinica de la Costa Ltda; CÔTE D'IVOIRE: Institut Pasteur de Côte d'Ivoire; EGYPT: Aswan University; Children's Cancer Hospital Egypt – 57357; Faculty of Medicine, Cairo University; Integrated Biobank of Mansoura, School of Medicine, Mansoura University; Medical Research Institute, Ain Shams University; Medical Research Institute, Alexandria University; National Cancer Institute; National Liver Institute; Shifaa Al Orman Hospital, Luxor; South Egypt Cancer Institute, Assiut University; ETHIOPIA: Jigjiga University; GHANA: Breast Care International, University of Health and Allied Sciences; INDONESIA: Faculty of Medicine, Universitas Gadjah Mada; IRAN: Golestan Cancer Biobank; JORDAN: King Hussein Cancer Center Biobank; KENYA: Ampath Reference Laboratory; Maseno University; LITHUANIA: National Cancer Institute; MEXICO: Instituto Nacional de Cancerología; NIGERIA: College of Medicine, University of Ibadan; Irrua Specialist Teaching Hospital; Obafemi Awolowo University Teaching Hospitals Complex; PAKISTAN: Liaquat University of Medical Health and Sciences; Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC); POLAND: Biobank Lab, Department of Molecular Biophysics, University of Lodz; Wrocław Research Centre EIT+ Biobank; SOUTH AFRICA: National Health Laboratory Service (NHLS), NHLS/Stellenbosch University Biobank; SUDAN: Institute of Endemic Diseases (IEND), University of Khartoum; Radio-Isotope Centre Khartoum; THAILAND: National Cancer Institute; THE GAMBIA: Medical Research Council (MRC) The Gambia Unit; MRC International Nutrition Group; UGANDA: Makerere University College of Health Sciences; UNITED REPUBLIC OF TANZANIA: Kilimanjaro Clinical Research Institute; ZAMBIA: Centre for Infectious Disease Research in Zambia; ZIMBABWE: African Institute of Biomedical Science & Technology; University of Zimbabwe College of Health Sciences.

To address the under-representation of biological resources in international research that come from low- and middle-income countries, the LMICs Biobank and Cohort building network (**BCNet; https://bcnet.iarc.fr/**) was established by IARC in 2013. Currently, 39 institutions from 24 countries are members of BCNet. During the last year, BCNet continued to provide information, expertise and to deliver presentations and training workshops to external collaborators (indicatively: Kenya, Indonesia, Philippines, AORTIC conference, etc.).

BCNet actions are funded by the Center for Global Health, National Cancer Institute, NIH, USA.

Focus on cancer in Sub-Saharan Africa – Lancet Oncology Commission

- The Lancet Oncology Commission summarized the current state of the art in Sub-Saharan Africa and listed a number of priorities.
- These are divided in first and second tier priorities.
- A timeline was put forward for their completion.

Ngwa W., et al. *The Lancet Oncology*, 23(6):e251-e312, 2022

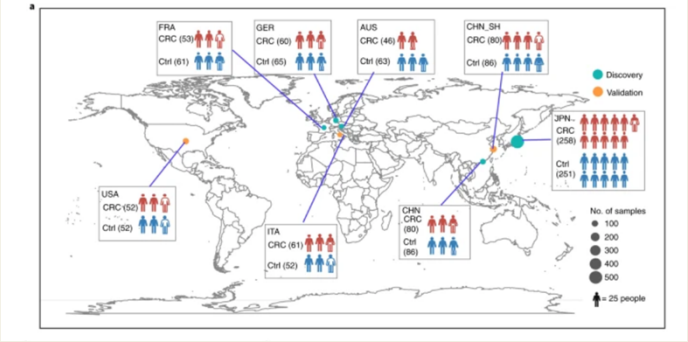
	Target	Timeline to be achieved by
First tier priorities		
1	Implementation of *The Lancet's* Commission for Global Pain and Palliative Care basic package[161] and the American Society of Clinical Oncology's resource-stratified guidelines[162]	2023
2	Implementation of model palliative care services[161] to improve the quality of life of patients with cancer and their families	2023
3	Palliative care research—patient-reported outcomes and descriptive studies	2023
4	Explicit integration of palliative and urgent radiotherapy	2024
5	Core palliative care competencies for all health systems staff	2024
6	Telephone-based mHealth and telehealth support	2025
7	Basic electronic medical records	2025
Second tier priorities		
1	Implementation of *The Lancet's* Commission for Global Pain and Palliative Care enhanced package[161] and the American Society of Clinical Oncology's standard palliative guidelines[162]	2030
2	Action plans for stereotactic palliative radiotherapy services	2035
3	Palliative care research—clinical trials	2035

Table 6: **Key targets for implementation of community-based palliative oncology in sub-Saharan Africa**

In sub-Saharan Africa (SSA), urgent action is needed to curb a growing crisis in cancer incidence and mortality.
The Commission details the state of cancer in SSA, recommends key actions on the basis of analysis, and highlights case studies and successful models that can be emulated, adapted, or improved across the region to reduce the growing cancer crises.
Recommended actions begin with the need to develop or update national cancer control plans in each country. Plans must include childhood cancer plans, managing comorbidities such as HIV and malnutrition, a reliable and predictable supply of medication, and the provision of psychosocial, supportive, and palliative care.
More substantial investment is needed in developing cancer registries and cancer diagnostics for core cancer tests.

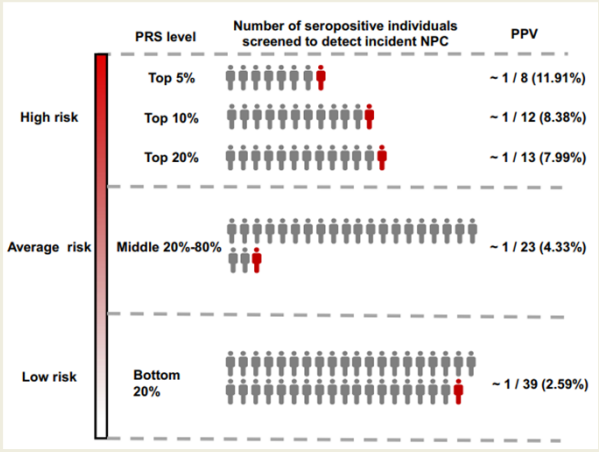
Leveraging existing cohorts for large-scale research

Fig. 1: Overview of the patient populations with CRC included in this study and their associated gut microbiome compositions.



- Multi-kingdom microbiota analyses identify bacterial–fungal interactions and biomarkers of colorectal cancer across cohorts

Liu, Ning-Ning, et al., *Nature microbiology,* 2022



- A polygenic risk score for nasopharyngeal carcinoma shows potential for risk stratification and personalized screening

He, YQ, et al. *Nature communications,* 2022

Leveraging existing cohorts for large-scale research: two studies have been published in 2022, as described below:

First study (Liu NN, et al.): findings uncovered colorectal cancer (CRC)-associated microbiota common across cohorts and demonstrate the applicability of multi-kingdom and functional markers as CRC diagnostic tools and, potentially, as therapeutic targets for the treatment of CRC.

Second study (He YQ, et al.): Impact of polygenic risk score on positive prediction value of EBV serological test for NPC. The numbers of seropositive individuals screened (colored gray and red) relative to the numbers of individuals receiving a benefit from the more thorough clinical assessments (colored red) are shown by the PRS subgroups (top 5th percentile, top decile, top quintile, middle three quintiles and bottom quintile of polygenic risk score). PRS polygenic risk score; PPV predictive prediction value.

Polygenic risk scores (PRS) have the potential to identify individuals at risk of diseases, optimizing treatment, and predicting survival outcomes. In this manuscript, we constructed and validated a genome-wide association study (GWAS) derived PRS for nasopharyngeal carcinoma (NPC), using a multi-center study of six populations (6059 NPC cases and 7582 controls), and evaluate its utility in a nested case-control study. In

summary, the GWAS-derived PRS, in combination with the EBV test, significantly improves NPC risk stratification and informs personalized screening.

Impact of COVID-19 on Cancer (IMCOCA) – focus on guidelines

- Guidelines established recommendations on triage, cancer care organization, and recommendations for specific age groups and by speciality early on (within a few weeks of the pandemic declared).
- Guidelines were not followed due to epistemological and ethical issues, including the lack of sufficient evidence, inadaptation to local resources, and different interpretations across the healthcare spectrum.
- Early evidence on impact shows delays in diagnostic procedures as well as some early evidence on negative impact on disease progression.

Table 1
Triage related guidelines.

Theme	Guidelines	Discussion
Diagnostics/ screening	Delayed or stopped during first crisis period and immediately following it; triage of early stage or biopsies for those with a low index of suspicion for cancer outside of the hospital.	During the post-lockdown period, the same triage guidelines were followed to deal with backlogs. A large amount of discussion exists about the effects of postponing screening but there is little data to support its impact at the current time.
Surgery	Recommended to be postponed	Delaying surgery caused

Table 2
Challenges with guidelines and lessons learned.

Challenges with guidelines	Lessons learned
Large number of guidelines published	Need to disseminate information from high-level organizations down to area-specific advice to ensure that there are no disparities in implementation.
Guidelines not fully comprehensive/ gaps	Training for specific groups; recommendations needed in pharmacy and dentistry; evaluations of guidelines by clinicians needed to better understand gaps.

PROJETS STRUCTURANTS
IMCOCA
Impact COVID Cancer

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

CLARA CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES

Bogaert B., Buisson V., Kozlakidis Z., & Saintigny P. *Critical Reviews in Oncology/Hematology*, 2022

This is a keystone study (projet structurant) funded by CLARA and in collaboration with the Centre Léon Bérard (CLB), investigating the impact of COVID-19 on cancer.
A large number of guidelines issued in English and pre-vaccine availability (n=175) were systematically reviewed, together with any evidence that they were followed and how well.
The study is currently ongoing to understand how this might have changed post-vaccine availability – as well as comparing the response to French regulations vs response to regulations in the francophone countries (utilizing the BCNet for the latter aspect).

Scientific highlights

Environment and Lifestyle Epidemiology

Epigenomic and Mechanisms

Early Detection, Prevention and Infections

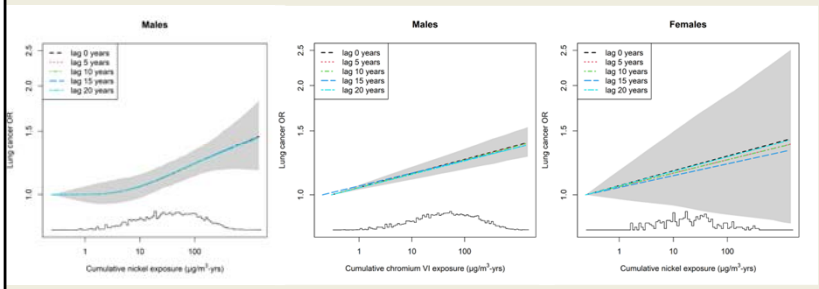
Pillar 3:

From understanding to prevention

The following slides present some scientific highlights for **Pillar 3 – from understanding to prevention**, that includes the Environment and Lifestyle Epidemiology (ENV) Branch, the Epigenomics and Mechanisms (EGM) Branch, and the Early Detection, Prevention and Infections (EPR) Branch.

Occupational exposure to chromium VI and nickel and lung cancer risk: results from a pooled analysis of case-control studies (SYNERGY)

- Chromium VI and nickel are known lung carcinogens but further characterization of the risk is useful
- The joint effect of smoking and chromium and nickel generally exceeded additivity



Worldwide **110 million workers** occasionally exposed to welding fumes

Scientific highlights – Pillar 3 - ENV 8-10 February 2023 32

The SYNERGY study is a pooled analysis of 14 case-control studies conducted in Europe and Canada including 17,000 lung cancer cases and 21,000 controls with information on lifetime occupational- and smoking histories. Chromium VI and nickel are known lung carcinogens but to further characterize the risk is important. Longer exposure duration and higher cumulative exposure were associated with increased risks, and the risk was present across smoking group strata. The joint effect of smoking and chromium or nickel generally exceeded additivity.

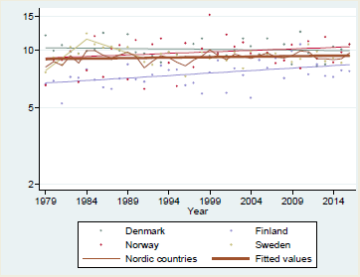
In the recent IARC Monographs on welding, volume 118, the working group estimated that 110 million workers around the world are occasionally exposed to welding fumes, and thereby most often chromium and nickel.

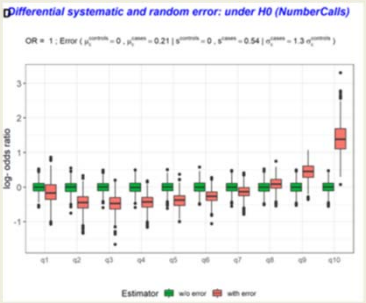
Results from the ENV research programme on radiofrequency electromagnetic fields and brain tumours

GliMoRi: Observed incidence rates of glioma in men in the Nordic countries are not compatible with mobile phone use-related increased glioma risks observed in some case-control studies, suggesting the latter are affected by bias (Deltour et al., *Environ Int*, 2022)

INTER-Cal: Modelling reporting errors from studies evaluating self-reported mobile phone use add evidence that the finding of an association between heavy mobile phone use and glioma risk of the Interphone study is caused by those reporting errors (Bouaoun et al., *under review*)

UK Million Women Study: In 800,000 British women followed for 14 years, daily mobile phone use or long term ever mobile phone use were not related to an increased risk of any type of brain tumour (Schüz et al., *J Natl Cancer Inst*, 2022)





Scientific highlights – Pillar 3 - ENV 8-10 February 2023 33

The **GliMoRi study** funded by the German Radiation Protection Office compared observed incidence rates of glioma in men in Denmark, Finland, Norway and Sweden with projected incidence rates if mobile phone use-related increased glioma risks observed in some case-control studies were true. Results show that the projections are incompatible with reality, strengthening the evidence that selection and recall bias have produced the findings in the case-control studies. When comparing with hypothetical scenarios, any risk increase of over 10% can be ruled out. Study was published recently in Environment International under the lead of ENV by Isabelle Deltour.

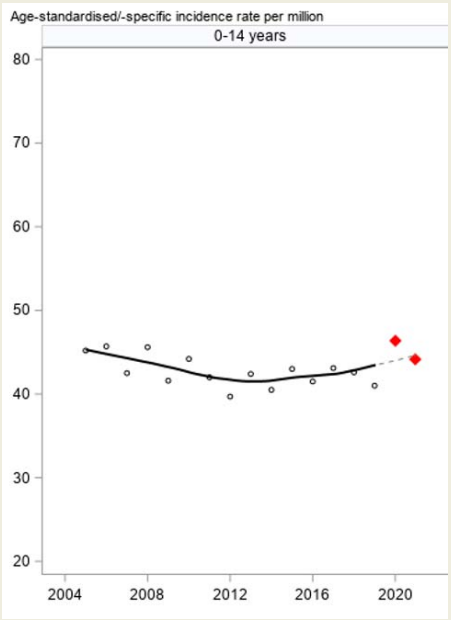
The **Inter-cal study** used data from validation surveys of the former Interphone study on mobile phone use and brain tumour risk, comparing traffic records from mobile phone operators with self-reported mobile phone use by brain tumour patients and their controls. If the reporting error observed in those surveys is applied to a hypothetical dataset of no association between mobile phones and glioma, it spuriously creates a J-shaped relationship of an association with an increased risk in the few percent of heavy users. This strongly adds to the evidence that the finding of association in heavy mobile phone users in Interphone is an artifact and not causal. The project was supported by ANSES and the publication under lead of ENV by Liacine Bouaoun was under review when this slide was prepared.

In the large-scale prospective cohort study called **UK Million Women Study** following 800,000 women for 14 years, no association was observed between daily mobile phone use or mobile phone use for more than 10 years and any type of brain tumour. There was also no association with temporal tumours whose location is the most exposed. This adds strong evidence that ordinary mobile phone use is not related to an increased brain tumour risk. The study did not include many heavy users as the cohort was only women of higher ages, but among them there was also no indication of risk. The findings were published in the Journal of the National Cancer Institute by Joachim Schüz and collaborators from University of Oxford.

Childhood leukaemia incidence in Germany during the Covid-19 pandemic

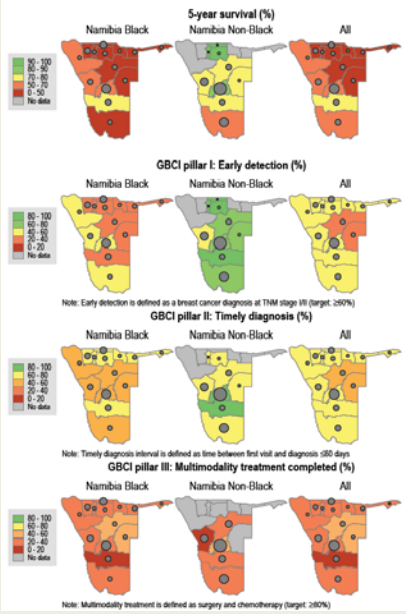
- Abrupt largest increase ever in all types of childhood cancer in Germany in 2020, suggesting increased awareness and faster referral
- Drop of incidence in 2021, for some cancer types but no leukaemia below the rates before the pandemic
- If hypothesis on lack of immunological training in early life for leukaemia should hold true, then the lockdown of childcare facilities may lead to an estimated increase of acute lymphoblastic leukaemia by 6-7%.

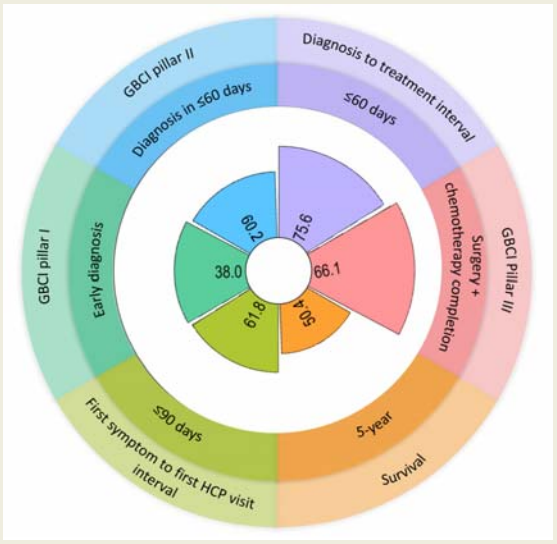
Erdmann et al., *Lancet Regional Health*, 2022; Schüz et al., *Int J Cancer*, 2022



After publication of anecdotal reports from some countries that, during the pandemic, fewer chilhdhood cancers were diagnosed due to unavailabilities of diagnostic facilities, this was systematically investigated in the 12 million 0-14 year old children in Germany using the nationwide German Childhood Cancer Registry operating since the 1980s. An increase as high as never seen before that started abruptly was observed for 2020, with 8-12% increase depending on cancer type, including about 10% for leukaemia. In 2021, there was a regression effect with the incidence dropping below the rates of before the pandemic for some cancer sites; for leukaemia there was also a drop but rates remained slightly higher than before the pandemic. Higher awareness among parents and family doctors with fast referral to specialized clinics is the most likely explanation, but for leukaemia there is the possibility of a true increase related to the lockdown measures. If hypothesis on lack of immunological training in early life should be true, it is estimated this would cause a 6-7% increase in acute lymphoblastic leukaemia in Germany. Results were published in *Lancet Regional Health Europe* and *International Journal of Cancer*.

ABC-DO input to WHO's Global Breast Cancer Initiative





Scientific highlights – Pillar 3 - ENV 8-10 February 2023 Boucheron et al. (*submitted*) 35

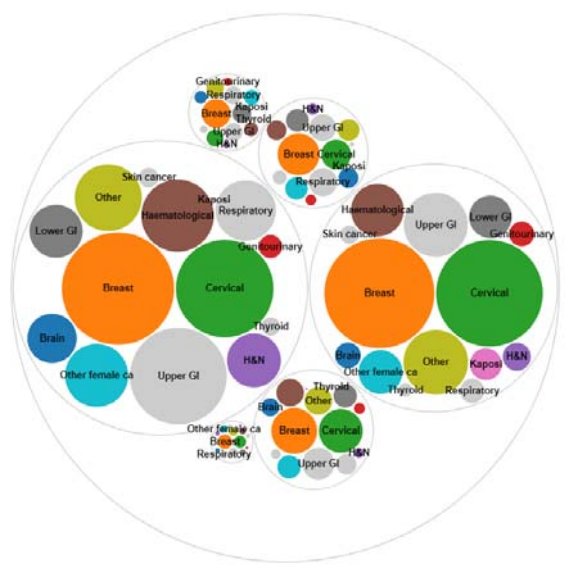
The African Breast Cancer Disparities in Outcomes (**ABC-DO**) cohort is an IARC-led breast cancer cohort of over 2200 women across five sub-Saharan African countries. This cohort has uniquely been actively followed for over 8 years now and has led to unique insights into the breast cancer burden, the impact of HIV on survival, and quantification of how to improve breast cancer survival. In the current analytical phase of the cohort, it is now being used to inform the WHO's Global Breast Cancer Initiative. We are evaluating whether key performance indicators for the three pillars of the Initiative can be measured and easily reported upon. The maps and radial bar-chart illustrate an example of work in progress towards these targets for Namibia, identifying priorities areas for interventions across the breast cancer journey.

The publication status of the submission will be updated during the SC.

Maternal orphans due to cancer

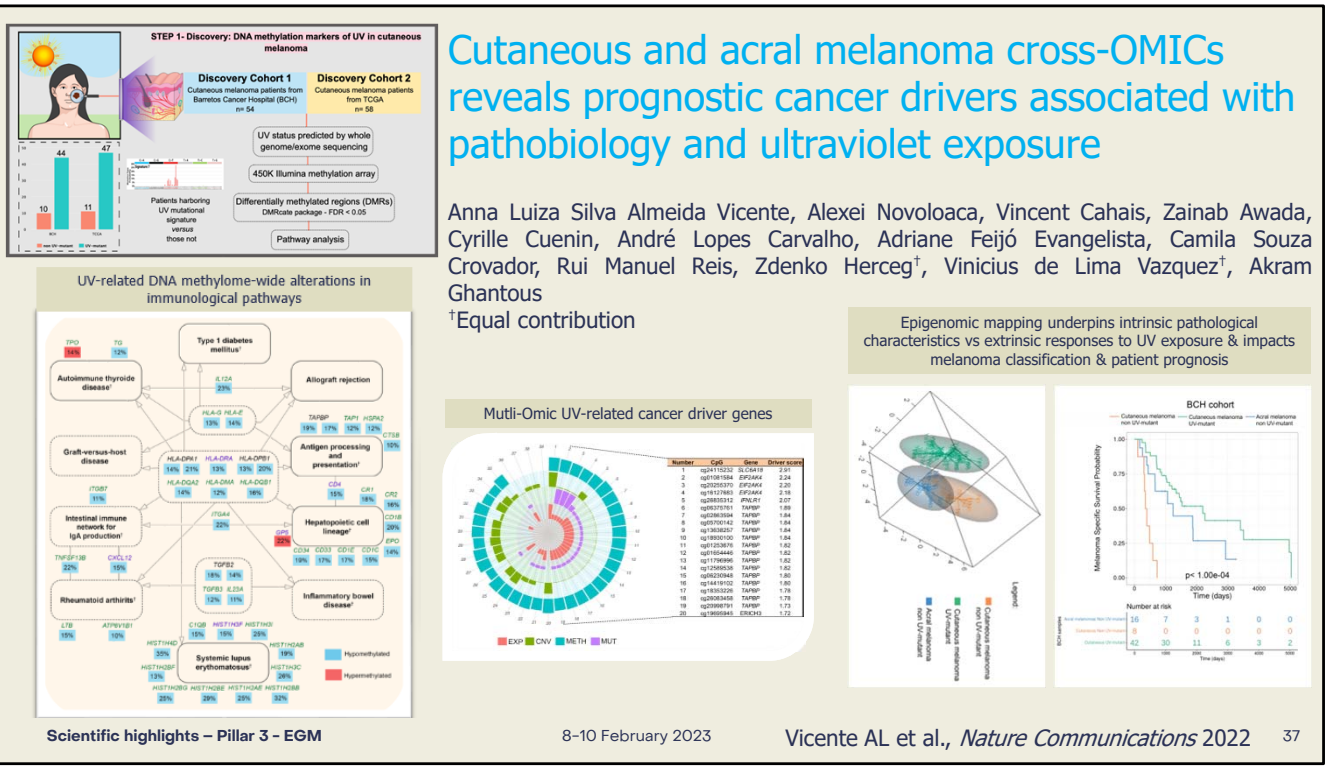
- Overlooked inter-generational effect of cancer deaths at younger ages
- **1 million children** lost their mother due to cancer in 2020
- **7 million children** were maternal orphans due to cancer in 2020

- Social inequity:
  - Perpetuation of a cycle of disadvantage and poverty
  - Highest risk of maternal orphaning per 100,000 children in low HDI countries
- Galukande et al, *JAMA Oncology*, 2022
- Guida et al, *Nat Med*, 2022
  (https://doi.org/10.1038/s41591-022-02109-2)

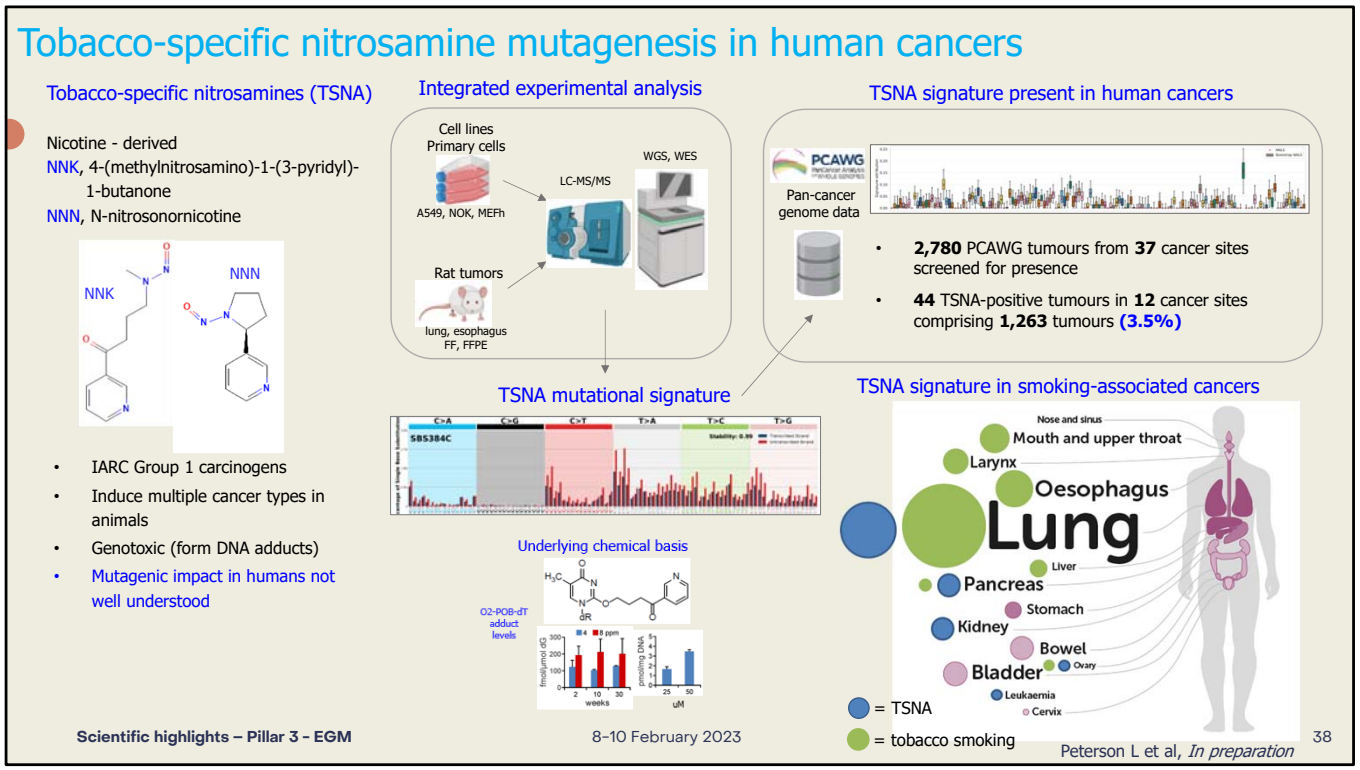


Prompted by findings in ABC-DO of the large number of children who became maternal orphans upon the passing of their mothers due to breast cancer deaths, we extended this study-based insight to a global perspective. We estimated the global, regional and country specific number of NEW and EXISTING maternal orphans due to cancer in 2020, based on GLOBOCAN data and world fertility estimates.

A staggering 1 million children became maternal orphans in that year. Asia and Africa had most of these children. By no coincidence, deaths from breast cancer and cervical cancer, the two female cancers targeted by WHO's breast cancer initiative, led to half of maternal orphans. This work further illustrates yet another reason for global action on preventable and premature cancer deaths, deaths which drive an intergenerational cycle of poverty.



Ultraviolet radiation (UV) is causally linked to cutaneous melanoma, yet the underlying epigenetic mechanisms, known as molecular sensors of exposure, have not been characterized in clinical biospecimen. We have identified multi-omics markers of exposure to UV that are critically involved in immune function, have the potential to drive cancer development, and could be used to predict the survival of patients with cutaneous melanoma, which occurs mainly in fair-skinned people. The study also reveals important features of melanomas that are not associated with UV exposure; this opens a window of translational opportunity for a less obvious population: patients with acral melanoma, which is the most common type of melanoma in darker-skinned people. These gene–environment interactions in people of different ethnic backgrounds reveal translationally impactful mechanisms in melanomagenesis.



1. EGM Branch investigates the little understood mutagenic effects of nicotine-derived nitrosamines and carcinogens NNK and NNN [CLICK].
2. In a unique, powerful multi-system analysis using exposure models, mass spectrometry and genome-scale sequencing [CLICK], EGM Branch and collaborators discovered a specific TSNA signature and the underlying chemical basis for its formation [CLICK].
3. The TSNA signature was then identified for the first time in 3.5% of public cancer genomes from 12 cancer sites [CLICK].
4. This included cancers associated with tobacco smoking not carrying the previously established tobacco-smoking signature – in pancreas, kidney, ovary, hematopoietic system.

This study offers a novel explanation of the TSNA contribution to human carcinogenesis in multiple organs.

Single dose HPV – Evidence on vaccine efficacy and population-level impact

India HPV vaccine trial

Immune responses [1] At 10 years after vaccination, the both the total antibody and neutralization titres induced by the single dose of the quadrivalent HPV vaccine are at least two time more efficient than those obtained from natural infection

Vaccine efficacy (VE) against HPV 16/18 persistent infection [2]

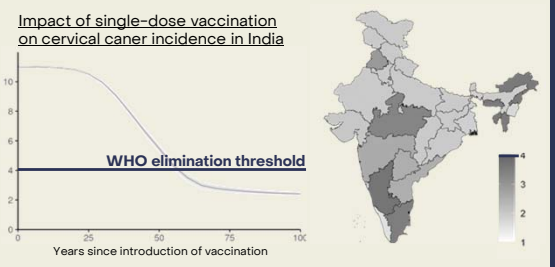
Endpoint	3-dose (N=1,649)	2-dose (N=1,685)	Single dose (N=2,454)
HPV16/18	91.2%	94.5%	94.2%
95%CI	(75.3 - 98.7)	(82.4 - 99.8)	(83.7 - 99.1)

Across the different HPV vaccine dose schedules, VE against persistent HPV-16/18 infections remains similarly high (>90%) up to at least 10 years post vaccination

Public Health Modelling

Projecting the **health benefits** [3] and **economic impact** [4] of single-dose HPV vaccination in India, using:

- IARC Public Health Decision Models: METHIS
- Context-specific data to inform the model



Key publicatons:
1. Vaccine (2018) for 4-yrs; submitted for 10-yrs data
2. Lancet Oncology (2021)
3. Lancet Oncology (2022)
4. Submitted

Scientific highlights – Pillar 3 - EPR 8-10 February 2023 39

India HPV vaccine trial: at 10 years after vaccination, both the total antibody and neutralization titres induced by the single dose of the quadrivalent HPV vaccine are at least two times more efficient than those obtained from natural infection.
Public health modelling impact:

- In this new study, researchers from IARC have projected the expected impact of a national **single-dose HPV vaccination** programme for girls in India.
- The projections are based on 10 years of data published by IARC in 2021 from a cohort study in India, in which 17 000 participants received one, two, or three doses of the quadrivalent HPV vaccine.
- IARC found that a national single-dose HPV vaccination programme for girls in India could substantially reduce the incidence of cervical cancer, **to below the incidence rate set by WHO** as the threshold for the elimination of cervical cancer as a public health problem.
- The threshold would be achieved both nationally and in each Indian state.
- If introduced now, HPV vaccination would prevent close to **1 million cases of cervical cancer** over the lifetime of birth cohorts currently aged 10 years or younger.
- Resources saved under a single-dose vaccination schedule could be used to

broaden the age group of girls vaccinated from the primary target of ages 9–14 years to age 15 years or 20 years, preventing up to 800 000 additional cases of cervical cancer in India.

Cancer burden and status of cancer control measures in fragile states: a comparative analysis of 31 countries

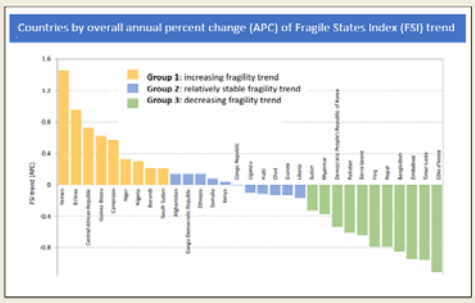
Mosquera I, Ilbawi A, Muwonge R, Basu P, Carvalho AL. *Lancet Glob Health*, 2022 Oct;10(10):e1443-e1452.

Objective To describe the **cancer burden and status of cancer control measures in fragile states**.

Methods

We selected countries with a Fragile States Index (FSI) ≥ 90.0 (alert for fragility) for at least 10 years in 2006-2020 period. They were mainly in Africa and Asia.

We categorized countries into three groups: group 1, with an increasing fragility trend; group 2, with a relatively stable fragility trend; and group 3, with a decreasing fragility trend.



Results: primary prevention (few examples)

High % of population exposed to household air pollution.

Current **prevalence of** tobacco use **in men increased from group 1** (increasing fragility trend) **to group 3** (decreasing fragility trend).

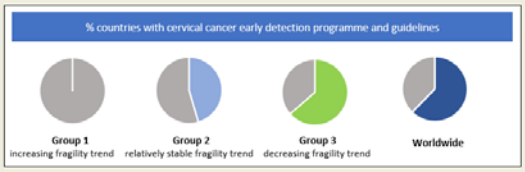
25 countries had 1 or none of the MPOWER measures established by WHO for tobacco control.

Results: cervical cancer (as an example)

Higher cervical cancer burden in fragile states than worldwide.

Only **8 countries (25.8%)** had HPV vaccination included in their immunization programme.

Only **12 countries (38.7%)** had cervical cancer early detection programme and guidelines.



Conclusions There is a **need to develop reliable** cancer control plans and guidelines and **to create** financial mechanisms for implementation.

Scientific highlights – Pillar 3 – EPR 8-10 February 2023 40

In a new study, scientists from the EPR Branch and the World Health Organization (WHO) provide a comprehensive overview of the cancer burden and cancer control measures in place in 31 fragile states. The study was published in the journal *The Lancet Global Health*.

The researchers found that the estimated cancer burden in the 31 selected fragile states was lower than worldwide rates, except for rates of cervical cancer and prostate cancer. The proportion of cancer cases attributable to infections was higher in fragile states than globally. Only half of the countries had an updated cancer control plan or cancer management guidelines, and only 39% had a cervical cancer early detection programme and guidelines.

Fragile states were selected based on the annual percentage change of their Fragile States Index (FSI) and categorized into three groups: group 1, with an increasing fragility trend; group 2, with a relatively stable fragility trend; and group 3, with a decreasing fragility trend.

In many countries in the study, a high percentage of the population was exposed to household air pollution. The current prevalence of tobacco use in men increased from group 1 to group 3. Lung cancer incidence and mortality rates were higher in states in group 3 (i.e. with a decreasing fragility trend). However, 25 of the countries had implemented only one or none of the MPOWER measures established by WHO for tobacco control.

Data related to the cancer burden or trends in fragile states are scarce, even though many of these countries are undergoing social and economic transitions that increase the risk of disease in the population. This new analysis shows that fragile states are still not implementing enough cancer control measures. There is a need to develop reliable cancer control plans and guidelines in these states, and to create financial mechanisms for their implementation.

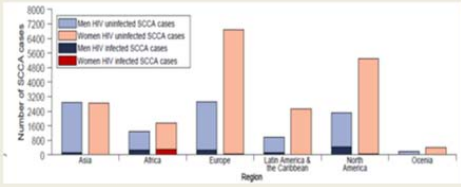
HPV-related anal cancer: epidemiology to inform prevention

HPV-related anal cancer

Global cancer incidence analysis (GLOBOCAN)

- Gender
- HIV status

Incidence of HPV-related anal cancer



- Two thirds of global anal cancer diagnosed in women
- 21% of male, and 3% of female anal cancer diagnosed among persons living with HIV

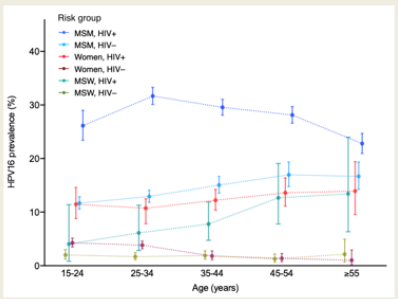
Deshmukh AA,..., Ferlay J, Georges D, Bray F, Clifford GM. *Int J Cancer,* 2022

Anal HPV prevalence

Collaborative pooled analysis of 90 studies

- Gender
- Male sexuality (MSM vs. MSW)
- HIV status

Age-specific anal HPV16 prevalence



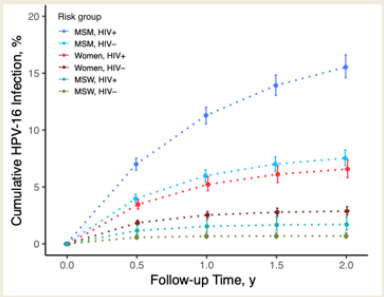
Wei F,..., Clifford GM. *J Infect Dis,* 2022

Anal HPV incidence and clearance

Collaborative pooled analysis of 34 studies

- Gender
- Male sexuality (MSM vs MSW)
- HIV status

Cumulative anal HPV16 incidence



Wei F,..., Georges D, Alberts CJ, Clifford GM. *Clin Infect Dis,* 2022

MSM = Men having sex with men **MSW = Men having sex with women**

Based on GLOBOCAN's estimates, two thirds of global anal cancer were diagnosed in women in 2020. 21% of male and 3% of female anal cancer were diagnosed among persons living with HIV.

Scientists from the EPR Branch reanalysed data from 34 studies with 16 164 individuals in six risk groups defined by HIV status, gender, and male sexuality: men who have sex with men (MSM) living with HIV (LWH) [MSMLWH], HIV-negative MSM, women LWH (WLWH), HIV-negative women, men who have sex with women (MSW) LWH (MSWLWH), and HIV-negative MSW. They used Markov models to estimate incidence and clearance of 13 hrHPV types and their determinants.

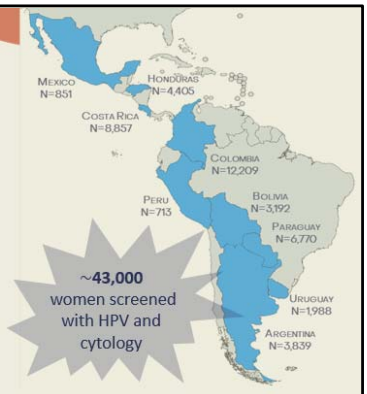
In HIV-negative women, HPV16 prevalence decreased significantly with age (4.3% at 15-24 years to 1.0% at ≥55 years; p trend=0.0026). Age-specific shifts in HPV16 prevalence from cervix to anus suggest that HPV infections in the anus persist longer, or occur later in life, than in the cervix. This is an important consideration when assessing the utility of cervical screening results to stratify anal cancer risk.

HPV16 had the highest incidence: clearance ratio of the hrHPV types. MSMLWH had highest hrHPV incidence (e.g. 15.5% newly HPV16-infected within two years), followed by HIV-negative MSM (7.5%), WLWH (6.6%), HIV-negative women (2.9%), MSWLWH (1.7%), and HIV-negative MSW (0.7%). Determinants of HPV16 incidence included HIV

status and number of sexual partners for MSM, women, and MSW, and anal sex behaviour for MSM only. HPV16 clearance was lower for people LWH (PLWH), and lower for prevalent than incident infection. Among MSM, increasing age was associated with lower clearance of prevalent, but not incident, HPV16 infection.

This robust and unifying analysis of anal hrHPV natural history is essential to designing and predicting the impact of HPV vaccination and HPV-based screening programmes on anal cancer prevention, particularly in MSM and PLWH. Importantly, it demonstrates the higher carcinogenic potential of longstanding anal prevalent hrHPV infection than more recent incident infection.

Progress towards HPV-based cervical screening in Latin America: contributions from the ESTAMPA study



Methods

~43,000 women aged 30-64 years were screened in 12 study centres with HPV and cytology and referred to colposcopy (biopsy and treatment as appropriate) if any screening positive result

We described the **HPV testing implementation process**, including monitoring and evaluation of HPV testing performance over time, of 12 laboratories in ESTAMPA

Several **triage approaches**, such as **VIA** and **colposcopy**, are being evaluated to risk stratify HPV-positive women

*Readiness of labs to perform HPV testing is not enough to implement HPV-based screening: a **"culture of quality"** should be established with regular training, robust monitoring and quality assurance systems tailored to local contexts.*
Front Med 2022 (*in press*)

***VIA** performed by providers with different levels of expertise and training detects **>80%** of cervical disease by halving the referral rate in HPV-positive women. We evidenced the need to improve the assessment of eligibility for ablative treatment.*
Int J Cancer 2022 (*in press*)

*A standardized **colposcopy** performed by trained specialists under a validated clinical management protocol optimally detects **90%** of cervical disease by only biopsying about half of women with a positive HPV test result.* *LGH* 2022 (*in press*)

In the Framework of the ESTAMPA study conducted in Latin America, IARC scientists described progress towards implementation of HPV-based cervical screening programme.

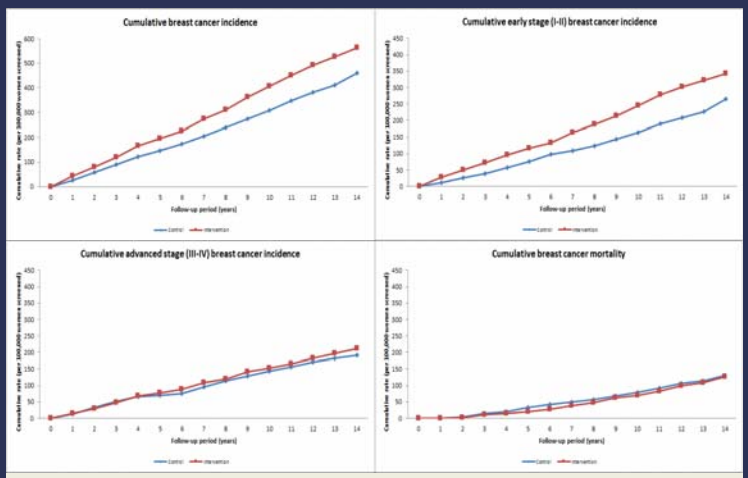
Effectiveness of triennial screening with clinical breast exam (CBE) – *14-years (2006-2020) follow-up outcomes of the RCT in India*

Methods:

- Women aged 30-69 years were randomly allocated to be either screened with CBE every 3 years (N=55,843) or no CBE screening (N=59,447)
- Women in either arm received awareness about breast cancer & self-exam & had access to high quality cancer detection and treatment services
- Follow up was done actively through home visits & passively through cancer registries

Key outcomes:

- ASR of early cancer (stages I/II) was 30.4/100,000 & 21.9/100,000 in the intervention & control groups [RR of 1.4; 95% CI 1.1-1.8]
- Among women diagnosed with breast cancer, a significant 26% reduction in death in the intervention group was observed compared to those in the control group (Adjusted HR=0.74; 95%CI=0.56-0.99)



In spite of significant increase in early-stage cancers & improved survival in the intervention arm, age-standardized breast cancer mortality rates were similar between two arms (RR: 1.1; 95% CI 0.8-1.5)

In this new study, scientists from the EPR Branch and partner institutions described the long-term impact of screening women aged 30–69 years with clinical breast examination (CBE) every 3 years. This study, which was published in the journal *Cancer*, is only the second randomized controlled trial to be published on long-term outcomes of CBE screening.

The researchers randomized nearly 115 000 women to either the study's intervention arm (with CBE screening) or the control arm (with existing routine care). They observed significant downstaging of breast cancers (i.e. a shift towards earlier stage at detection) and improved survival in the women randomized to the screening arm compared with those in the control arm. However, no significant reduction in breast cancer-specific mortality was observed after 14 years of follow-up.

The women in the control arm were provided with materials to raise awareness about breast cancer, its early signs, and the importance of early detection, and they had access to good-quality diagnostic and treatment services.

The study results may indicate that improving breast awareness and ensuring access to timely treatment (an early diagnosis pathway) are almost as good as systematic CBE screening in reducing mortality from breast cancer. CBE is a valuable tool for diagnosis of breast cancer in symptomatic women, especially in areas where mammography and/or breast cancer screening programmes are not widely available. This information will be very useful in the context of developing strategies for the Global Breast Cancer Initiative, recently launched by the World Health Organization.

Scientific highlights

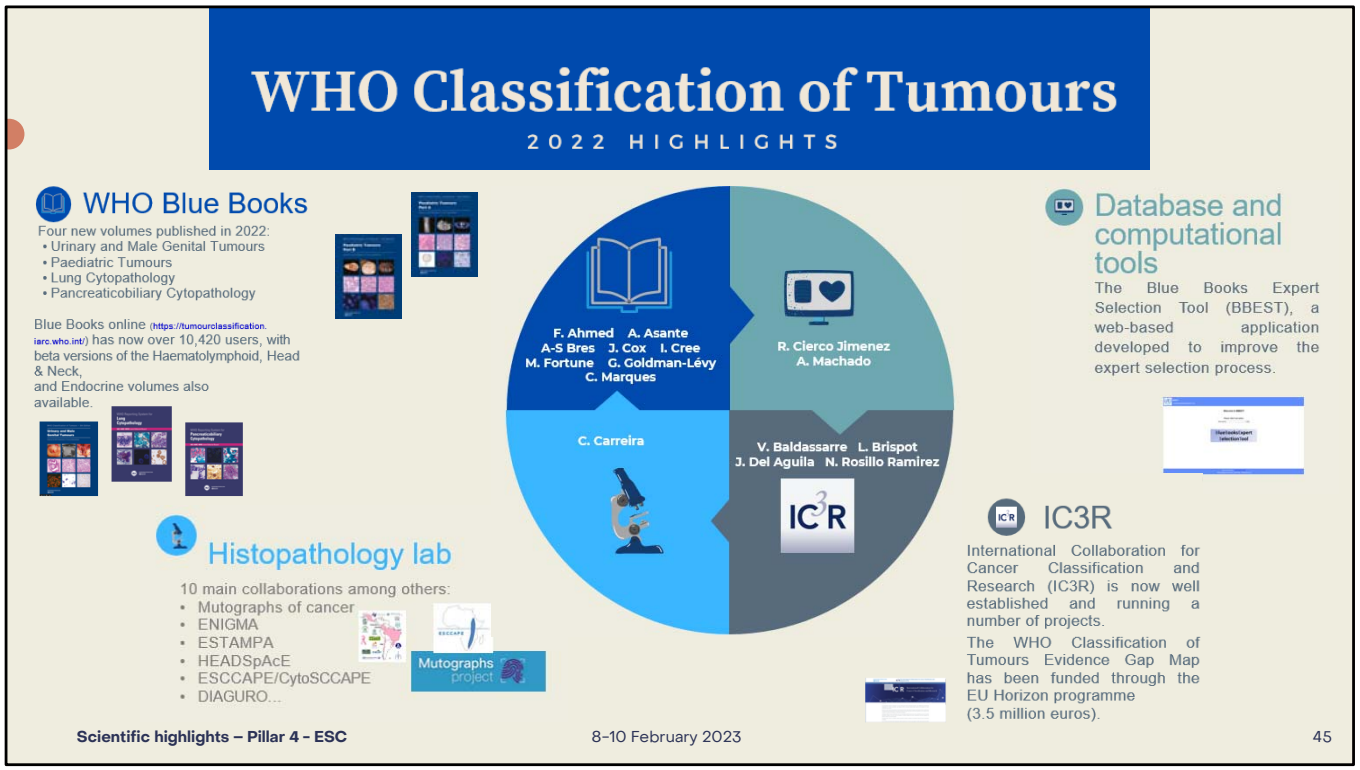
Evidence Synthesis and Classification

Learning and Capacity Building

Pillar 4:

Knowledge Mobilization

The following slides present some scientific highlights for **Pillar 4 – knowledge mobilization**, that includes the Evidence Synthesis and Classification (ESC) Branch, and the Learning and Capacity Building (LCB) Branch.



2022 scientific highlights are presented for the WHO Classification of Tumours programme.

WHO Blue Books: 4 new volumes have been published in 2022.

Histopathology laboratory: 10 main collaborations have been established focused on several projects at IARC.

Database and computational tools: The Blue Books Expert Selection Tool is a web-based application that was developed to improve the expert selection process.

IC3R is now well established and running a number of projects.

IARC Handbooks (IHB)

- **Handbook 18 – Cervical Cancer Screening (Oct. 2020)**
  - Publication on-line and in print
- **Handbook 19 – Oral cancer Prevention (Dec. 2021)**
  - NEJM article published 18.10.2022
  - Book publication planned in early 2023
- **Handbook 19 Supplement (on-going)**
  - Cost-effectiveness models for oral cancer screening *(collab. WHO-HQ)*
  - Evidence and Gap Map of oral cancer prevention studies *(collab. F. Campbell, UK & A. Santos Silva, Brazil)*
  - Population-attributable fraction of cancers due to consumption of smokeless tobacco or areca nut *(collab. CSU & expert Working Group)*
- **Handbook 20 – Reduction of alcohol consumption (May 2023)**
  - INCa grant to fully fund Handbook 20
  - Collaboration with WHO-EURO

Primary prevention – Step 2

Quitting exposure to risk factor	Strength of evidence
Smoked tobacco (SLT)	*Sufficient*
Alcohol consumption	*Sufficient*
Smokeless tobacco	*Inadequate*
Areca-nut (AN) products (including betel quid) with or without tobacco	*Sufficient*

Primary prevention – Step 1

Intervention to quit consumption of SLT/AN products	Strength of evidence
Pharmacological	*Limited*
Behavioural – adults	*Sufficient*
Behavioural – youth	*Limited*
Combined	*Limited*

Secondary prevention – Screening

Screening method	Evaluation
Clinical oral examination in high-risk populations	Group B

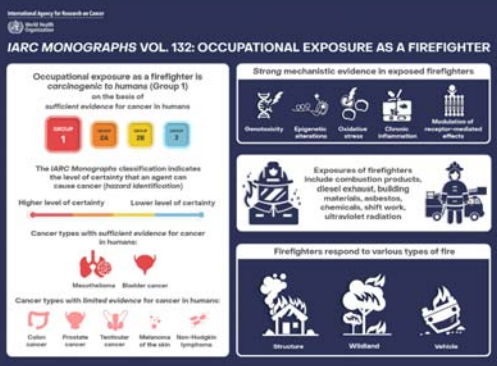
2022 Scientific highlights for the IARC Handbooks of cancer prevention programme are presented in this slide.

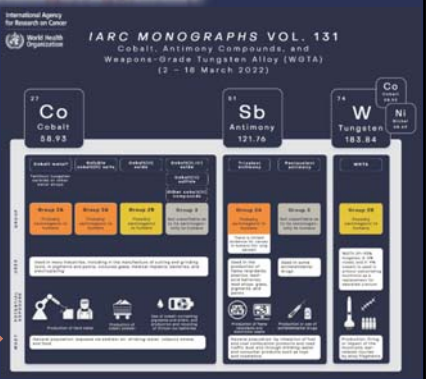
IARC Monographs Programme (IMO)

Accomplishments in 2022

- Held *Monographs* meetings 131 & 132 and Scientific Workshop
- New or updated classifications for 8 agents
  - **Group 1**: Occupational exposure as a firefighter
  - **Group 2A**: Trivalent antimony, cobalt metal, soluble cobalt (II) salts
  - **Group 2B**: cobalt (II) oxide, weapons-grade tungsten alloy

Aim: identify preventable causes of human cancer through systematic review and expert evidence evaluation





- Published two articles in *The Lancet Oncology*
- Published two *Monographs* volumes
  - v.129: Several dyes
  - v.130: Five industrial chemicals

Scientific highlights – Pillar 4 - ESC 8-10 February 2023 47

2022 Scientific highlights for the IARC Monographs programme are presented in this slide.

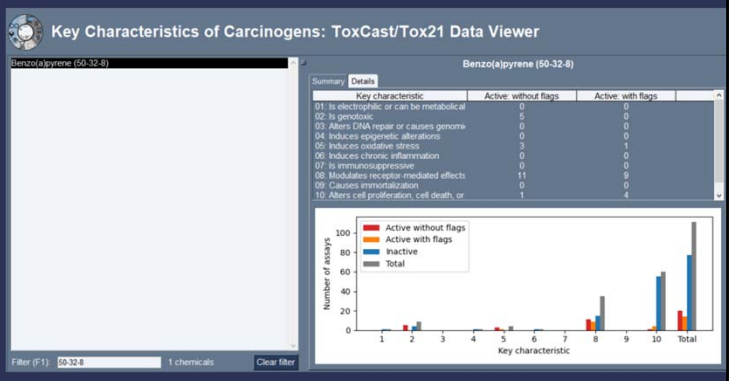
IARC Monographs Programme (IMO)

Scientific accomplishments in 2022

- Other publications and activities:
  - Scientific Workshop to develop "Statistical Methods in Cancer Research, vol. V: Bias Assessment in Case-Control and Cohort Studies for Cancer Hazard Identification"

"kc-hits" development

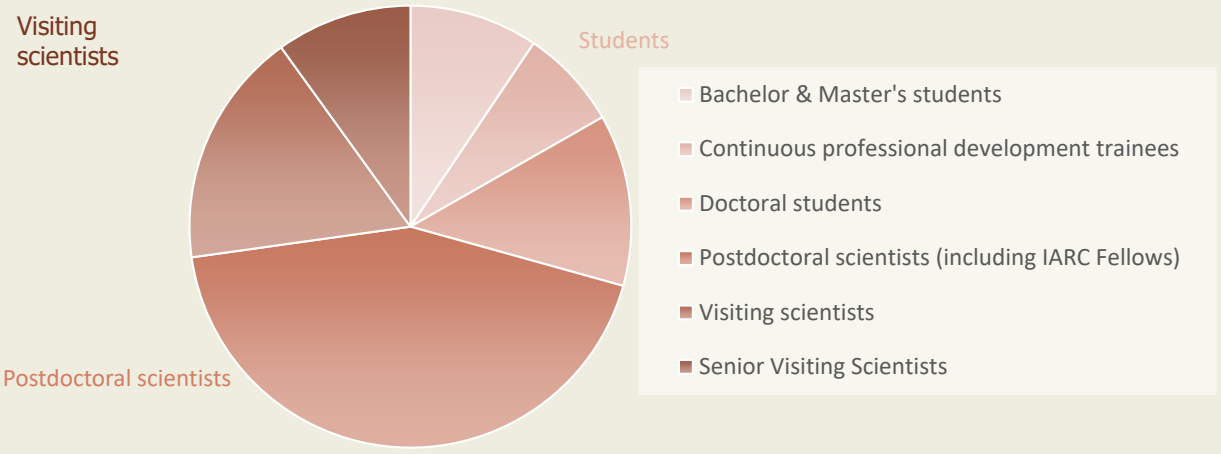
Creation of high-throughput screening discovery tool for mechanistic evidence of the key characteristics of carcinogens (Reisfeld et al. 2022; www.cancer.idsl.me)



2022 Scientific highlights for the IARC Monographs programme are presented in this slide.

IARC Research Training and Fellowship Programme

In 2022, over 190 students, postdoctoral and visiting scientists, funded from IARC Branches grants or IARC Fellowships



The IARC Research Training and Fellowship Programme offers researchers at different levels of their career opportunities to get trained at IARC through their participation in collaborative research projects.

IARC Fellowships - LMICs

October 2022 call – selection ongoing

Post-doctoral fellowships

- For postdoctoral scientists wanting to pursue research relevant to IARC's missions
- Lasts 2 years starting Autumn 2023
- 6-7 funded on RB, pending confirmation at the next GC
- 2 focusing on childhood cancers, supported by Children with Cancer UK

Mid-career scientist award

- For senior scientists in their mid-career
- For a period of 6 to 12 months
- 2-3 awards

Negotiations with other potential donors ongoing

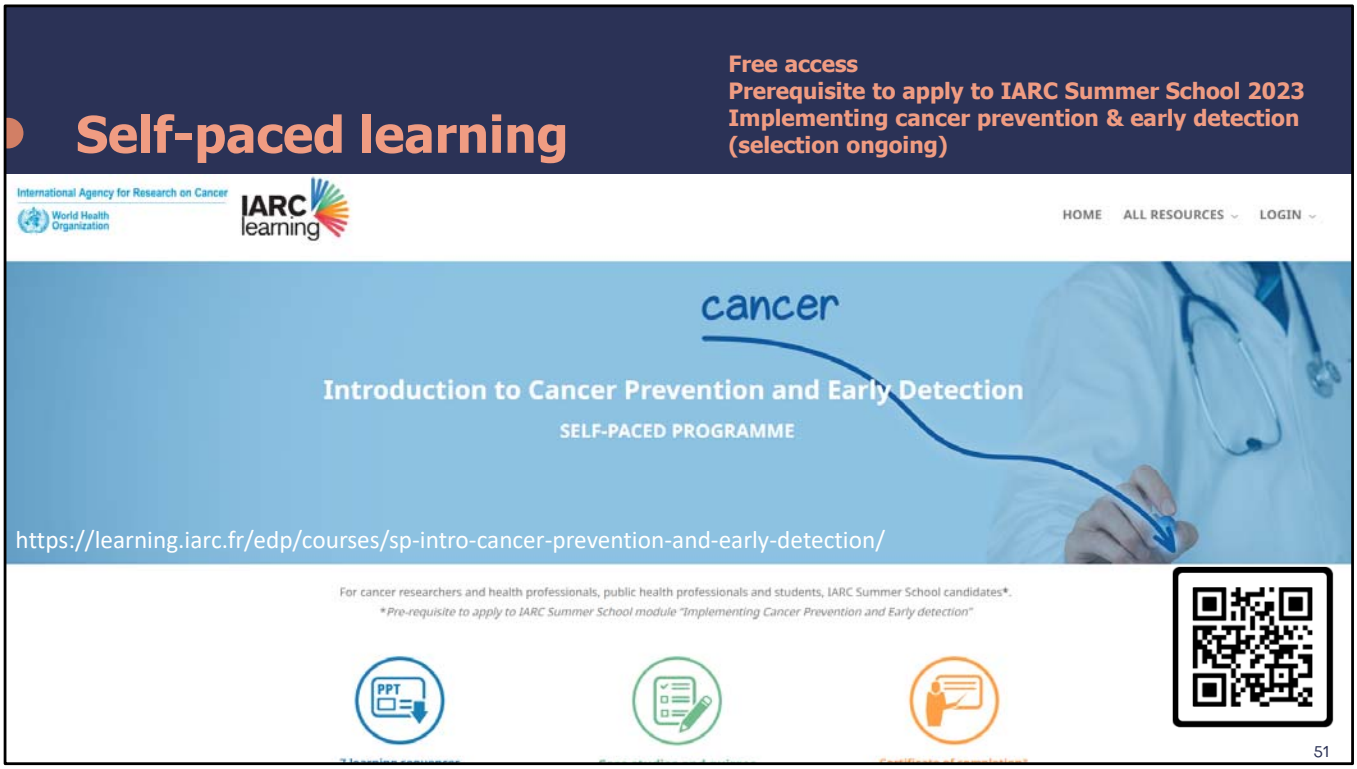
The call for IARC Fellowships was launched in October 2022, targeting low-and middle-income countries (LMICs).

The selection is ongoing, with results communicated after the budget discussions in the Governing Council (GC) in May 2023.

If the budget is approved, there will be 7 postdoctoral fellowships of 2 years each, funded on the Regular Budget (RB). In addition, fund raising efforts have led to renewed support of Children with cancer UK, who will support 2 additional fellowships on childhood cancer research.

As supported by the Scientific Council (SC) in 2022, applications for 2-3 mid-career scientist awards are also being reviewed.

Negotiations with other potential donors are ongoing, to increase the amount of awardees from this selection.



A new self paced learning programme was launched, Introduction to cancer Prevention and Early Detection.

Based on a combination of IARC learning material, this learning path introduces the concepts of cancer surveillance and the role of cancer registration in cancer control. It provides an overview of primary and secondary prevention concepts and strategies, an understanding of measures to improve the quality of cancer screening programmes and of the benefit of robust health systems to support cancer control efforts. Some basic concepts of implementation research will also be of interest for anyone involved in cancer prevention.

This introductory learning path was a prerequisite to apply for the corresponding module of the IARC Summer School 2023, whose selection process is being completed.

IARC also launched a training toolkit designed to support anyone involved in transmitting knowledge and skills on cancer research for cancer prevention. The material can be used in a modular and flexible way. It can also be adapted for use in different countries or settings.

The first module of the toolkit, "**Rationale and Scope of Cancer Research for Cancer Prevention**" was launched in September 2022. It consists of a PowerPoint file, including:

- modifiable slides for lectures, with an attractive, attention-grabbing design
- text that trainers can use to prepare their sessions
- links to the sources of the figures, and advice on how to adapt them to the context
- suggested quizzes and exercises, including instructions for trainers

The second module "**Cancer Epidemiology. Describing and Understanding Cancer**" will be launched soon.

In line with IARC's commitment to open science, the material in this training toolkit is published under a Creative Commons licence (Attribution-NonCommercial-ShareAlike 3.0 IGO (CC BY-NC-SA 3.0 IGO), meaning it can be shared and adapted under the following terms:

- *Attribution — You must give appropriate credit, provide a link to the license, and*

indicate if changes were made. You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use.

- *NonCommercial — You may not use the material for commercial purposes.*
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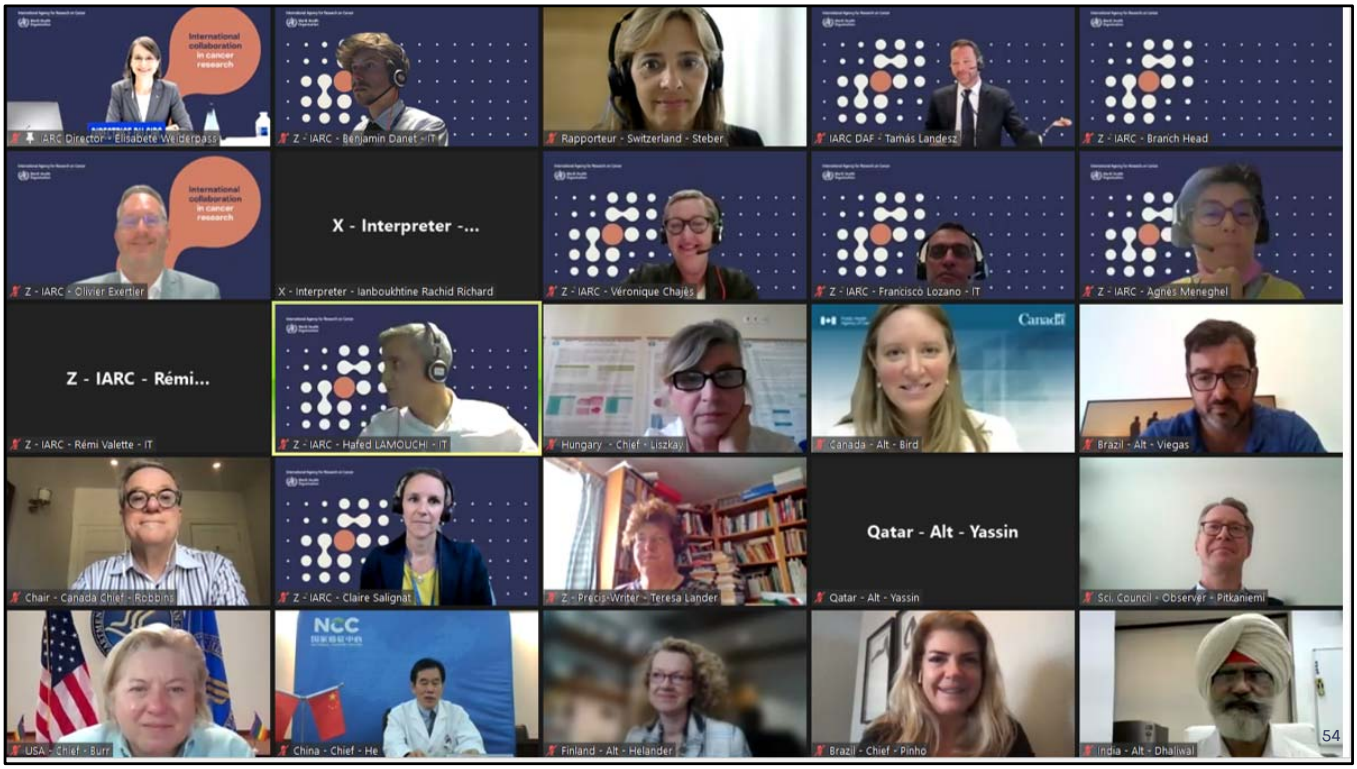
The following slides report some highlights from the meeting of the 64th Session of the Governing Council held in May 2022.



For the 3rd consecutive year, the Governing Council was held remotely and went well.

DIRECTOR'S REPORT

The Governing Council:

- THANKED the Director for the **Report and for the Key Performance Indicators (KPIs)** provided.
- NOTED with satisfaction the continued efforts made towards further **strengthening coordination and communication between IARC and WHO.**
- THANKED the Secretariat for its report on IARC engagement under the Framework of Engagement with Non-State Actors (**FENSA**).
- NOTED that, in support of the IARC MTS 2021–2025, the Director will make partial use of the unbudgeted assessments of new Participating States in the biennium 2022–2023 to **modernize IARC's administrative management system**, by joining WHO's new Business Management System project, and to **strengthen IARC's data protection framework** and **scientific data management systems**.
- EXPRESSED its satisfaction with the Director's written and oral Reports.

IARC'S COVID-19 AND CANCER INITIATIVE: REQUEST FOR SUPPORT AND FUNDING

The Governing Council:

- REQUESTED the IARC Secretariat to further develop the initiative and coordinate with existing initiatives in this area, including the WHO Hub for Pandemic and Epidemic Intelligence, in order to complement and enhance collective efforts.
- SUPPORTED the funding of this initiative **through voluntary mechanisms** such as voluntary contributions by Participating States and others.
- ENCOURAGED Participating States to make voluntary contributions and provide support to the resource mobilization efforts towards this initiative.

UPDATE ON THE "NOUVEAU CENTRE" AND ON RESOURCE MOBILIZATION

The Governing Council:

- EXPRESSED its appreciation to the City of Lyon, for their continued efforts and strong support; and to the French national authorities, the Région Auvergne-Rhône-Alpes, the Métropole de Lyon, and the City of Lyon for the continued support received and progress made on the "Nouveau Centre".
- EXPRESSED its appreciation to the IARC Secretariat for closely monitoring the building works and for its efforts to mobilize funds.
- EXPRESSED its deep appreciation to the donors for their generous contributions, in cash or in kind, to the "Nouveau Centre".
- ACKNOWLEDGED the remaining funding gap of €4.59 million for a fully operational, modern, smart and open building, beyond "Priority 1" needs, prior to the move to the Nouveau Centre.
- AUTHORIZED the Director to accept further donations in cash or in kind for the purpose of furnishing and equipping the Nouveau Centre.
- DECIDED to extend the authorization to future miscellaneous revenue originating from the sale of old equipment and furniture to be used towards the Nouveau Centre project during the biennium 2022–2023.

EVALUATION FRAMEWORK OF THE IARC MEDIUM-TERM STRATEGY (MTS) 2021–2025 AND ITS KEY PERFORMANCE INDICATORS (KPIs)

The Governing Council:

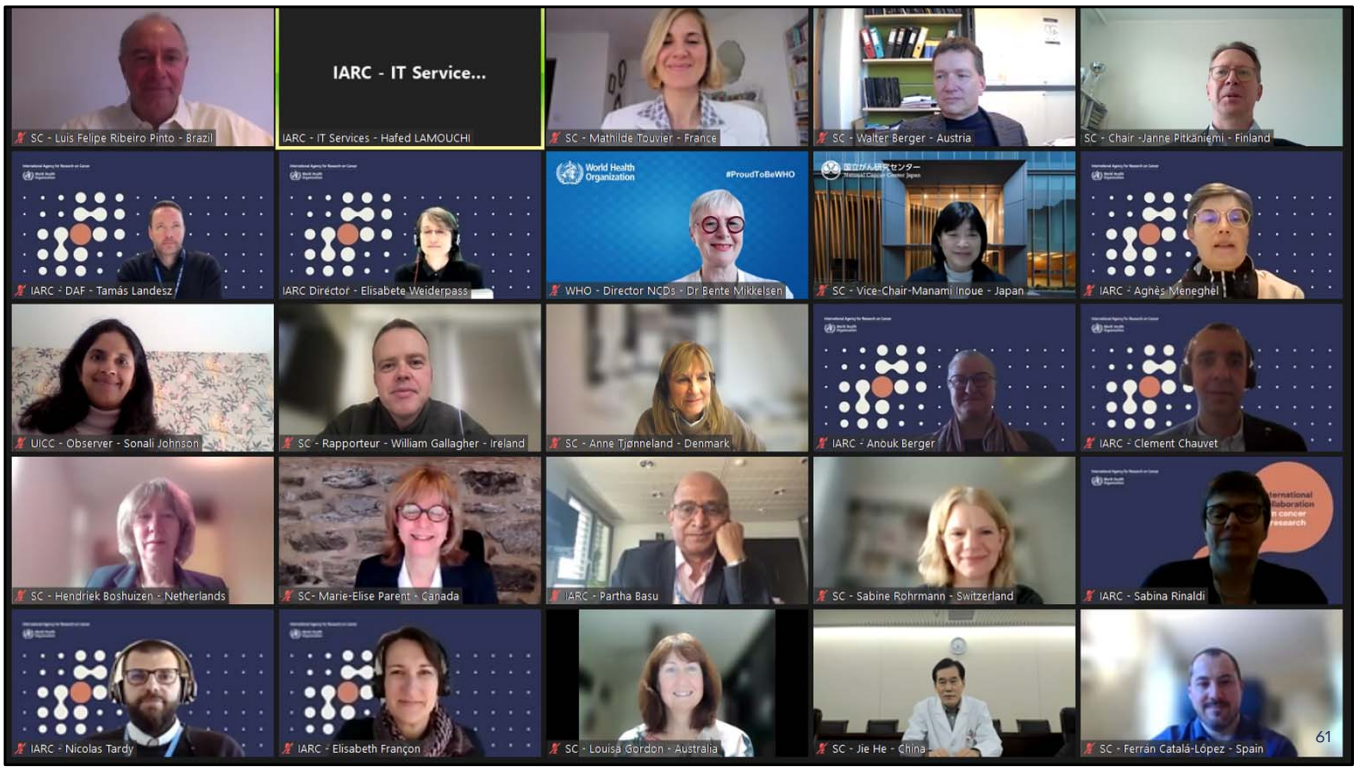
- APPROVED the proposed evaluation approach as well as the list of KPIs.
- Composition of the Working Group on the 2021–2025 MTS Evaluation Framework:
  - IARC Secretariat
  - Governing Council (Dr Yui Sekitani, Japan)
  - Scientific Council (Dr Luis Felipe Ribeiro Pinto, Brazil and Dr Mathilde Touvier, France)
  - With support from the WHO Evaluation Office.

DATA PROTECTION

Way forward:

- IARC established a comprehensive Register of Records of Data Processing Activities (ROPA) for all scientific and non-scientific data processed at IARC;
- The IARC Data Protection Policy, focussing on the processing of personal data for scientific purposes, was published on IARC's public website;
- IARC worked closely with WHO to review and advise on WHO's Data Protection Policy;
- IARC created a Data Protection General Awareness training which will be mandatory for all personnel;
- IARC established a permanent Data Protection Officer position;
- IARC continues to collaborate with the European Commission, the European Data Protection Supervisor, several networks of International Organizations, data protection authorities and data protection officers of our collaborators **to find long-term solutions** to enable data sharing with IARC.

The following slides report some highlights from the 58th session of the Scientific Council held in February 2022.



The Scientific Council, virtual for the second time in 2022, went very well, thanks to IT.

DISCUSSION ON THE DIRECTOR'S REPORT

- The Scientific Council (SC) congratulated the Director on the **IARC Biennial Report 2020–2021**, and on the development of its **new IT platform**.

SC recommendations:

- To improve communication actions towards citizens and health practitioners in the field of cancer prevention.

➢ IARC to develop new IARC strategies to reach out to a wider audience of stakeholders, including the public, through new visuals/graphics.

- To generate a publicly facing platform for factual communication to combat misinformation (vaccination).

➢ IARC does not have a specific programme on combating fake news in the vaccination space, but working synergistically with WHO (which has such a platform) would be useful.

EVALUATION FRAMEWORK OF THE IARC MTS 2021-2025

- The SC appreciated the increased focus on **qualitative evaluation of outputs**, as opposed to purely quantitative measures (in light of DORA and Leiden guidelines) in the evaluation framework.
- The SC appreciated the inclusion of **KPIs related to gender equity and minorities** in the evaluation framework.
- The SC endorses the recruitment of new Participating States, where feasible. It was suggested that members of the SC could aid in recruitment of new Participating States.

➢ **The SC strongly endorsed the evaluation framework**

BIENNIAL REPORT ON IARC EDUCATION AND TRAINING ACTIVITIES 2020-2021

- The SC congratulated IARC on its endeavours in education and training.
- The SC suggested to construct **a permanent alumni programme** to help build and sustain networks.
- The SC suggested exploring possibilities of further interaction with the WHO Academy, as well as investigating opportunities afforded by the Nouveau Centre.
- The SC supports the proposal to **convert the 12-month Senior Visiting Scientist Award into shorter Mid-Career Visiting Scientist Awards**.
- The SC recommends **some flexibility in the duration of the Mid-Career Visiting Scientist Awards**, with an average of 6 months but varying from 3 months to 9-12 months depending on the specific project.
- The SC would favour **increased participation from LMICs**.

UPDATE ON THE NOUVEAU CENTRE AND ON RESOURCE MOBILIZATION

- The SC congratulated IARC on their tireless work in respect of fundraising efforts.
- The SC requested that a **short media pack be circulated to SC members** so as to facilitate dissemination of this opportunity.
- The SC suggested to use **more visuals relating to specific laboratory work** and environments when fundraising for the Nouveau Centre, particularly pertaining to the **biobanking activities**.

International Agency for Research on Cancer

World Health Organization

Director's Report

4. Highlights from the Biennial Report of the IARC Ethics Committee (IEC) 2021-2022

Mission and scope of the IEC

TO ENSURE:

- The protection of the safety, well-being and privacy of participants in studies carried out by IARC, to enable and promote conduct of good quality research.
- That Agency's studies demonstrate the respect for the most rigorous ethical principles and standards.
- That Agency's studies reflect the values of WHO and of the UN family.

- Conducting international cancer research to a high level of quality, as this is the case for IARC, carries not only scientific challenges, but also ethical responsibilities.
- The research conducted by IARC relies on the participation of humans from different sociocultural and economic contexts.
- In this context, the mission of the IEC is to ensure that the research conducted by IARC conforms with international ethical standards for research involving humans and that measures are in place to safeguard the rights and welfare of participants.

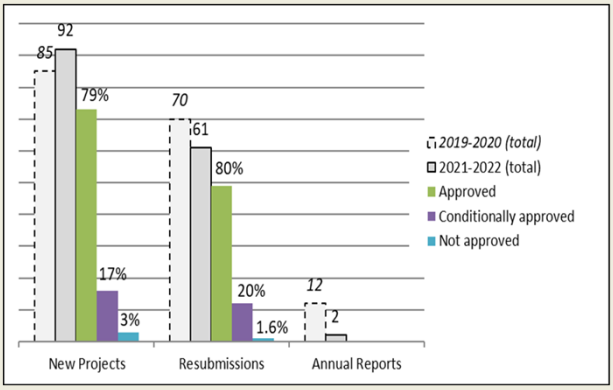
Composition of the IEC

- Eleven senior individuals with diverse backgrounds and nationalities (Brazil, China, Denmark, France, Iran, Italy, United Kingdom, Saudi Arabia).
- Representing sciences, medical care, ethics, law, and the general population.

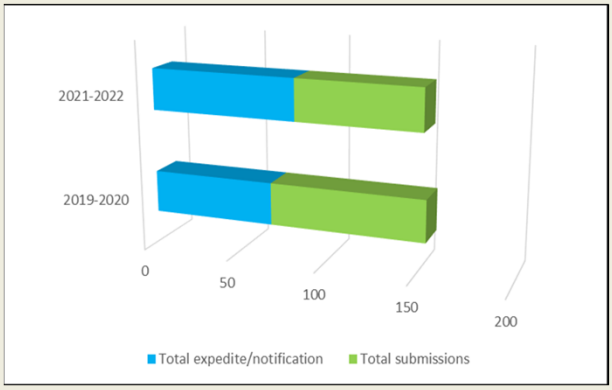
The broad diversity of experience and knowledge among IEC members ensures that the ethical review of research carried out at IARC is thoroughly addressed trough its different components.

IEC evaluations

Evaluations over the biennium



Increased evaluations in-between meetings



- On the left: the total number of projects reviewed by the IEC (including both new projects and re-submissions) remained almost equal to the previous biennium. The approval rate of submitted projects was recorded very high, at approximately 80%.
- On the right: though the total number of total evaluations remained almost equal to the previous biennium, an increased 9.7% of projects cleared in-between meetings though the expedite review and notification procedures was recorded.

Other activities

- Regular update of Standard Operating Procedures;
- Monitoring of potential Conflicts of Interest in research studies;
- Monitoring of the *Asbest* study;
- Training in biomedical research ethics; and
- Collaborations with WHO and other UN Agencies.

- The IEC Procedures were updated to enhance the efficacy of projects' evaluation in support of IARC PIs
- Conflicts of interest were strictly monitored to ensure the unbiased evaluation of projects.
- Trainings on ethics in research were delivered by the Secretary to new IEC members, to IARC early career scientists and new IARC scientists; and a publicly available online module for participants of the 2021 IARC Summer School, was produced.
- The IEC is collaborating with the WHO to produce a common IARC/WHO ethical framework for the review of studies on Artificial Intelligence, and with the UN Inter-Agency Committee on bioethics areas of mutual interest.

IARC personnel in IARC's premises on 29 September 2022.

Thank you

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