International Agency for Research on Cancer

World Health Organization

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Lyon, 19–20 May 2016
Auditorium

ACCEPTANCE OF GRANTS AND CONTRACTS, INCLUDING REPORT ON INTEREST APPORTIONMENT

1. Post facto reporting

The Governing Council is invited to note the post facto reporting of grants and contracts accepted by the Director over €100 000 per annum, including sums passed to third parties, as detailed below.

Biomarkers Group (BMA) and Nutritional Epidemiology Group (NEP)

1.1 Project title: **Body composition and breast cancer risk: disentangling the underlying mechanisms**

Breast cancer (BC) is a major public health problem in France and in Europe, as it is the most common cancer in women from high-income countries (HICs), but its incidence is increasing very steadily also in low- and middle-income countries (LMICs). Obesity and physical inactivity are important risk factors for post-menopausal BC, but the etiology of pre-menopausal BC is still largely unknown. Obesity involves many metabolic changes, including changes in glucose and lipid metabolism, in choline, amino acids and creatinine. However, so far little is known about the specific metabolic alterations and dysfunctions linking obesity to cancer, and of the impact of diet and lifestyle on these metabolic changes. Contrary to what is observed in post-menopausal women, obesity in young women has been repeatedly (though not systematically) associated with a reduction in BC risk. However, the mechanisms of this inverse association have not been fully elucidated, although it is suggested that they may be associated with differences in fat distribution in young versus older women, as well as with important differences in the subtypes of cancers developed.

The aim of this project is to apply targeted high-throughput technologies to plasma samples from the large European Prospective Investigation into Nutrition and Cancer (EPIC), to better understand the link between obesity and BC risk in women. Specifically, we will:

1) measure more than 150 intermediary metabolites (acylcarnitines, amino acids, biogenic amines, hexoses, phosphor- and sphingolipids) with a well-validated targeted mass spectrometry method (UPLC/MS/MS) in prospectively collected plasma samples from 1500 pre- and post-menopausal BC cases (with known receptor status of the tumour) and 1500 matched controls within EPIC.

2)   study the association of these biomarkers with BC risk, overall and by menopausal and receptor status.

3)   examine and quantify the relationships of these biomarkers with variable degrees of adiposity (Body Mass Index, waist circumference) and physical activity, and with serum levels of C-peptide, sex steroid hormones, fatty acids, vitamin D, folate, anti-oxidants which have been measured previously in samples from the same cases and controls.

4)   examine the relationship of measured biomarkers with BC risk independently of the other obesity-related metabolic risk factors, to develop a multivariate metabolic risk score for BC.

The proposed study will be carried out within EPIC, an ongoing prospective study investigating risk factors for cancer and other chronic diseases. Amongst cohort participants who provided a blood sample, 1537 cases of BC have been selected, and include all cases diagnosed before age 50, all estrogen receptor negative (ER-) cases and an equivalent number of age>50 estrogen receptor positive (ER+) cases. For each case subject, one control subject has been selected randomly by incident density sampling, but matching the cases for selected criteria.

All laboratory measurements will be performed at the laboratories of the Biomarkers Group at IARC. Metabolomics measurements will be performed by UPLC/MS/MS by using the AbsoluteIDQ p180 Kit produced by Biocrates (Innsbruck, Austria). Relative risks of BC by level of each of the biomarkers will be estimated by conditional logistic regression. Linear regression methods and PLS approaches will be used to examine cross-sectional relationships of anthropometric measures, physical activity levels and metabolic and hormonal markers with each of the new markers, and between the markers. Multivariate logistic regression models will be used to examine to what extent increased risk in BC in overweight or obese women can be explained by weight-associated variation in metabolic and inflammatory/immune markers, and to examine a confounding effect of androgens, estrogens, C-peptide and other metabolic markers (mediation analysis). Factorial analyses will be used to construct scores of metabolic markers.

With about 1500 BC cases and one control per case, the statistical power will be above 0.8 to detect an exposure-disease association equivalent to an expected OR of 1.32 between the extreme quartiles of the population exposure distribution. With 591 cases diagnosed <50 we can detect an OR of 1.56 in this subgroup (and $OR_{min}=1.42$ in >50). With 551 ER- cases, we can detect an OR of 1.58 in this subgroup (and OR=1.41 in ER+).

Donor:	Institut National du Cancer (INCa), France
Duration:	35 months
Funds for IARC:	€318 305 (US$ 349 786)
Funds for partners:	€30 882 (US$ 33 936)
Total:	€349 187 (US$ 383 722)

Partners:

Institut National de la Santé et de Recherche (INSERM), France, €15 441 (US$ 16 968)
Université Claude Bernard Lyon, France, €15 441 (US$ 16 968)

Biomarkers Group (BMA) and Epigenetics Group (EGE)

1.2   Project title: **A randomized placebo controlled phase II study with metformin in metabolically-unbalanced breast cancer survivors at higher risk for recurrence**

Metabolically unbalanced conditions, which can include the presence of metabolic syndrome, weight gain, central obesity, elevated serum insulin and glucose levels, and insulin resistance, have been strongly associated with breast cancer (BC) recurrence and worse outcomes after treatment. Preclinical and clinical studies have demonstrated the efficacy of metformin, the oral insulin-sensitizing drug most widely prescribed for the treatment of type 2 diabetes, to inhibit the growth of BC cells. In particular, a recent pre-surgical clinical study has shown the efficacy of a 4-week treatment with metformin to reduce Ki-67 (a well-established biomarker for cell proliferation) in BC cells specifically in nondiabetic metabolically unbalanced subjects.

It is postulated that the commonly used and cheap oral anti-diabetic drug, given for one year, may decrease epithelial cell proliferation also in healthy, metabolically unbalanced BC survivors. Thus it is hypothesized that these effects may induce a possible reduction of early and late BC recurrence/second primary cancer.

This project proposes a randomized, placebo-controlled, phase II study (one year of accrual, one year of treatment, and one year of follow-up and analysis of results) with metformin/placebo in 236 pre- and postmenopausal (aged 18–70), metabolically unbalanced (BMI >25 Kg/m2) BC survivors at higher risk for recurrence. We will randomize nondiabetic patients with prior triple negative BC (TNBC), or estrogen receptor (ER) negative progesterone receptor (PgR) negative HER2 positive BC, or Luminal B HER2 positive BC at the end of standard adjuvant therapies (no later than 2 years from the cessation).

The primary endpoint is the effect of treatment on the change of Ki-67 in contralateral unaffected breast biopsies after 12 months of treatment.

Secondary endpoints are the effects of metformin on a series of circulating and molecular biomarkers, the validation of metformin anticancer-action pathways, and various transcriptomic, epigenomic and metabolomic analyses. Safety and toxicity of the treatment will be additional endpoints.

The joint effort of the research consortium will contribute to better elucidate the clinical and molecular effects of metformin and to confirm its role in tertiary prevention of high risk patients.

Donor:	Institut National du Cancer (INCa), France as part of the ERA-Net Translational Cancer Research (TRANSCAN)
Duration:	36 months
Funds for IARC:	€407 320 (US$ 443 704)
Funds for partners:	€825 000 (US$ 898 693)
Total:	€1 232 320 (US$ 1 342 397)

Partners:

European Institute of Oncology, Italy, €250 000 (US$ 272 331)

University of Bergen, Norway, €575 000 (US$ 626 362)

Section of Cancer Surveillance (CSU)

1.3   Project title: **Fostering partnerships between Cancer Research UK (CRUK) and IARC in developing up-to-date approaches to international cancer survival benchmarking**

Cancer survival is one of the key measures in assessing the performance of health care systems and the effectiveness of early detection strategies, alongside the quality of clinical care and management. In the last decades, the cancer control landscape has altered, with many actions having a marked but complex impact on incidence, mortality and survival of common cancers. Changing diagnostic practices and a number of breakthroughs in therapy and management have been accompanied by the adoption of population-level screening programmes (breast and cervical cancer). Screening for colorectal cancer is now implemented in several high income countries (HICs), while campaigns aimed at the early diagnosis of common cancers including melanoma and lung cancer have also been recently introduced.

Regular updates of a comprehensive set of survival indicators (alongside corresponding indicators of incidence and mortality) are needed to enable evaluation of the national cancer control programme. International benchmarking remains key to exploring reasons for differences in cancer survival in different populations. A number of international collaborations have had profound influence on national cancer policies aimed at improving population-based cancer survival. At the same time pioneering statistical methods have articulated outcome differences in cross-country comparisons.

IARC is developing its global survival portfolio and seeks to foster collaborations in survival estimation in HICs as well as in low- and middle-income countries (LMICs). Survival is a key indicator of the cancer burden, and survival analysis is an intrinsic part of CSU activities. Through its worldwide estimation exercises, the Agency attempts to capture the Post-2015 Development Agenda and the inequalities evident in diagnosis and treatment, as captured in disease metrics of survival, premature mortality and quality of life. This project provides an important opportunity for IARC and CRUK to further develop collaborations in population-based research on survival, as well as exchange knowledge through mutual staff visits.

Donor:	Cancer Research UK, United Kingdom
Duration:	36 months
Funds for IARC:	€368 640 (US$ 390 095)
Funds for partners:	-
Total:	€368 640 (US$ 390 095)
Partners:	**n/a**

1.4   Project title: **Definition of priorities in cancer prevention in metropolitan France: Assessment of the proportion of cancer attributable to lifestyle and environmental factors in 2015**

Cancer is a major cause of morbidity and mortality in France with over 355 000 new cases per year and around 150 000 deaths in 2012. Over the last 30 years the annual number of new cancer cases has doubled and despite improvements in early detection and treatment, cancer remains the first cause of death in France. As such, primary prevention through lifestyle and environmental changes offers the best option for reducing the burden of cancer.

Previous work published as an IARC Working Group Report on attributable causes of cancer in France in 2000 reported that 35% of cancers are thought to be preventable. This report however did not include several important, recently established, risk factors including dietary factors and air pollution. Recent improvements in methods have accounted for the cumulative impact of smoking on cancer and enabled the estimation of attributable fractions of cancer related to infection. Additionally, cancer risk factors in France continue to change, and up-to-date information on exposure must be utilized.

The project is estimating the proportion of cancer occurring in France in 2016 that can be attributed to sub-optimal past exposure of 26 lifestyle and environmental risk factors. In addition, where possible, variations in attributable fractions by socioeconomic status will be assessed.

Donor:	Institut National du Cancer (INCa), France
Duration:	30 months
Funds for IARC:	€321 485 (US$ 350 202)
Funds for partners:	-
Total:	€321 485 (US$ 350 202)
Partners:	**n/a**

1.5   Project title: **Making cancer data count: IARC strategies to support the development of population-based cancer registries in low- and middle-income countries for cancer control planning (GICR)**

Linking in with the global political agenda tackling noncommunicable diseases (NCDs), GICR is a multi-partner initiative coordinated by IARC providing measurable improvements in the coverage, quality and networking capacity of cancer registries in low- and middle-income countries (LMICs). Officially designated as IARC Regional Hubs for Cancer Registration, the centres aim to accelerate the availability and enhance the quality of data to inform national cancer control policies.

The project focuses on strategic development of the GICR and the Regional Hubs, the delivery of targeted training courses to develop local expertise, and the production of accompanying tools to enhance global statistics and assist with the planning and operations of cancer registry systems in LMICs defined in six Hub regions (1. Sub-Saharan Africa, 2. Northern Africa & Central

and Western Asia, 3. Southern, Eastern and South-Eastern Asia, 4. Latin America, 5. The Caribbean and 6. The Pacific Islands).

In order to ensure coordination across the Regional Hubs, IARC coordinates a Hub Executive (HEX) whereby the principal investigators of the Hubs, IARC staff and other experts are able to exchange experiences to ensure best practice across the Hub network.

Donor:	Medical Research Council (MRC), United Kingdom
Duration:	24 months
Funds for IARC:	€633 333 (US$ 694 444)
Funds for partners:	-
Total:	€633 333 (US$ 694 444)
Partners:	**n/a**

Epigenetics Group (EGE)

1.6   Project title: **Identification of epigenetic precursors of childhood cancer and associated in utero determinants and early life exposure**

The overall incidence of childhood cancer (CC) has been steadily increasing worldwide, and although CC is rare in the general human population, it remains the leading cause of disease-related mortality in children and adolescents (ages up to 19 years). Our understanding of the causal pathways underlying these malignancies remains limited, due to the small size and lack of statistical power of many previous studies. Moreover, the majority of associations in observational studies have relied on retrospective evidence, often prone to biases, and mostly highlighting risks attributed to rare genetic syndromes in only a small fraction of cases. Similarly, for disease etiology, due to mixed results, compelling evidence linking environmental exposures to CC is still lacking. Perhaps the most consistent association linking CC to exposure is ionizing radiation from World War II atomic bombs and accidents at nuclear power plants. Therefore, studying CC in multiple cohorts worldwide might be crucial to accumulate enough evidence on environmental causes, particularly those linked to different geographies, and to combine sample sizes that are sufficiently powered to study relevant associations. If coupled to prospective designs and associated biospecimens, such studies constitute new opportunities for taking a 'leap forward' in identifying robust predictors of cancer risk and associated environmental determinants.

This project is based on both prospective and retrospective studies encompassing multiple cohorts, with biospecimens and exposure data available from various geographical regions in the world. Namely, the prospective samples are available from the International Childhood Cancer Cohort Consortium (I4C), which is the largest birth cohort consortium comprising 316 000 subjects (800 CC cases). The retrospective samples are available from the French ESTELLE/ESCALE cohort (500 CC cases), whereas additional prospective and retrospective samples from other cohorts will also be used for independent validations. Building on materials obtained from these cohorts, we plan to test for the first time the association between prospectively collected exposure data and epigenomic measures obtained from prospective

biospecimens collected at birth, and subsequent incident CC. Using both the exposure and epigenomic measures, we will explore in detail the associations for those risk factors for which some evidence has already emerged from previous case-control and biological studies. These include folate intake, infections and parental exposure to environmental chemicals and ionizing radiation. We will also investigate whether it is possible to identify causal pathways or mechanisms that explain associations and how they compare between the prospective and retrospective designs.

This study should improve our knowledge concerning the etiology of CC, thus providing an evidence-base for cancer prevention. It should also provide further opportunities to initiate mechanistic studies on developmental origins of CC.

Donor: Institut National de la Santé et de Recherche (INSERM), France

Duration: 36 months

Funds for IARC: €441 322 (US$ 484 969)

Funds for partners: €134 680 (US$ 148 000)

Total: €576 002 (US$ 632 969)

Partners:

Institut National de la Santé et de Recherche (INSERM), France, €134 680 (US$ 148 000)

Genetic Epidemiology Group (GEP)

1.7 Project title: **Biomarkers of human papillomavirus (HPV) infection and risk of two increasing cancers**

Oropharyngeal cancer and anal cancer have been recently highlighted in the annual 'Report to the Nation on the Status of Cancer' as being the two cancers in the US that are increasing among both men and women. Our proposal focuses on these two cancers.

Our pilot data from the European Prospective Investigation into Nutrition and Cancer (EPIC) cohort indicate that circulating HPV16 E6 antibodies are present over 10 years before diagnosis in a large proportion of people who develop oropharyngeal cancer (35%), whilst being rare among controls (0.6%). We have subsequently identified HPV16 E6 antibodies in 29% of anal cancers and, again, being extremely rare among a separate group of controls (0.6%). These results are noteworthy as they indicate that a HPV-driven neoplastic process is present many years prior to diagnosis for both of these cancers, and raises the possibility that HPV16 E6 antibodies can be used as a highly specific biomarker to predict cancer onset. We have already established a cohort consortium in order to evaluate the sensitivity, specificity, and true latent period of HPV16 E6 antibody response before diagnosis, as well as survival outcome among all head and neck cancers for those who test positive. By bringing together 10 prospective cohorts from the US and Northern Europe, two populations where HPV infection now being recognized as the predominant cause of oropharynx cancer, we plan to identify 252 new oropharyngeal cancers and 180 anal cancer cases with pre-diagnostic blood samples available for analysis. We will also collect tumour tissue from 100 oropharynx cancer cases and 50 anal cases to evaluate the correlation between serology and tumour biomarkers of HPV infection.

Donor:	National Institutes of Health/National Cancer Institute (NIH/NCI), USA
Duration:	48 months
Funds for IARC:	€1 018 567 (US$ 1 145 745)
Funds for partners:	€621 806 (US$ 699 444)
Total:	€1 640 373 (US$ 1 845 189)

Partners:

Johns Hopkins University, USA, €63 390 (US$ 71 305)

Uppsala University, Sweden, €21 619 (US$ 24 318)

Albert Einstein College of Medicine, USA, €61 646 (US$ 69 343)

Fred Hutchinson, USA, €68 952 (US$ 77 561)

Norwegian University of Science and Technology, Norway, €18 069 (US$ 20 325)

Brigham and Women's Hospital, Harvard Medical School, USA, €213 722 (US$ 240 407)

Vanderbilt University, USA, €50 996 (US$ 57 364)

North Carolina at Chapel Hill, USA, €59 085 (US$ 66 462)

German Cancer Research Center (DKFZ), Germany, €64 327 (US$ 72 359)

Cancer Council Victoria, Australia, 0€ (US$ 0)

Laboratory Services and Biobank Group (LSB) and Education and Training Group (ETR)

1.8   Project title: **Bridging Europe-Africa biobanking and biomedical research (B3Africa)**

Bridging biobanking and biomedical research across Europe and Africa will dramatically improve and facilitate the development of better predictive, preventive and personalized healthcare worldwide. The rapidly evolving African biobanks are an invaluable resource: the African population has the greatest genomic diversity on the planet and represents an important resource of information to advance biomedical research. This project aims to implement a cooperation platform and technical informatics framework for biobank integration between Africa and Europe. The collaboration harmonizes the ethical and legal frameworks, biobank data representation and bioinformatics pipelines for sharing data and knowledge among biobanks and allowing access for researchers from both continents. Main actors from the relevant initiatives including Human Heredity and Health in Africa project (H3Africa), European Biobanking and Biomolecular Resources research infrastructure (BBMRI-ERIC) and the LMIC Biobank and Cohort Network (BCNet) collaborate in B3Africa to address the following objectives:

Defining an ethical and regulatory framework for biobank data sharing between Europe and Africa, defining data models for representing biobank and research data based on existing best practices, standards and ontologies, designing an informatics platform using existing open-source software (with eBioKit and BiBBox as essential modules) integrating workflows for biobank applications, implementing of an education and training system for information and capacity building, validating the B3Africa concept with existing biobanks from both continents.

B3Africa provides the critical mass to maximize efficiency in biomedical research, supports defragmentation through integration and allows efficient leverage of existing biobanks and e-infrastructures in Europe and Africa. The technical informatics framework will be designed for easy upscaling and integration with other research infrastructures.

Donor: European Commission, Directorate General for Research and Innovation, Belgium

Duration: 36 months

Funds for IARC: €365 000 (US$ 397 603)

Funds for partners: €1 636 250 (US$ 1 782 407)

Total: €2 001 250 (US$ 2 180 010)

Partners:

Swedish University of Agricultural Sciences, Sweden, €441 250 (US$ 480,664)

Biobanking and BioMolecular Resources Research Infrastructure, Austria, €70 000 (US$ 76 253)

Karolinska Institut, Sweden, €210 000 (US$ 228 758)

Uppsala University, Sweden, €150 000 (US$ 163 398)

University of The Western Cape, South Africa, €210 000 (US$ 228 758)

Makerere University, Uganda, €70 000 (US$ 76 253)

Stellenbosch University, South Africa, €70 000 (US$ 76 253)

International Livestock Research Institute, Kenya, €110 000 (US$ 119 826)

Medical University Graz, Austria, €235 000 (US$ 255 991)

Institute Of Human Virology Nigeria, Nigeria, €70 000 (US$ 76 253)

Nutritional Epidemiology Group (NEP) and Epigenetics Group (EGE)

1.9 Project title: **Biomarkers of fatty acids, the epigenome and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort**

Breast cancer (BC) is by far the most frequent cancer among women with an estimated 1.68 million new cancer cases diagnosed in 2012 (25% of all cancers). While multiple risk factors for BC such as family history, obesity, lactation, and reproductive history, are well established, the disease has very few well known modifiable risk factors. Therefore, the environment, diet and lifestyle with their great potential for modification, has become a major focus in BC research.

Among risk factors avoidable due to prevention, diet has been suggested to account for up to 25–40% of preventable causes of cancers. Much discrepancy has surrounded the epidemiological link between dietary intake of fat and risk of BC. Dietary measurement error inherent to the use of food frequency questionnaires could explain, at least in part, the chronic inconsistency of evidence among epidemiological findings, and could have masked true associations. In contrast, plasma phospholipid fatty acid levels offer validated biomarkers of dietary intake of fatty acids and lipid metabolism. We provided preliminary evidence that a high

level of endogenously synthesized monounsaturated and dietary industrial trans fatty acids (ITFA) are modifiable risk factors for BC in the French E3N-EPIC cohort. The large-scale replication of these findings, along with the identification of underlying mechanisms, is crucial for providing specific dietary recommendations.

Fatty acids can alter the epigenome, although the epidemiological evidence is still poorly documented. Moreover, the role of epigenetic changes as a crucial mechanism deregulating gene expression and then a wide range of key metabolic pathways and cellular processes has emerged in many cancer types, including BC. So far, there is no prospective epidemiological data on the relationship between dietary fatty acids and the epigenome, and their impact on BC development.

The overall objective is to evaluate the associations between biomarkers of dietary fatty acids and fatty acid metabolism and DNA methylation content in relation to BC risk in a case-control study nested within the EPIC study.

A case-control study nested within the EPIC cohort among women who completed the dietary questionnaire and provided blood samples was designed. This study includes 4852 cases with invasive BC. For each case subject, one matched control was chosen randomly among cancer-free cohort participants. Control subjects were matched to cases on age, menopausal status at recruitment, recruitment centre and recruitment date. Measurement of plasma phospholipid fatty acids through validated gas chromatography methodology are in progress at IARC. Genome-wide DNA methylome profiling in white blood cells (WBC) will be conducted in randomly selected 715 cases and 715 controls from this population study, and will be followed by a two-step replication analysis of 20 top hits genes in larger series of samples. The panel will be subjected to methylation analysis by pyrosequencing using WBC samples from the EPIC sub-cohort of 1500 BC cases and 1500 matched controls.

Most recent techniques of multivariate analyses will be used to fully explore the variability and the relationship between DNA methylation states in differentially methylated genes and plasma levels of fatty acids, using principal component partial R-square and partial least square analyses. Multivariate mediation analysis will help investigate the mode of action of fatty acids and epigenetic profiles in relation to the risk of BC.

The study is the first large prospective epidemiological study on the relationship between biomarkers of a large panel of fatty acids and the epigenome, and their impact on BC risk. It will clarify whether relevant modifiable risk factors exert their biological effects on the development of BC through epigenetic deregulation.

Donor:	Institut National du Cancer (INCa), France
Duration:	24 months
Funds for IARC:	€349 359 (US$ 369 692)
Funds for partners:	-
Total:	€349 359 (US$ 369 692)
Partners:	**n/a**

Nutritional Epidemiology Group (NEP)

1.10 Project title: **The influence of metabolic syndrome and circulating bile acid levels on the development of hepatocellular carcinoma and biliary tract cancers**

Increasing rates of highly malignant hepatocellular carcinoma (HCC) and biliary tract cancers (GBTC) observed in Western populations may be related to obesogenic lifestyle factors and their metabolic consequences, such as metabolic syndrome (MetS), inflammation and altered production of bile acids (BA). Such lifestyle behaviours may induce changes in the gut microflora which in turn affect BA profiles, increasing their carcinogenicity. Some elevated BA may be oncogenic in exposed liver, bile ducts and gall bladder. Data from case-control studies show higher blood BA in patients with various liver diseases, but from these designs it is unclear if the differences in BA levels are etiologic or consequential. To date no prospective studies have investigated the role of circulating BA levels in the development of HCC/GBTC, nor any potential interactions with diet, obesity and MetS. Interestingly, Vertical Sleeve Gastrectomy (VSG), an anti-obesity intervention, may alter BA profiles.

This project is composed of two complementary studies designed to explore the role of BA in obesity, liver function and tumorigenesis. The first study is a case-control study of hepatobiliary cancers (191 HCC; 266 GBTC; 457 matched controls) nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) with extensive and detailed dietary/lifestyle data, body size measures and biological samples taken at baseline prior to disease development. The aim of this study is to explore associations between pre-diagnostic MetS markers and BA levels and the risk of HCC and GBTC, and to establish whether the observed associations are modulated, in part, by dietary/lifestyle factors or metabolic dysfunction.

The second study is based on a clinical setting and aims to recruit 100 morbidly obese subjects undergoing VSG to compare their BA and metabolic profiles pre- to one year post-surgery. This study is based on observations that post-VSG BA synthesis is increased, but changes in BA composition towards possibly harmful profiles have not previously been studied. It is also hypothesized that the degree of weight loss and metabolic improvement in VSG patients may be related to pre-surgical BA profiles.

In both studies, comprehensive panel of 17 serum BA (primary, secondary, (un)-conjugated, sulphated) and metabolic biomarkers (inflammation, liver function, dyslipidemia, HbA1c, MetS indicators, hepatitis status) will be assessed using validated methods. Study 2 will also assess expression of liver FXR, a BA receptor gene.

The project is based on two related concepts. First, that lifestyle behaviours and obesity may alter gut microflora leading to changes in BA metabolism, enhancing production of specific BA known to be cancer promoting. Second, observations of increased BA levels post-VSG surgery, which may improve metabolic function, but some BA may be pro-carcinogenic over the longer term. The project will provide improved understanding of the inter-relations between BA, lifestyle behaviours and metabolic factors and the development of hepatobiliary cancers. It will also identify specific BA most strongly associated with these highly malignant cancers. The findings will contribute to the evidence base for advice on lifestyle and metabolic modifications for cancer prevention. The clinical implications are two-fold: first, the findings will provide insight

as to whether BA profiles are predictive of the efficacy of VSG with potential implications in personalized medicine, and second, identified biomarker profiles may be used for more refined risk stratification for development of these cancers and subsequent closer patients' surveillance for early detection.

Donor:	Institut National du Cancer (INCa), France
Duration:	36 months
Funds for IARC:	€341 113 (US$ 381 558)
Funds for partners:	€116 979 (US$ 130 849)
Total:	€458 092 (US$ 512 407)

Partners:

Hôpital Antoine-Béclère, Paris, France, €81 006 (US$ 90 611)

Centre de recherche en épidémiologie et santé des populations, France, €35 973 (US$ 40 238)

Prevention and Implementation Group (PRI)

1.11 Project title: **Prevention At PRImary Care level (PAPRICA)**

Oncogenic human papillomavirus (HPV) infection is the cause of nearly all cervical cancers and a proportion of other anogenital and oropharyngeal cancers. A bivalent vaccine containing HPV 16 and 18 antigens and a quadrivalent vaccine containing HPV 6, 11, 16, and 18 antigens are in use in vaccination programmes around the world. In clinical trials, the vaccine provided 90–100% protection against cervical infection and pre-cancer related to HPV 16 and 18. The vaccines were also efficacious at the prevention of HPV 16 and 18 infections at other anatomical sites in both sexes. Pre-licensure and post-licensure studies have provided data supporting vaccine safety. Data from several countries have shown the effect of vaccination on HPV infection and associated disease, and provided evidence of herd immunity. By specifically targeting young girls for vaccination before HPV infection, and women for screening at the age of risk to develop cervical cancers, these two strategies have the potential to yield a greater benefit when implemented together rather than separately.

Besides implementing a national organized cervical cancer screening programme, another goal of the French Cancer Plan 2014–2019 is to obtain a 60% coverage for HPV vaccination. Currently available data on 3-dose HPV vaccination shows that the coverage is low in France (29%), comparing to other EU countries like Italy (66%) or the United Kingdom (80%). The vaccine was introduced into the French immunization schedule in 2007. The target population was originally 14 year old females but this was changed to 11–14 (11–14 (Cervarix®) or 11–13 (Gardasil®)) year old females in 2013 to match the age of the Diphtheria-tetanus-poliomyelitis (DTP) booster. Since 2014, a 2-dose vaccination schedule with a 6-month interval is recommended if administered before age 14 (Cervarix®) or 15 (Gardasil®). The vaccine is physician administered and immunization is opportunistic depending both on parents and practitioners' acceptability and willingness. Qualitative surveys have shown that concern about possible side effects is the major barrier to wider acceptance of the HPV vaccine

in France. However, the general practitioner (GP) is still considered as a trusted source for providing HPV vaccination recommendation.

Because the DTP booster coverage is high in France (about 90%), we reasoned that GPs ensuring that as many of the girls attending DTP booster appointment as possible receive the relevant information about HPV vaccination and its potential contributions to reducing HPV-related cancers might be an easy way to increase HPV coverage.

The PAPRICA study aims to test if an intervention directed to health-care providers to train them in methods for recommending HPV vaccine is effective to increase HPV vaccination coverage in France. As each health professional is associated in France to a specific reference number, i.e. "ADELI number", ADELI numbers for all GPs and paediatricians from the City of Lyon will be randomly allocated either to the intervention arm or to the control arm to ensure that each arm contains 50% of the total number of GPs and 50% paediatricians. After allocation, GPs and paediatricians in the allocation arm will be identified and invited to attend the intervention, i.e. a 3-hour workshop at IARC in the presence of HPV vaccination specialists. The effect of the intervention on the HPV vaccination coverage in Lyon will be measured through HPV vaccines reimbursement data extracted from the Inter-Scheme National Information System within the National Health Insurance System (SNIIR-AM: Système National d'Information Inter-Régimes de l'Assurance Maladie). Linkable data between girls and GPs/paediatricians via ADELI numbers will allow us to allocate girls either in the intervention or the control arm. Vaccination coverage will be estimated within each of these cohorts, i.e. number of HPV vaccines reimbursed and time interval between reimbursements will be extracted. These two indicators will give information about whether or not the vaccination schedule was completed: fully vaccinated girls are girls who received both two doses (current HPV vaccination recommendation) or all three doses (previous recommendation) over six months. We will collect also data related to DTP vaccination booster. Because the coverage is high for DTP booster vaccination, we expect that the intervention will reduce discrepancy between vaccination coverage for HPV and vaccination coverage for DTP. By focussing on optimizing the delivery of an existing system rather than focussing on the development of a new system, our intervention has the potential to interest French policy makers; the educational intervention could be easily implemented in other settings. It has also the potential to be interesting for other countries, e.g. the US where HPV vaccination coverage is problematic.

Donor:	Institut National du Cancer (INCa), France
Duration:	36 months
Funds for IARC:	€320 247 (US$ 363 092)
Funds for partners:	€0 (US$ 0)
Total:	€320 247 (US$ 363 092)

Partners:

University College London (UCL), United Kingdom, €0 (US$ 0)

Centre Léon Bérard, France, €0 (US$ 0)

2.   Prior approval for projects in collaboration with the private sector

Please note that the following two projects have been provisionally approved by the Chairperson of the Governing Council.

Section of Cancer Surveillance (CSU), Prevention and Implementation Group (PRI), Education and Training Group (ETR) and Laboratory Services and Biobank Group (LSB)

2.1   Project title: **Global Initiative on Cancer Registries (GICR), ESTAMPA, IARC Summer Course, and BCNet biobanking**

The NCI Center for Global Health (NCI CGH) and IARC have an existing Memorandum of Understanding (MoU) to support areas of mutual interest, including support of global cancer registry work, training, cancer control and biobanking. During the last Governing Council in May 2015, the NCI CGH informed IARC that a total of US$ 640 000 was earmarked to support IARC in various activities under the existing MoU. While these contributions were previously formalized individually through IARC's standard Direct Contribution Agreements (DCAs), it was proposed to route them through an organization called CRDF Global in order to heighten project oversight. IARC was informed that CRDF had been used by other NIH services for that purpose.

CRDF Global – which was established in 1995 – is an independent nonprofit organization that promotes international scientific and technical collaboration through grants, technical resources, training and services. It designs and manages international research funding programmes and supports emerging science and technology infrastructure in over 30 countries. Of the total funding to IARC, the funds are to be disbursed to the following projects:

1. The Global Initiative on Cancer Registries (GICR) €467 460 (US$ 530 000)

2. The ESTAMPA project €44 100 (US$ 50 000)

3. The IARC Summer course for 2015 €26 460 (US$ 30 000)

4. The BCNet biobanking project €26 460 (US$ 30 000)

Donor:	National Institutes of Health, National Cancer Institute (NIH/NCI), USA (though CRDF Global)
Duration:	10 months
Funds for IARC:	€564 480 (US$ 640 000)
Funds for partners:	-
Total:	€564 480 (US$ 640 000)
Partners:	**n/a**

Section of Environment and Radiation (ENV)

2.2   Project title: **Coordination of the International Birth Cohort Harmonisation Group**

The International Birth Cohort Harmonisation Group has been established to strengthen the collaboration and coordinate the activities of the birth cohorts from Japan, China, France and

Germany. This joining of forces is essential to achieve the scientifically most reliable results from those studies. Even large cohorts are hardly big enough to investigate effects on health outcomes in children, as most of them are not common, although very severe, such as sudden infant death or childhood cancer. This is why pooling of data is necessary to increase the statistical power of studies to detect any associations between environmental exposures and health outcomes. An important prerequisite of pooling however is comparability of data, which applies both to how the exposure information is collected and operationalized, and how the outcomes are assessed. This requires procedures for harmonization of data. Successful harmonization requires the moderation of a neutral coordinator ensuring that the most scientifically rigorous approach is taken and every country has an equal opportunity to participate in this process.

IARC has vast experience in the scientific coordination of international consortia and harmonization of data collected in different settings. IARC has also a scientific interest in investigating early life exposures on cancer risk and therefore an interest to contribute to the group's activities in setting up scientific projects within the consortium. This proposal is to have IARC as the coordinator of the International Birth Cohort Harmonisation Group for an initial period of two years.

A tripartite collaboration between the Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety, Germany, and the Ministry of the Environment, Japan and IARC has been set up for this. The Japanese Ministry has mandated Janus, Ltd to handle on their behalf the contracting with IARC. This service provider was chosen by the Ministry through an open bidding process and has been providing services to the Ministry over a period of 20 years.

Japan NUS Co. Ltd. Active in technical consulting concerning the environment, energy and systems. Consulting services concerning the environmental economy and energy economy. Founded in June 1971, JANUS currently employs 160 staff members. Its shareholders are JGC corporation (88.88%), Tokyo electric power company (5.55%), the Kansai electric power company incorporated (2.77%) and the Chubu electric power company incorporated (2.77%). JANUS' main activities relate to providing advice to foreigners willing to carry out activities in Japan. It provides them with information about Japan's energy situation and its various environment regulations. This company also conducts quantitative evaluations on the biodiversity and the protection of the natural environment.

http://www.janus.co.jp/eng/

Donor:	Ministry of the Environment, Japan (through Japan NUS Co., Ltd.)
Duration:	24 months
Funds for IARC:	€65 540 (US$ 71 864)
Funds for partners:	-
Total:	€65 540 (US$ 71 864)
Partners:	**n/a**

3. Prior approval for projects over €500 000 per annum

The Governing Council is invited to consider, for approval, projects submitted over €500 000 per annum, excluding sums passed on to collaborating institutions, and projects that require more than €100 000 per annum, excluding the principal investigator's staff costs, from the IARC regular budget, as detailed below.

Please note that the following project has been provisionally approved by the Chairperson of the Governing Council.

Screening Group (SCR)

3.1 Project title: **Extended follow-up of the participants of IARC-INDIA HPV vaccination study to evaluate the effectiveness of one, two and three doses of quadrivalent HPV vaccine in preventing cervical neoplasia**

Cervical cancer is a major cause of morbidity, mortality and premature deaths among women in developing countries, and these countries account for more than 80% of an estimated 528 000 new cases and 266 000 deaths worldwide annually. If effective prevention interventions are not implemented, over one million women will suffer from cervical cancer annually by the year 2030, leading to an even greater disparity in risk and suffering as compared to developed nations, and increasing the social inequalities.

While early detection of asymptomatic precancerous lesions by screening and their effective treatment lead to the prevention of invasive cervical cancer and premature deaths caused by it, the fact that persistent infection by some oncogenic human papillomavirus (HPV) types causes cervical cancer provides another effective and safe opportunity for prevention through vaccination against the virus.

It has been estimated that HPV types 16/18 are responsible for approximately 70% of all cervical cancers. Vaccines have been developed, primarily to prevent infection from HPV types 16 and 18, and have the potential to prevent nearly 370 000 cervical cancers annually worldwide. One of the vaccines also target HPV types 6 and 11, which cause more than 90% of the genital warts in men and women.

Both the bivalent (targeting HPV 16, 18) and the quadrivalent (targeting HPV 6, 11, 16, 18) HPV L1 virus-like particle (VLP) vaccines demonstrated high efficacies in Phase III clinical trials. The published results from these studies indicate with remarkable consistency that a regimen of three intramuscular injections of HPV vaccine offers HPV–naïve women a very high level of protection (~99%) from persistent HPV infections and high-grade cervical intraepithelial neoplasia (CIN) associated with the HPV types included in the vaccine. The vaccines were safe and well tolerated with relatively few side effects. Currently the vaccine is being administered to adolescent girls through routine immunization programmes in more than 70 countries across the globe. The high cost of the vaccine is a major barrier for many of the low- and middle-income countries to introduce the vaccine in the national programmes.

IARC initiated a multi-centric cluster-randomized trial in India in the year 2007 to evaluate the effectiveness of two doses (days 1 and 180) of quadrivalent vaccine compared to three doses (days 1, 60 and 180) of the same vaccine. This study is supported by the Bill & Melinda Gates Foundation. The study aimed to recruit 20 000 girls and women between 10 to 18 years of age equally distributed between the two study arms. In April 2010, the Indian authorities suspended HPV vaccination of the girls due to events unrelated to the study. At that time the study had recruited 17 729 girls. Suspension of recruitment and vaccination in the trial led to loss of randomization and resulted in a cohort study of four instead of the planned two study groups: 4348 girls receiving three doses on days 1, 60 and ≥180, 4979 receiving two doses on days 1 and ≥180, 3452 receiving two doses on days 1 and 60 by default, and 4950 receiving one dose by default. All the girls/women have been followed up for five years (up to 2015) to evaluate the immunogenicity and safety of the vaccine and efficacy against incident/persistent HPV infections. In addition, we recruited an ad-hoc "control" group of 1450 age-matched unvaccinated girls/women in 2013 who are being followed-up to facilitate the "within the study" comparison of vaccinated and unvaccinated cohorts.

The preliminary results of the study, recently published in the Lancet Oncology, demonstrated that two doses of the vaccine administered at the minimum interval of six months can induce robust immune response that is similar to that achieved after three doses of the vaccine. Two doses were equally effective as three doses to prevent incident and persistent infection of targeted HPV types. Even a single dose of the vaccine elicited an immune response and had similar protective effect against HPV infection as that of two or three doses.

In the extended phase of the same study we aim to follow up all the girls/women in both the vaccinated and unvaccinated cohorts for a further five years to establish the frequency of persistent HPV infections and CIN caused by vaccine targeted and non-targeted HPV types in the different dose groups to assess the long-term clinical efficacy of two doses and a single dose of the HPV vaccine compared with three doses. Proof of the efficacy against long-term clinical outcomes will strengthen the evidence base for the current WHO recommendation of two doses for adolescent girls and will contribute to the evidence base if one dose may be efficacious for cervical cancer prevention in pre-adolescent and adolescent girls. The public health implication of either of the findings will be immense, as this will allow many of the resource-limited countries to introduce the vaccination programmes at a substantially lower cost and improve compliance and access to vaccination. The proposed long-term follow-up in this study has public health relevance for developed countries as well given the fact that a significant proportion of HPV vaccinees actually receive a single or two doses in high-income countries. Given the real possibility that many developing countries may not adequately invest in organizing cervical screening services, HPV vaccination is the singularly most potentially useful and effective intervention in the long-term. The extended study will also address important issues related to the screening of the vaccinated women. During this extended five-year period starting on 1 August 2016 and up to 31 July 2021, many of the participants in the present study will reach 25 years of age and will be eligible for screening. Screening of these women with HPV testing will allow us to evaluate the performance of HPV screening in the vaccinated women, regarding which very little information is available in the literature.

Donor:	Bill & Melinda Gates Foundation, USA
Duration:	60 months
Funds for IARC:	€2 670 697 (US$ 2 928 396)
Funds for partners:	€4 014 807 (US$ 4 402 200)
Total funds:	€6 685 504 (US$ 7 330 596)

Partners:

German Cancer Research Centre, Germany, €414 960 (US$ 455 000)

Gujarat Cancer Research & Institute, Ahmedabad, India, €120 954 (US$ 132 625)

Christian Hospital, Ambillikai, India, €399 228 (US$ 437 750)

Nargis Dutt Memorial Cancer Hospital, Barshi, India, €830 034 (US$ 910 125)

All India Institute of Medical Sciences, New Delhi, India, €136 914 (US$ 150 125)

MNJ Cancer Institute, Hyderabad, India, €124 944 (US$ 137 000)

Cancer Foundation of India, Kolkata, India, €26 175 (US$ 28 700)

Civil Hospital, Aizawl, Mizoram, India, €68 400 (US$ 75 000)

Tata Memorial Hospital, Mumbai, India, €58 596 (US$ 64 250)

Jehangir Clinical Development Centre, Pune, India, €389 766 (US$ 427 375)

STNM Hospital, Gangtok, Sikkim, India, €76 836 (US$ 84 250)

Rajiv Gandhi Centre for Biotechnology, Trivandrum, India, €1 368 000 (US$ 1 500 000)

4. Interest income from grants

In accordance with the standing authorization provided to the Director under resolution GC/55/R23 and the conditions set forth in the signed agreements, interest income totalling €9986 was apportioned to five grants in 2015. Details are provided in the table below.

Grant No.	Project	Donor	Interest in €
100097	Randomized trial of 2 versus 3 doses of HPV vaccine in India	Bill and Melinda Gates Foundation	2 619
100401	Monitoring HPV vaccination and HPV screening programs to promote sustained implementation in low and middle income countries	Bill and Melinda Gates Foundation	2 401
100485	Understanding mechanisms and identifying biomarkers for the relationship between aflatoxin exposure and child stunting	Bill and Melinda Gates Foundation	305
100496	Aflatoxin control measures: a basis for improved health in developing countries	Bill and Melinda Gates Foundation	1 964
100639	Extended Follow-up of the Participants of IARC-INDIA HPV Vaccination Study to Evaluate the Effectiveness of one, two and three Doses of Quadrivalent HPV Vaccine in Preventing Cervical Neoplasia	Bill and Melinda Gates Foundation	2 697
Total interest income apportioned to grants			**9 986**