IARC Interim Annual Report 2012
Foreword

This Interim Annual Report contains many examples of the high-quality, interdisciplinary collaborative research that IARC conducts worldwide. It serves as an illustration of the relevance of the Agency's work to cancer control and is a testimony to how its core mission of promoting international cooperation in cancer research is being achieved. This is ever more valuable as recognition grows of the rising burden of cancer and its implications for sustainable development in the coming decades.

The United Nations High-Level Meeting of September 2011 focused the attention of the world’s leaders on the impending crisis of non-communicable diseases (NCDs), including cancer. The Political Declaration of the Meeting reflected not only the realization of the need for a swift and coordinated response involving all sectors of society, but also the recognition that “prevention must be the cornerstone of the global response to non-communicable diseases”.

The scale of the projected rise in the burden of cancer, particularly in low- and middle-income countries, is such that the only realistic response from a public health perspective, as well as from an economic and social one, is a strong commitment to prevention and early detection. IARC’s contribution to this global effort is both to produce the scientific evidence that underpins policy development and to support the translation of evidence into practice through cooperation with its network of partners in the scientific community and in civil society.

IARC is well positioned to respond to these challenges; supporting cancer prevention and control, particularly in low-resource settings, has been at the core of the Agency’s purpose since its inception, and through its relationship with WHO it has a direct channel for translation of its research into practice. In addition, IARC has increasingly directed its research activities in support of cancer prevention by focusing on four priority areas:

• cancer surveillance – describing the global cancer burden to assist the definition of regional and local priorities for cancer prevention and control, and for monitoring the effectiveness of specific interventions and public health programmes
• cancer etiology – using a multidisciplinary approach that incorporates the insights about the mechanisms of carcinogenesis into population-based studies, to characterize and evaluate the causes of human cancers and to inform policies for primary prevention
• cancer prevention – evaluating the effectiveness of interventions for prevention and early detection of cancer, in particular of simple, affordable methods and policies that can be appropriately implemented in low-resource settings
• implementation research – identifying the most effective approaches for the successful implementation of prevention programmes as well as the barriers to the participation of target populations in specific socioeconomic and cultural contexts.

To ensure the effective implementation of this overall strategy and the achievement of specific objectives in individual research sections, the Agency continued to build a broad support platform through an ongoing programme of investment and developments in:

• scientific leadership – attracting excellent scientists to lead research programs; recruitment of committed mid-career scientists, highly experienced senior visiting scientists, and motivated postdocs from around the world; creation of a collegiate and dynamic research environment

• infrastructure – investment in scientific equipment and IT capacity to ensure IARC’s research remains competitive; a programme of building renovation and ongoing discussions regarding the projects for a new building; review and optimization of business processes and administrative support to research

• resources – new Participating States; increase in competitive extra-budgetary sources; establishment of bilateral agreements and other voluntary contributions

• partnerships – expansion of the network of collaborations with national centres and international partners; establishment of relations with regional cancer networks; supporting and coordination with WHO regarding initiatives on NCD agenda

• communication – a renewed focus on external communication; completely redesigned web site; public profile and media relations.

The combination of excellent people, facilities, and collaborators is the foundation on which the cancer research described in this report is based. The next few years offer many opportunities, but at a time of severe economic constraints on research globally. This will require the Agency to be focused, efficient, and creative in response. However, I am confident that through its scientific strategy, its scientific leadership, the dedication of its researchers and support staff, and its wide network of collaborators and partners, IARC is well equipped and well placed to make a significant contribution to this global effort.

Dr Christopher Wild
IARC Director
Section of Cancer Information (CIN)

IARC is the definitive reference source for the provision of information about global statistics on the burden of cancer, and this activity is coordinated within the Section of Cancer Information (CIN). The monitoring of cancer occurrence provides baseline information for the development of cancer control planning, for the evaluation of public health interventions, and for etiological research programmes. The systematic recording of incidence, mortality, prevalence, and survival at national and regional levels provides estimates of the cancer burden that are relevant across the domains of cancer control, providing information about the underlying risk of disease as well as the efficacy of prevention, early detection, and treatment in different populations.

To undertake this activity, CIN coordinates the systematic collection, analysis, and dissemination of data from population-based cancer registries (PBCRs) worldwide. CIN also conducts a programme of research making use of these and other data for analyses of geographical patterns, time trends, and estimation of the future burden of the disease. These objectives can only be accomplished through the collaboration and support of cancer registries worldwide. CIN provides the secretariat for the International Association of Cancer Registries (IACR; http://www.iacr.com.fr) and the European Network of Cancer Registries (ENCR; http://www.encr.com.fr). The 34th IACR Annual Meeting was held in Cork, Ireland, in September 2012, hosted by the Irish National Cancer Registry under the scientific theme of “Better cancer control through better information”. The ENCR Scientific Meeting that followed highlighted the most significant achievements of the Network over the previous 5 years.

To increase the worldwide coverage and quality of PBCR data, CIN leads, on behalf of IARC, the Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries (GICR), a multi-agency programme to support capacity building in countries seeking to establish high-quality PBCRs. Several IARC Regional Hubs for Cancer Registration are being launched in selected locations in Africa, Asia, and Latin America and the Caribbean to put the GICR principles into practice through regional programmes of training, direct support, advocacy, and research.

GLOBOCAN (http://globocan.iarc.fr) is the unique database and online analysis tool for the provision of global, regional, and national estimates of the burden of cancer, currently for 2008. These estimates were enhanced in 2012 by the inclusion of two additional indicators, prevalence and disability-adjusted life years (DALYs). The prevalence figures provide a global estimate of almost 29 million persons living with cancer in 2008 diagnosed within the previous 5 years. This is supplemented in GLOBOCAN by estimates of cancer DALYs, with the global figure of 169 million years of healthy life lost due to cancer in 2008 indicative of the combined impact of fatal cancer and disabling non-fatal disease outcomes. These indicators, alongside incidence, mortality, and survival, provide a solid basis for determining the resource needs of patients in different regions of the world (Bray et al., 2012a; Soerjomataram et al., 2012a, 2012b).

Numerous studies from CIN have made use of the GLOBOCAN 2008 data set, and these include, in collaboration with the American Cancer Society (ACS), a detailed examination of cancer patterns in Africa (Jemal et al., 2012; see also ACS, 2011), and an analysis of the female global cancer burden highlighting the major differences in the sex-specific cancer profiles worldwide (McCormack et al., 2012). Another research direction has been to use the GLOBOCAN 2008 data in the estimation of burden of cancer associated with specific risk factors. In collaboration with ICE, we have estimated the attributable fraction of cancers associated with established infectious causes both worldwide and regionally (de Martel et al., 2012). This showed that 2 million (16.1%) of the total 12.7 million new cancer cases estimated in 2008 were attributable mainly to four major infections: human papilloma virus (HPV), hepatitis B and C virus, and
Helicobacter pylori. This fraction is higher in less developed countries (22.9%) than in more developed countries (7.4%). An analogous study on the burden of cancer associated with obesity has commenced in collaboration with NME and BST.

CIN is responsible for the production of Cancer Incidence in Five Continents (C15; http://ci5.iarc.fr). Produced in collaboration with the IARC, this serial publication contains comparable cancer incidence data made available by high-quality PBCRs worldwide. Work has been progressing on the development of the tenth volume in this series, to be published in 2013, and meetings of the Editorial Board have reviewed data sets supplied by more than 350 cancer registries in 81 countries, reporting incident cancers in the period 2003–2007. Work is also proceeding on a similar timescale for the third volume in the companion series, International Incidence of Childhood Cancer (IICC; http://iicc.iarc.fr).

The Cancer Mondial web site provides access to these and other databases (including the WHO mortality database and NORDCAN) and serves as a basis for descriptive epidemiological research. CIN has provided up-to-date reports on the global patterns and trends for several specific cancer sites in 2012. International variation in time trends of malignant melanoma incidence was examined using age–period–cohort models, in collaboration with ENV (Erdmann et al., 2012), while prostate cancer incidence and mortality rates were evaluated using joint-point regression, in collaboration with the ACS (Center et al., 2012). Two other studies making use of CI5-derived data, both with United States National Cancer Institute investigators, involve analyses of variation in the age-incidence pattern of Burkitt lymphoma (Mbulaiteye et al., 2012) and in the incidence of male breast cancer (Ly et al., 2012). There have also been international comparative studies of oropharyngeal cancer (de Camargo Cancela et al., 2012) and human immunodeficiency virus (HIV)-associated cancers in Africa (Chaabna et al., 2012).

Global and regional overviews, making use of all the data sources available to CIN, have been published on HPV-associated cancers (Bray et al., 2012b; Forman et al., 2012). An innovative study recently focused on cancer in relation to current levels of human development and the changing global cancer burden and profile as a result of the ongoing epidemiological transition worldwide (Bray et al., 2012c). This review evaluated cancer incidence and mortality in relation to the Human Development Index, a more comprehensive indicator of social and economic development than those used hitherto. Also incorporated were assessments of the future burden of cancer, building in estimates of future changes in risk of the major types of the disease to those resulting from population ageing and population growth.

CIN continues its practice of collaborating with individual PBCRs to provide support in data analysis and interpretation and has recently worked with the Croatia national registry to investigate trends in testicular cancer (Sincić et al., 2012; Znaor and Bray, 2012); with the Shanghai, China, registry on hepatocellular carcinoma (Gao et al., 2012); and with the Mumbai, India, registry on breast cancer (Dikshit et al., 2012a). Other collaborative work has had a more applied methodological focus, for example examining cure models to determine the proportion of cured patients and the median survival of fatal cases for different cancer types (Cvancarova et al., 2012) and the value of verbal autopsy procedures in making mortality estimates in India (Dikshit et al., 2012b). The former study provided key data for use in estimating cancer DALYs worldwide (Soerjomataram et al., 2012a, 2012b).

CIN is exploring new approaches to the visual presentation of global cancer statistics to reach out to a broader audience and, in collaboration with Cancer Research United Kingdom and the Union for International Cancer Control (UICC), has produced a new World Cancer Factsheet using novel graphical descriptions (Cancer Research UK, 2012). Similarly, the adoption of up-to-date web technology has been used in a major relaunch of the European Cancer Observatory
(ECO) web site (http://eco.iarc.fr), which has provided enhanced and flexible user-friendly access to data provided by more than 110 European regional and national PBCRs, as well as new 2012 estimates for the burden of cancer incidence, mortality, and prevalence in 40 European countries. This was partly funded through the EU FP7 EUROCOUSE ERA-NET project (http://www.eurocourse.org), and the technology used will be applied across the range of web sites hosted by CIN to modernize our overall web presence, and specifically the main platform Cancer Mondial.

Project work within CIN was initiated in 2012 on a new study, CAN EVOLUTION (funded by the EU Marie Curie programme), to investigate the global impact of population ageing on the changing dynamics of cancer patterns. A further project established in 2012 has been the International Research Network investigating Cancer among Indigenous Peoples (IRNCIP) with a study launched to compare cancer rates within such populations in Australia, Canada, New Zealand, and the USA combined with literature reviews of cancer in indigenous peoples in Latin America and the Caribbean, the circumpolar region, and Oceania. CIN contributes to the EU FP7-funded European Network for Cancer Research in Children and Adolescents (ENCCA; http://www.encca.eu) and PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup; http://www.pancaresurfup.eu) by coordinating an investigation into the feasibility of extending PBCR data collection in Europe, as a means to facilitate short- and long-term follow-up of these patients, and thus improve outcomes.

The GICR (http://gicr.iarc.fr) was formally launched in November 2011 to ensure the further establishment of PBCRs globally and to prioritize the specific needs of low- and middle-income countries. The overall objective is to bring about year-on-year incremental increases in the reporting of cancer data to a population-based standard so that these may inform national cancer control policies and, in the longer term, reach a quality that might be considered for publication in CI5. The GICR has coordinated the publication of advocacy material and, together with UICC, the development of a fundraising programme.

A key component of the GICR is the development of IARC Regional Hubs for Cancer Registration, which will offer a localized means to provide registries with direct support, training, research, and advocacy, and enable regional networking. A hub has been formally inaugurated in Mumbai, India, in October 2012 to cover South, Central, and East Asia. The establishment of Collaborative Research Agreements with registries in Sri Lanka, Indonesia, and Mongolia in 2012 provides a direct means of support to these registries with a high potential of becoming population-based. Site visits to Nepal in 2012 and Bhutan early in 2013 should provide key information on the status of the respective registries and may pave the way for future collaborative support. Agreements have been reached to launch by the end of 2012 a further hub in Izmir, Turkey, to cover Western Asia and Northern Africa. In collaboration with the International Network for Cancer Treatment and Research, an agreement will develop the African Cancer Registry Network into a regional hub covering sub-Saharan Africa. Active discussions are under way regarding a hub initiative for Central and South America.

CIN has provided a long-standing programme in the provision of training for PBCR staff at the annual IARC Summer School and also in regional courses. Now being integrated within GICR training developments, regional courses have been held in Cairo, Egypt (in French; November 2011); Mumbai, India (February 2012); Cali, Colombia (in Spanish; October 2012); and Abuja, Nigeria (November 2012). A major element in training is to provide guidance in the use of and transition to the IARC registration software, CanReg5, and during 2012, CIN has designed a series of webinars on CanReg5 use, reflecting a commitment to developing distance learning tools to deliver training. More generally, relevant course components have been recorded; their potential as online audiovisual training materials is being explored.
References


Section of IARC Monographs (IMO)

In 2012, the *IARC Monographs Programme* organized three international Working Group meetings of experts in carcinogenesis and public health, to develop new *IARC Monographs*. In addition, two Workshops were organized as a follow-up to the recently completed Volume 100 of the *IARC Monographs*, “A review of human carcinogens”. The purpose, scope, and outcome of these meetings are summarized below.

Monographs Working Groups convened at IARC, each for a period of 8 days, in February, June, and October. The reviews and evaluations of these Working Groups will be published in book and electronic form as Volumes 104, 105, and 106 of the *IARC Monographs* series.

**IARC Monographs Working Group on "Polyomaviruses (SV40, BK, JC, and Merkel cell viruses) and malaria", Volume 104, 7–14 February 2012**

The *World Health Organization* estimates the annual incidence of malaria cases at 216 million, the majority of which (> 90%) are due to infection with the protozoan parasite *Plasmodium falciparum*. Most deaths occur in children younger than 5 years, predominantly in sub-Saharan Africa and in Papua New Guinea. In these regions the transmission is holoendemic, which is defined as a parasite prevalence of > 75% in the 1-year age group.

"Malaria caused by infection with *Plasmodium falciparum* in holoendemic areas" was classified as “probably carcinogenic to humans” (Group 2A). The evaluation was based on limited epidemiological evidence that malaria is associated with endemic Burkitt lymphoma (eBL) and strong mechanistic evidence that *P. falciparum* disturbs the immature immune system in young children and reactivates the ubiquitous Epstein–Barr virus, a necessary agent for the development of eBL.

BK virus (BKV) and JC virus (JCV) are highly prevalent viruses in humans worldwide and are responsible for lethal non-cancerous diseases in immunosuppressed individuals (haemorrhagic cystitis and nephropathy for BKV, multifocal leukoencephalopathy for JCV). Based on “sufficient evidence” in experimental animals and “inadequate evidence” in humans, both viruses were classified as "possibly carcinogenic to humans" (Group 2B).

Merkel cell virus (MCV) has been recently discovered in a rare human skin cancer, Merkel cell carcinoma (MCC). An etiological role of MCV in MCC is supported by a small number of case–control studies, several case series, and strong mechanistic data. MCV was classified as "probably carcinogenic to humans" (Group 2A).

In the 1950s and early 1960s, millions of people across the world received vaccines against poliovirus that were contaminated with Simian virus 40 (SV40), a virus that naturally infects the rhesus monkey. SV40 was subsequently shown to induce tumours in newborn hamsters. The potential infection of humans raised serious concerns that this virus may cause cancer in humans. Reviewing the extensive data available, the Working Group did not find compelling evidence that SV40 infects humans or that transmission from human to human exists. SV40 was evaluated as “not classifiable as to its carcinogenicity to humans” (Group 3).

**IARC Monographs Working Group on “Diesel and gasoline engine exhausts and some nitroarenes”, Volume 105, 5–12 June 2012**

Diesel engines are used for on-road and non-road transport (e.g. trains, ships) and (heavy) equipment in various industrial sectors (e.g. mining, construction), and in electricity generators, particularly in developing countries. Gasoline engines are used for cars and hand-held equipment (e.g. chainsaws). The qualitative and quantitative composition of combustion-engine
exhausts depends on the fuel, the type and age of the engine, the state of its tuning and maintenance, the emission control system, and the pattern of use. Exhausts from diesel engines with no or limited emission controls contain more particulate matter. In the past two decades, progressively tighter emission standards for on-road vehicles, introduced in North America, Europe, and elsewhere, have triggered advances in diesel technology that resulted in lower emission of particulate matter, nitrogen oxides, and hydrocarbons. Emission standards in non-road applications are lagging and therefore these emissions are still largely uncontrolled today. Moreover, in many less developed countries standards are not in place for both on-road and non-road use of diesel and gasoline engines.

The most influential epidemiological studies assessing cancer risks associated with diesel engine exhausts investigated occupational exposure among non-metal miners, railroad workers, and workers in the trucking industry. For each of these groups, the studies support a causal association between exposure to diesel engine exhaust and lung cancer. An increased risk for bladder cancer was noted in many case–control studies but not in the cohort studies. The Working Group concluded that there was “sufficient evidence” in humans for the carcinogenicity of diesel engine exhaust.

With respect to animal cancer studies, the Working Group concluded that there was “sufficient evidence” in experimental animals for the carcinogenicity of whole diesel engine exhaust, of diesel engine exhaust particles, and of extracts of diesel engine exhaust particles. Positive genotoxicity biomarkers of exposure and effect were also observed in humans exposed to diesel engine exhaust. The Working Group concluded that there is “strong evidence” for the ability of whole diesel engine exhaust to induce cancer in humans through genotoxicity.

The association between exposure to gasoline engine exhaust and cancer risk was investigated in only a few epidemiological studies and, because of the difficulty of separating the effects of diesel and gasoline exhaust, the evidence for carcinogenicity was evaluated as “inadequate”. As to studies in experimental animals, the Working Group concluded that there was “sufficient evidence” for the carcinogenicity of condensates of gasoline engine exhaust.

Overall, the Working Group classified diesel engine exhaust as “carcinogenic to humans” (Group 1) and gasoline engine exhaust as “possibly carcinogenic to humans” (Group 2B).

The Working Group also evaluated 10 nitroarenes that occur in diesel engine exhaust. Biomonitoring studies have shown that workers and the general population are exposed to these substances. All the nitroarenes were genotoxic to various extents in different assays. The Working Group reaffirmed the Group 2B classification of seven of them. Strong evidence for genotoxicity led to an upgrade of 3-nitrobenzanthrone to Group 2B, and similar findings in human cells led to an upgrade of 1-nitropyrene and 6-nitrochrysene to Group 2A.

IARC Monographs Working Group on “Trichloroethylene, some other chlorinated solvents, and their metabolites”, Volume 106, 2–9 October 2012
Several chlorinated solvents (trichloroethylene, tetrachloroethylene, 1,1,2-tetrachloroethane, or 1,1,2,2-tetrachloroethane) and some of their metabolites (dichloroacetic acid, trichloroacetic acid, and chloral hydrate) were reviewed by the Volume 106 Working Group.

Trichloroethylene (TCE) is a chlorinated solvent that was widely used for degreasing metal parts until the 1990s, and in dry cleaning from the 1930s to 1950s. It is still used to remove stains from fabric, but it is primarily used in chlorinated chemical production. The general population is exposed through consumer products, including food, and through TCE-contaminated water.
The Working Group classified TCE as "carcinogenic to humans" (Group 1) on the basis of an increased risk of kidney cancer; there was also limited evidence for an association between TCE exposure and liver cancer or non-Hodgkin lymphoma (NHL). Several case–control studies of renal cell carcinoma, adjusted for tobacco smoking and other potential confounders, and a meta-analysis provide consistent and robust evidence for a positive association with TCE exposure. Experimental studies consistently show that metabolites of TCE formed via glutathione conjugation (by glutathione S-transferase [GST] enzymes) are genotoxic, particularly in kidney cells, where in situ metabolism occurs. The Working Group concluded that there was "sufficient evidence" for carcinogenicity in experimental animals, and the findings were remarkably consistent with the human data. Notably, an increased incidence of tumours of the liver, kidney, lung, testes, and haematopoietic system were observed in both sexes of mice and rats by both oral and inhalation routes of exposure in multiple studies.

Tetrachloroethylene is among the most widely used chlorinated solvents worldwide. From the 1950s to 1980s, its main use was in dry cleaning, for which it is still widely used. It was used to a lesser extent in metal degreasing, but its current primary use is for chlorofluorocarbon production. Current sources of exposure to the general population are from dry cleaning and environmental contaminations (through outdoor or indoor air, and drinking-water).

The majority of the epidemiological studies reported an increased risk of bladder cancer, after adjustment for tobacco smoking and other potential confounders. However, the epidemiological evidence was evaluated as limited because employment in dry cleaning was the only indicator of exposure to tetrachloroethylene in most studies, the number of exposed cases was small, and evidence for an exposure–response relationship was weak. The Working Group concluded that there was "sufficient evidence" for carcinogenicity in experimental animals. Tetrachloroethylene was classified as "probably carcinogenic to humans" (Group 2A).

Chloral hydrate (CH) is used as a sedative before medical procedures and also occurs as a by-product of water disinfection together with other chemicals. Evidence for the carcinogenicity of CH was evaluated to be "inadequate" in humans and "sufficient" in experimental animals. CH was upgraded to Group 2A, on the basis of strong evidence of its genotoxicity in most experimental systems and exposed humans.

Multiple chronic bioassays in mice demonstrated that dichloroacetic acid, trichloroacetic acid, 1,1,1,2-tetrachloroethane, or 1,1,2,2-tetrachloroethane increased the incidence of hepatocellular tumours. These agents were classified as "possibly carcinogenic to humans" (Group 2B) based on "sufficient evidence" for carcinogenicity in experimental animals.

Workshops on "Tumour concordance and mechanisms of carcinogenesis" (16–18 April 2012 and 28–30 November 2012)

These two Workshops will develop scientific publications that build on the reviews of the human carcinogens in the Volume 100 series of the IARC Monographs. The two major topics are "Tumour concordance between humans and experimental animals" and "Mechanisms involved in human carcinogenesis". A group of experts with broad expertise in epidemiology, animal cancer studies, and toxicology, most of whom have participated in the Volume 100 series, was invited to participate in both Workshops and to consider the two topics in conjunction, realizing that a discussion on concordance and discordance would necessarily include mechanistic considerations.

Before the first Workshop, a start was made with the extraction of animal cancer data from Volume 100, which would lead to a database for the analysis of concordance and discordance. The first Workshop opened with invited lectures on key issues and recent insights in toxicology
and carcinogenesis, followed by discussions in subgroups and in plenary sessions, exploring how analyses of and insights from tumour concordance and mechanisms can benefit from each other, and which additional data analyses should be done in preparation for the second Workshop. Agreement was reached on the fine-tuning of the animal cancer data, and on the development of a data set on mechanisms, based on a list of key terms identifying the most important mechanistic pathways. A draft table of contents with writing assignments for different chapters was also discussed.

In the two months after the first Workshop, the data sets were finalized and made available to all participants for further analysis. The second Workshop will discuss the results of these analyses and their interpretation, and aim to reach consensus on the conclusions with regard to future hazard identification.
Section of Mechanisms of Carcinogenesis (MCA)

The broad long-term goal of the Section of Mechanisms of Carcinogenesis (MCA) is to advance understanding of mechanisms of carcinogenesis and to contribute to cancer prevention. This is achieved through a multifaceted programme investigating interactions between genes, the epigenome, and the environment. In collaboration with epidemiology groups, MCA contributes to the development of translational studies through the discovery and validation of biomarkers of tumorigenesis and environmental exposures. The Section also aims to promote the development of cancer research relevant, although not exclusive, to low- and medium-resource countries and common cancers related to these regions of the world. Another focus of MCA is the development of genetic/epigenetic methods that are applicable to biobanks associated with case–control and population-based studies.

Molecular Mechanisms and Biomarkers Group (MMB)

MMB conducts studies aimed at improving understanding of molecular mechanisms of carcinogenesis and identifying biomarkers applicable in molecular epidemiology and cancer prevention. This is achieved through studies of molecular and genetic changes, gene function, and gene–environment interactions. MMB also aims to investigate the effects of environmental exposures on molecular changes to discover and validate new cancer biomarkers. MMB also maintains and publishes on the web a comprehensive database of all TP53 mutations published in the literature.

Role of TP53 somatic mutations as prognostic and predictive markers in breast cancer

The TP53 gene has a major tumour suppressor role in breast cancer and is inactivated by mutation in about 30% of breast tumours. While several studies have demonstrated the prognostic value of TP53 mutations, the predictive role of p53 status in patients treated with a controlled treatment regimen in the context of a clinical trial has not been investigated. In collaboration with the BIG clinical network, we have assessed the prognosis and predictive value of TP53 somatic mutations in the BIG 02-98 randomized phase II trial, in which women with node-positive breast cancer were treated with adjuvant doxorubicin-based chemotherapy with or without docetaxel (ClinicalTrials.gov identifier NCT00174655). While overall TP53 mutations were not associated with prognosis or time to recurrence, truncating mutations showed significant independent prognostic value, with an increased recurrence risk compared with patients with other types of mutations or no mutations (hazard ratio = 3.21, 95% CI = 1.740–5.935, \( P = 0.0002 \)). p53 status had no significant predictive value for response to docetaxel. These results confirmed that loss of wild-type p53 through protein-truncating mutations is associated with poor prognosis in breast cancer, but could not identify a significant predictive role for p53 status regarding docetaxel (Fernández-Cuesta et al., 2012).

TP53 R249S mutation, genetic variations in HBX, and risk of hepatocellular carcinoma

In regions with high prevalence of chronic hepatitis B virus (HBV) infection and dietary aflatoxin exposure, hepatocellular carcinomas (HCCs) often contain TP53 mutation at codon 249 (R249S). Interestingly, R249S mutations can be detected in asymptomatic subjects (Villar et al., 2011). We evaluated the association between R249S and HBX status in relation to HCC in a West African population. HBX (complete or 3′-truncated) and HBS genes were assessed in cell-free DNA (CFDNA) from plasma of subjects recruited in a hospital-based case–control study conducted in The Gambia. These samples had been previously analysed for R249S and HBV serological status. Complete HBX sequence was frequently detected in CFDNA of HCC-R249S positive (77%) compared with HCC-R249S negative cases (44%). Conversely, the proportion of 3′-truncated HBX gene was significantly higher in HCC-R249S negative than positive cases (34%
Moreover, HBV mutation analysis revealed that double mutation at nucleotides 1762T/1764A was associated with diagnosis of cirrhosis or HCC (Gouas et al., 2012). These findings suggest that in HCCs from The Gambia, complete HBX sequences are often associated with the presence of TP53 R249S mutation.

**Preferential occurrence of TP53 R249S-mutated DNA in liver cancer developing in the absence of cirrhosis**

Most HCCs are associated with chronic HBV infection, while a G→T mutation at codon 249 of the TP53 gene, R249S, specific for exposure to aflatoxin, is also detected in a significant fraction of tumours. Previous studies showed that circulating free DNA (CFDNA) from plasma is a suitable surrogate source of liver-derived DNA for detection of R249S mutations (Gormally et al., 2007). In this study, plasma samples collected in a case-referent design at the National Cancer Institute, Bangkok, were used to evaluate the association of R249S-mutated DNA plasma concentrations with the occurrence of HCC, cholangiocarcinoma (CC), or chronic liver disease. The short oligonucleotide mass analysis (SOMA) assay was used to quantify free circulating R249S-mutated DNA in plasma samples. Plasma R249S-mutated DNA was detectable at low concentrations (≥ 67 copies/mL) in 53–64% of patients with primary liver cancer or chronic liver disease and in 19% of controls. Also, 44% of patients with HCC and no evidence of cirrhosis had plasma concentrations of R249S-mutated DNA ≥ 150 copies/mL, compared with 21% of patients with both HCC and cirrhosis, 22% of CC patients, and 12% of patients with non-cancer chronic liver disease. Thus, plasma concentrations of R249S-mutated DNA ≥ 150 copies/mL tended to be more common in patients with HCC developing without pre-existing cirrhosis (Villar et al., 2012). These results support the preferential occurrence of R249S-mutated DNA in HCC developing in the absence of cirrhosis in a context of chronic HBV infection.

**Disseminating knowledge on the master tumour suppressor gene TP53**

MBB maintains a public molecular epidemiology database, the IARC TP53 Database (http://www-p53.iarc.fr), an internationally recognized resource in the field for the analysis and interpretation of human TP53 mutation in sporadic and inherited cancers. With the advent of next-generation sequencing technologies and the flood of sequencing data, the interpretation of gene variations and the identification of driver mutations rely on annotations compiled in databases such as the IARC TP53 Database. The database provides extensive annotations on the prevalence, type, phenotype, and predicted or experimentally assessed functional impact of TP53 mutations, which are useful to identify functional variants. Recent database developments have aimed at (1) extending the scope of annotations, (2) improving data accessibility by redesigning the web interface, and (3) sharing and integrating data with central genetic resources such as COSMIC, NCBI dbSNP, or UniProtKB/Swiss-Prot. In 2012, the group has produced a book describing how research on p53 has advanced our understanding of the molecular basis of human cancer, and how this knowledge is starting to affect cancer management and therapy (Hainaut et al., 2012).

**Epigenetics Group (EGE)**

Over the past decade, research in epigenetics has been making it into mainstream research, owing to the fact that epigenetic changes have emerged as key mechanisms in cancer development and progression. The ubiquity and intrinsic reversibility make epigenetic events attractive subjects for biomarker discovery and strategies for cancer prevention (Herceg and Vaissière, 2011; Nogueira da Costa and Herceg, 2012). The EGE Group conducts research projects aiming to (i) gain a better mechanistic understanding of tumorigenesis and (ii) discover and validate new epigenetic biomarkers. This programme exploits new concepts in cancer epigenetics and recent technological advances in epigenetics and epigenomics, and is carried out in close collaboration with IARC laboratory scientists and epidemiologists as well as external groups and consortia.
Epigenetic mechanisms in control of cellular processes and cancer

We have previously shown that histone modifications and remodelling are important to provide accessibility to DNA lesions and for efficient DNA repair (Murr et al., 2006; Gospodinov et al., 2011). In this study, we have identified TRRAP, a critical component of histone acetyltransferase (HAT) complexes, as a novel target of proteolytic degradation in a cell-cycle dependent manner. TRRAP overexpression or mutation-induced stabilization resulted in multiple mitotic defects, including lagging chromosomes, chromosome bridges, lack of sister chromatid cohesion, and impaired chromosome condensation. We further found that mitotic defects are associated with a global histone H4 hyperacetylation, indicating that TRRAP and TRRAP-mediated histone acetylation are necessary for proper condensation of chromatin, chromosome segregation, and genomic stability (Ichim et al., submitted). Together with recent findings of recurrent mutations in the TRRAP gene in several cancer types, such as melanoma, pancreatic adenocarcinomas, and HCC, our results argue that deregulation of TRRAP/HATs and histone acetylation and consequent changes in chromatin compaction states may represent an important mechanism of chromosome instability and tumorigenesis.

Epigenetic changes associated with risk factors in upper aerodigestive tract (UADT) cancer

Deregulation of the epigenome by environmental, dietary, and lifestyle exposure is believed to disrupt different cellular processes and contribute to cancer risk. We combined quantitative profiling of DNA methylation states in a wide panel of cancer-associated genes using Illumina microarray technology or high-throughput pyrosequencing with case–control studies of UADT cancer. The aim of this study was to examine the global deregulation of epigenetic (DNA methylation) states in oesophageal squamous cell carcinoma (ESCC) and identify potential early cancer biomarkers. We performed a large-scale analysis of promoter methylation in ESCC and normal surrounding tissues as well as in oesophageal mucosa from healthy individuals. To this end, we used a bead array analysis of more than 800 cancer-related genes. A total of 37 CpG sites were found to be differentially methylated between tumours and surrounding tissues. These CpG sites were significantly enriched in genes related to several pathways, including the IL-10 anti-inflammatory signalling pathway and cell communication pathway (Lima et al., 2011; manuscript in preparation). This is the first study to address methylation changes in ESCC in a large panel of genes. These data may prove to be the reference for future studies identifying potential biomarkers and molecular targets in ESCC.

We further analysed changes in DNA methylation in UADT cancers and their potential association with primary risk factors. To this end, we have taken advantage of a case–control study of UADT cancer involving seven centres in South America, using detailed lifestyle information and quantitative analysis of DNA methylation in a panel of cancer-associated genes. Our analyses revealed a high frequency of aberrant hypermethylation of specific genes, among which we identified new genes (including the nicotinic acetylcholine receptor gene, CHRN3, and the downstream of tyrosine kinases 1 gene, DOK1), suggesting that epigenetic deregulation of these genes may promote the development of UADT cancer (Mani et al., 2012; Saulnier et al., 2012; Siouda et al., 2012). Importantly, we found that sex and age are associated with the methylation states, whereas tobacco smoking and alcohol intake may also influence the methylation levels in specific genes (Mani et al., 2012).

Together, these studies identify aberrant DNA methylation patterns in UADT and gastric cancer and suggest a potential mechanism by which environmental factors may deregulate key cellular genes involved in tumour suppression and contribute to these common human cancers.
Epigenetic changes in surrogate tissue as cancer biomarkers

Because DNA methylation profiles of the human genome are tissue-specific, we tested the possibility that global methylation levels in surrogate tissues, such as blood, may be exploited in epidemiologic studies. We used two independent but complementary methods to assess global methylation levels in peripheral blood DNA from a well-characterized population-based case-control study (the Long Island Breast Cancer Study Project [LIBCSP], with more than 2100 peripheral blood samples). Our results obtained by pyrosequencing-based assay (LUMA) and genome-wide methylation (Illumina Infinium arrays) profiling revealed greater promoter hypermethylation in breast cancer cases, while methylation levels in repetitive elements (as revealed by LINE-1 methylation assay) were not associated with breast cancer risk (Xu et al., 2012). This study shows that global promoter hypermethylation measured in peripheral blood may be used in breast cancer risk assessment. Further studies on the samples from a prospective cohort (EPIC) are under way to assess the value of this marker and address the potential influence of the disease onset (reverse causality) and one-carbon metabolism on the methylome of blood DNA (Demetriou et al., 2012, submitted).

References


Section of Molecular Pathology (MPA)

Molecular pathology of tumours
The Section of Molecular Pathology (MPA) focuses on the elucidation of the molecular basis and genetic pathways of human neoplasms, in particular brain tumours, with the objectives of correlating histologically recognized phenotypes with genotypes, and identifying reliable molecular markers for classification and progression of tumours. Some highlights of 2012 are described below.

Molecular mechanisms of mesenchymal differentiation in gliosarcomas
Gliosarcoma is a rare variant of glioblastoma that is characterized by a biphasic tissue pattern with alternating areas displaying glial or mesenchymal differentiation. We compared genome-wide chromosomal imbalances using array CGH (105K) in glial and mesenchymal tumour areas of 13 gliosarcomas. Patterns of gain and loss were similar, except for gain at 13q13.3–q14.1 (log2 ratio > 3.0), which was restricted to the mesenchymal tumour area of a single gliosarcoma. Further analyses of 64 gliosarcomas using quantitative polymerase chain reaction (PCR) showed amplification of the STOML3, FREM2, and LHFP genes at 13q13.3–q14.1 in 14 (21%), 10 (15%), and 7 (11%) of mesenchymal tumour areas, respectively, but not in glial tumour areas. Immunohistochemistry confirmed that overexpression of STOML3 and FREM2 was more extensive in mesenchymal than in glial tumour areas. We also assessed 40 gliosarcomas for immunoreactivity of Slug, Twist, MMP-2, and MMP-9, which are involved in epithelial–mesenchymal transition (EMT). Nuclear expression of Slug was observed in > 50% of neoplastic cells in mesenchymal tumour areas of 33 (83%) gliosarcomas, but not in glial tumour areas. Nuclear expression of Twist was observed in > 50% of neoplastic cells in mesenchymal tumour areas of 35 (88%) gliosarcomas, but glial tumour areas were largely negative. Expression of MMP-2 and MMP-9 was also significantly more extensive in mesenchymal than in glial tumour areas. None of 20 ordinary glioblastomas showed expression of Slug or Twist in > 10% of neoplastic cells. These results suggest that mesenchymal components of a small fraction of gliosarcomas may be derived from glial cells that have acquired genetic alterations that distinguish them from other glial cells in the tumour, and that mechanisms involved in EMT in epithelial neoplasms may also play roles in mesenchymal differentiation in gliosarcoma (Nagaishi et al., 2012a, 2012b).

BRAF gain and the BRAF-KIAA1549 fusion gene in low-grade diffuse gliomas
Chromosomal 7q34 duplication and BRAF-KIAA1549 fusion are characteristic genetic alterations in pilocytic astrocytomas. Gain of 7q34 appears to be common in diffuse astrocytomas, but its significance is unclear. We assessed BRAF gain and BRAF mutations in 123 low-grade diffuse gliomas (diffuse astrocytomas, oligoastrocytomas, and oligodendrogliomas). Quantitative PCR revealed BRAF gain in 34% of oligodendrogliomas, a significantly higher frequency than in diffuse astrocytomas (13%). BRAF gain was common in low-grade diffuse gliomas with 1p/19q loss (39%) and those lacking any of the genetic alterations analysed (31%), but was rare in those with TP53 mutations (2%). Logistic regression analysis showed a significant positive association between 1p/19q loss and BRAF gain, and a significant negative association between TP53 mutations and BRAF gain. These results suggest that low-grade diffuse gliomas with 1p/19q loss have frequent BRAF gains (Kim et al., 2012). We also found the BRAF-KIAA1549 fusion gene in 17 out of 185 diffuse gliomas cases (9%), suggesting that, as in pilocytic astrocytomas, the KIAA1549-BRAF fusion gene may be responsible for deregulation of the Ras-RAF-ERK signalling pathway in a small fraction of diffuse gliomas (Badiali et al., 2012).
Pace of malignant progression from diffuse astrocytoma to secondary glioblastoma

Most glioblastomas develop with a short clinical history, without evidence for less malignant precursor lesions (primary glioblastomas); in contrast, secondary glioblastomas develop slowly via progression from diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III). IDH1 mutations reliably distinguish between primary glioblastomas (without IDH1 mutations) and secondary glioblastomas (with IDH1 mutations) (Kleihues et al., 2012; Ohgaki, 2012). The time to progression and the clinical outcome of diffuse astrocytomas vary significantly among patients. The ability to predict the pace of progression from low-grade diffuse astrocytoma to secondary glioblastoma, which is however not possible histopathologically, would be clinically very important, giving oncologists a rational basis for deciding whether and at what stage to administer adjuvant radiotherapy.

Despite possessing distinctive genetic alterations, primary and secondary glioblastomas have similar histological features, which may be attributable to those genetic alterations that are common to both subtypes. The most frequent genetic alteration shared by primary and secondary glioblastomas is loss of heterozygosity (LOH) at 10q (up to 60% of cases). When we searched for commonly deleted genes at 10q25–qter in The Cancer Genome Atlas (TCGA), 10 genes were identified with log-ratio thresholds of −1.0. Of these, DMBT1 at 10q26.13 was the only homozygously deleted gene in glioblastomas with or without IDH1 mutations (12.5% vs 8.0%). We demonstrated the presence of DMBT1 homozygous deletion at a similar frequency in an independent set of primary and secondary glioblastomas (20% vs 21%). A small fraction (11%) of diffuse astrocytomas also showed homozygous deletion of DMBT1, and this was significantly associated with shorter overall patient survival (Motomura et al., 2012). A similar approach was used to search for commonly amplified genes in glioblastomas with and without IDH1 mutations in the TCGA database. A total of 25 genes were identified, of which 21 were located at 7q31–34. Further analyses revealed gain of the MET gene at 7q31.2 in primary glioblastomas (47%) and secondary glioblastomas (44%). Interestingly, MET gain is also common in diffuse astrocytomas (38%), and is associated with shorter survival. These results indicate that several genetic alterations that are frequent in both primary and secondary glioblastomas may be responsible for the identical histological phenotype and, if already present in diffuse astrocytomas, may predict unfavourable clinical outcome (Pierscianek et al., 2012).

Genetic alterations in microRNAs in medulloblastomas

MicroRNAs (miRNAs) regulate a variety of cellular processes via the regulation of multiple target genes. We screened 48 medulloblastomas for mutation, deletion, and amplification of 9 miRNA genes that were selected on the basis of the presence of potential target sequences within the 3′-untranslated region of the MYCC mRNA. Differential PCR revealed deletions in miR-186 (15%), miR-135a-1 (33%), miR-548d-1 (42%), miR-548d-2 (21%), and miR-512-2 (33%) genes, whereas deletion or amplification was detected in miR-135b (23%) and miR-135a-2 (15%). In miR-33b, deletion, amplification, or a mutation at the precursor miRNA were detected in 10% of medulloblastomas. Overall, 35 out of 48 (73%) medulloblastomas had at least one alteration. Real-time RT-PCR revealed MYCC overexpression in 11 out of 37 (30%) medulloblastomas, and there was a significant correlation between MYCC overexpression and miR-512-2 gene deletion. Antisense-based knockdown of miR-512-5p (mature sequence of miR-512-2) resulted in significant upregulation of MYCC expression in HeLa and A549 cells, while forced overexpression of miR-512-2 in medulloblastoma/primitive neuroectodermal tumour (PNET) cell lines DAOY, UW-228-2, and PFSK resulted in downregulation of MYCC protein. Furthermore, the results of luciferase reporter assays suggested that miR-512-2 targets the MYCC gene. These results indicate that alterations in the miRNA genes may be an alternative mechanism leading to MYCC overexpression in medulloblastomas (Lv et al., 2012).
**WHO Classification of Tumours series**

MPA is responsible for the publication of the 4th edition of the WHO Classification of Tumours series (WHO Blue Books). The objective of this project is to establish a histological and genetic classification of tumours that reflects recent advances in histopathology and cancer genetics, and that is accepted and used worldwide. These authoritative, concise reference books provide an international standard for oncologists and pathologists and serve as indispensable guides for the design of studies monitoring response to therapy and clinical outcome.

**WHO Classification of Tumours of the Breast**

The 4th volume of the 4th edition of the WHO Classification of Tumours series, this book was prepared by 90 authors from 24 countries, and was published in June 2012. The volume editors are Dr Sunil R. Lakhani, The Royal Brisbane and Women’s Hospital, Brisbane, Australia; Dr Ian Ellis, Nottingham University Hospitals, Nottingham, United Kingdom; Dr Stuart Schnitt, Harvard Medical School, Boston, USA; Dr Puay Hoon Tan, Singapore General Hospital, Singapore; and Dr Marc J. van de Vijver, Academic Medical Center, Amsterdam, The Netherlands.

**WHO Classification of Tumours of Soft Tissue and Bone**

This is the 5th volume of the 4th edition, edited by Dr Christopher D. M. Fletcher, Brigham and Women’s Hospital, Boston, USA; Dr Julia A. Bridge, Nebraska Medical Center, Omaha, USA; Dr Pancras C.W. Hogendoorn, Leiden University Medical Center, Leiden, The Netherlands; and Dr Fredrik Mertens, Lund University, Lund, Sweden. In July 2011, 156 experts from 23 countries were invited to contribute. The Consensus and Editorial Meeting was held in April 2012 in Zurich, Switzerland, in collaboration with and with the support of the University of Zurich and the Charles Rodolphe Brupbacher Foundation. Publication is scheduled for early 2013.

**WHO Classification of Tumours of Female Reproductive Organs**

This will be the 6th volume of the 4th edition. The volume editors, invited in spring 2012, are Dr Robert J. Kurman, Johns Hopkins University, Baltimore, USA; Dr Maria Luisa Carcangiu, Istituto Nazionale dei Tumori, Milano, Italy; Dr Simon Herrington, Ninewells Hospital and Medical School, Dundee, United Kingdom; and Dr Robert H. Young, Massachusetts General Hospital, Harvard Medical School, Boston, USA. We are currently preparing the draft WHO Classification, the structure of the book, and the list of contributors to be invited. The Consensus and Editorial Meeting for this volume is scheduled for early summer 2013.

**References**


Section of Infections (INF)

The Section of Infections (INF) comprises the Infections and Cancer Biology Group (ICB) and the Infections and Cancer Epidemiology Group (ICE). Both Groups focus on infectious agents and different aspects of the infection/cancer relationship, including worldwide distribution and trends over time of cancer-associated infections; range of tumours associated with infection, and strength of the association; transformation mechanisms; meaning of viral variants; role of innate and acquired immunity; and new virological and bacteriological tests for epidemiological studies. Agents studied are mucosal and cutaneous human papillomavirus (HPV) types; human immunodeficiency virus (HIV), in combination with other cancer-associated viruses; Helicobacter species; hepatitis B and C virus (HBV/HCV); Epstein–Barr virus (EBV); and Merkel cell polyomavirus (MCP). Some aspects are exclusive to ICB (transformation mechanisms) or ICE (worldwide distribution and trends). On other aspects (role of innate and acquired immunity, different HPV variants), collaborations are possible with the increasing availability in ICB of tests suitable for large-scale application. One of INF’s greatest assets is collaboration on methodology. ICB provides advice about decisions on INF biological protocols; ICE provides guidance on statistical matters in INF protocols and publications. In 2012, INF has had 60 articles published, covering a wide range of topics.

Infections and Cancer Biology Group (ICB)

ICB’s research is focused on the establishment of a causal role of specific infectious agents in human cancer. Two complementary strategies are currently followed: (i) Characterization of the biological properties of proteins from potential oncogenic viruses using in vitro and in vivo model systems; and (ii) Development and validation of laboratory assays for the detection of infections in human specimens that can be used in epidemiological studies.

The following viruses are currently included in ICB studies: mucosal and cutaneous HPV types, MCP and related polyomaviruses, and EBV.

Biological studies

One of the goals of the ICB Group is to evaluate the role of cutaneous β HPV types in the development of non-melanoma skin cancer (NMSC). We have performed several studies to characterize the biological properties of the main oncoproteins E6 and E7 from many β HPV types (Chiantore et al., 2012; Cornet et al., 2012a). In particular, we observed that only E6 and E7 from some β HPV types displayed in vitro transforming properties (i.e. HPV38 and HPV49), supporting the hypothesis that β HPV types may differently impact on carcinogenesis. HPV49 E6 shares with mucosal high-risk HPV16 E6 the same mechanism in targeting the tumour suppressor protein p53. Indeed, both viral proteins induce p53 degradation via the proteasome pathway (Cornet et al., 2012a). In contrast, we have previously shown that HPV38 inactivates the p53-regulated pathways inducing accumulation of ΔNp73α, a strong inhibitor of the p53 transcriptional functions. Interestingly, recent data from our group showed that also EBV, via the oncoprotein LMP-1, inactivates p53 functions increasing ΔNp73α mRNA and protein levels (Accardi et al., submitted). We are currently exploring whether additional oncogenic viruses have the properties to target the p53-regulated transcription via accumulation of ΔNp73α.

Epidemiological studies

Another activity of the ICB Group is to perform epidemiological studies in collaboration with colleagues at IARC and external researchers. We have developed novel assays for the detection of more than 100 infectious agents, including 68 HPV types, all known polyomaviruses, and all herpes viruses. These assays are based on the use of multiplex polymerase chain reaction (PCR) protocols and bead-based technology (Luminex). Validation studies demonstrated the high sensitivity and specificity of these assays, which allow the use of DNA extracted from a broad
spectrum of biological specimens, e.g. saliva, paraffin-embedded tissue, urine, cervical cells, and skin swabs (Comar et al., 2012; Deodhar et al., 2012; Gheit et al., 2012; Halec et al., 2012; Iannacone et al., 2012). Case–control studies in Florida, where a high incidence of NMSC is recorded, provided strong evidence for the association of β HPV infections with the development of squamous cell carcinoma (SCC) (Iannacone et al., 2012). In an independent study in the same population, we have observed that MCV infections increase the risk of SCC development (Rollison et al., 2012). In addition to skin cancer, we have performed epidemiological studies to evaluate the role of oncogenic virus infections in cancer of several anatomical regions, e.g. lung and bladder (Gheit et al., 2012; Polesel et al., 2012).

Infections and Cancer Epidemiology Group (ICE)
ICE’s goal is to elucidate the contribution of infectious agents, such as HPV, HIV, HBV/HCV, Kaposi sarcoma herpes virus (KSHV), and H. pylori, to the etiology of cancer.

HPV
In 2012, ICE’s main focus was HPV. For HPV vaccines and HPV-based screening to be successful, accurate knowledge of the infection burden and type-specific distribution of HPV types in different parts of the world is needed. ICE carried out new population-based HPV prevalence surveys in Vanuatu (Aruhuri et al., 2012), the Islamic Republic of Iran (Khodakarami et al., 2012), and Bhutan (manuscript in preparation). Work in Bhutan was the first step of a multi-year project meant to demonstrate the early impact of successful implementation of vaccination against HPV in two low-resource countries (the other being Rwanda). Bhutan and Rwanda, in addition of having achieved the highest HPV vaccine coverage in developing countries, are also committed to improving their screening programme through the introduction of HPV test-based screening. ICE will therefore jointly evaluate the impact of vaccination and screening. In addition, ICE released the first systematic comparison of the distribution of individual HPV types in 115,789 HPV-positive women with and without cervical cancer or pre-neoplastic lesion (Guan et al., 2012). To further expand the study of factors that influence the geographical variability and different prognosis of HPV infections, HPV16 variants were evaluated, in collaboration with ICB (Cornet et al., 2012b).

The contribution of HPV infection to cancer of the head and neck is controversial and varies substantially by population. ICE took advantage of registry-based data from the USA to show that the presence of HPV was high (50%) and was associated with better survival exclusively in oropharyngeal sites (Sethi et al., 2012). Tobacco smoking was also, however, a very strong prognostic factor.

HIV/AIDS
Cancer risk in people with HIV/AIDS (PWHA) is a very important subject to ICE now that highly active antiretroviral therapy (HAART) has improved survival in PWHA as well as the age-related cancer burden. A new record-linkage study from the Swiss HIV Cohort suggested that the approximately 3-fold excess of lung cancer in people with HIV compared with the general population was not clearly associated, among HIV-positive people, with the severity of immunosuppression. Lung cancer excess is mainly attributable to heavy smoking (Clifford et al., 2012).

A second line of research has focused on how HIV infection modifies the cancer potential of HPV infections in countries at very high risk for both infections (Kenya and South Africa) (De Vuyst et al., 2012b). A study of 498 HIV-positive women in Nairobi, Kenya, showed that the burden of high-risk HPV (hrHPV) and cervical intraepithelial neoplasia grade 2 or worse (CIN2/3) was high and was related to immunosuppression level. Use of combination antiretroviral therapy (cART)
for 2 years or longer had a favourable effect on hrHPV prevalence but not on CIN2/3. cART use in our population may have been started too late to prevent CIN2/3 (De Vuyst et al., 2012a).

Finally, better statistical methods were devised to evaluate and project the benefits of HPV vaccination and screening in HIV-negative and HIV-positive women. Concerns were, for instance, expressed on the lack of specificity of HPV testing in African women and, notably, HIV-positive women, due to very high hrHPV prevalence. We showed that the positive predictive value (PPV) for CIN2/3 of HPV testing in high-risk populations was very high, notably in women aged 45 years or older as CIN2/3 accumulates over time if adequate screening for women is lacking (Giorgi-Rossi et al., 2012). High PPV demonstrates the effectiveness and potential cost-effectiveness of HPV testing in high-risk women despite low test specificity.

**Global burden of cancer attributable to infections**

ICE, in collaboration with CIN, used data from GLOBOCAN and a variety of literature sources to calculate the fraction of cancer attributable to infection worldwide and in eight geographical regions (de Martel et al., 2012). Overall, 2 million (16.1%) of the total 12.7 million new cancer cases that occurred in 2008 are attributable to infections. This fraction is higher in less developed countries (22.9%) than in more developed countries (7.4%) and varies 10-fold by region, from 3.3% in Australia/New Zealand to 32.7% in sub-Saharan Africa. The most important infectious agents are *H. pylori*, HBV/HCV, and HPV, which together are responsible for 1.9 million cases of gastric, liver, and cervix uteri cancers, respectively. Application of existing public health methods for infection prevention, such as vaccination, safer injection practice, or antimicrobial treatments, could have a major impact on the future burden of cancer worldwide.

**References**


Section of Environment and Radiation (ENV)

The overall objectives of the Section of Environment and Radiation (ENV) are to investigate environmental, lifestyle, occupational, and radiation-related causes of cancer in human populations. ENV investigates these exogenous factors with the aim of contributing to primary prevention of cancer and to increasing the understanding of biological mechanisms of carcinogenesis. These objectives are achieved through collaborative international epidemiological studies using a multidisciplinary approach when possible or through the initiation of individual analytical epidemiological studies. A second approach used by ENV is the coordination of international consortia of epidemiological studies.

Investigation of external environmental exposures such as pollutants and occupational exposures are core tasks of ENV. One major area of research is pesticides. ENV coordinates the newly established consortium of agricultural cohort studies (AGRICOH), allowing the investigation of various research questions. In addition, ENV conducts studies on testicular cancer and childhood cancer in the offspring of parents exposed to pesticides; both these research questions are addressed with multiple but complementary study designs. Another large effort is ENV's coordination of a consortium of case–control studies on occupational risk factors for lung cancer (SYNERGY). ENV coordinates a pooling project of European cohort studies investigating cancer risks in workers in the contemporary rubber industry and participates in further investigation of asbestos-related cancer risks.

Research on lifestyle-related factors comprises tobacco and other drugs of abuse, specifically qat chewing, for which a pilot study has started in Ethiopia. Lifestyle-related questions are also part of comprehensive studies of particular cancers when there is potential interplay between environmental and other factors. Further research comprises the launch of studies on the etiology of oesophageal and breast cancer as well as childhood cancer in low- and middle-income countries. Cancers of particular interest in ENV in the context of ongoing studies are brain tumours, testicular cancer, upper digestive tract cancer (particularly oesophageal cancer), childhood cancer, and breast cancer, the latter also in a broader context of using mammographic density as an intermediate marker of risk. A future aim of ENV is to launch studies in Africa, where some environmental and occupational exposures are higher and people's protection is less rigorous than in high-income countries, to address the rapidly increasing cancer burden in that continent (McCormack and Schüz, 2012).

Related to ionizing radiation, ENV has projects on the effects of protracted low doses of external ionizing radiation from medical diagnostic examinations (cohort study of children and adolescents exposed to computed tomography [EPI-CT]) and from occupational activities (follow-up of the international study of cancer risk among radiation workers in the nuclear industry); studies of populations exposed to Chernobyl fallout (development of the Agenda for Research on Chernobyl Health [ARCH], thyroid cancer risk in clean-up workers); studies on in utero exposure to ionizing radiation in the Southern Urals (SOLO); and studies on the interaction between ionizing radiation and genetic factors (e.g. case–control study of thyroid cancer in young people in the wake of the Chernobyl accident). In the GENE-RAD-RISK project on radiation exposures at an early age, the impact of genotype on breast cancer risk is investigated.

With regard to non-ionizing radiation, research activities include a large international collaborative case–control study on mobile phone use and the risk of brain tumours, acoustic neuroma, and salivary gland tumours (INTERPHONE); collaboration in a Danish cohort study of mobile phone subscribers; a pilot study to set up a prospective cohort study of mobile phone users in France; and collaboration in studies on extremely low-frequency magnetic fields and
childhood cancer. The INTERPHONE study and collaboration in an international study on brain tumours in teenagers and adolescents (CEFALO) allows the investigation of various possible environmental and genetic risk factors of brain tumours.

**Consortium of agricultural cohort studies (AGRICOH)**
Agricultural worker populations in many countries show distinctive exposure and disease profiles. These populations appear to have lower risk of some diseases, including colon and lung cancer, which has been attributed to frequent exposure to microbial agents and healthier habits, including reduced tobacco use and increased physical activity. In contrast, regular exposure to certain pesticides, ultraviolet radiation, diesel exhaust and solvents, and high dust levels has been reported to be associated with increased risks of several cancer types. The purpose of AGRICOH is to promote and sustain collaboration and data sharing/pooling to assess the association between various agricultural exposures and a wide range of health outcomes, with a particular focus on those associations that cannot easily be investigated in individual studies because of rare exposures or relatively rare outcomes (Leon *et al*., 2011). As of mid-2012, 26 cohorts from 5 continents are included in AGRICOH. Recently launched projects, both led by ENV, are on overall cancer risks in various agricultural activities and on the risk of haematological malignancies in farmers.

**Consortium of case–control studies on occupational exposures and lung cancer risk (SYNERGY)**
The aim of the SYNERGY project is to estimate joint effects of five selected occupational carcinogens (asbestos, respirable crystalline silica [RCS], polycyclic aromatic hydrocarbons [PAHs], chromium, and nickel) in the development of lung cancer. The results should provide a scientific basis for recognition of lung cancer as an occupational disease in workers with exposures to more than one lung carcinogen in combination with tobacco smoking. A total of 17,705 lung cancer cases and 21,813 controls are available from 14 case–control studies. The quantitative job-exposure matrix SYN-JEM was created based on a database of exposure measurements for the five selected carcinogens, containing 360,000 measurements from multiple countries covering more than 50 years. Analyses are in the process of being finalized. In an analysis on occupational diesel motor exhaust (DME), cumulative DME was associated with a significant 30% increase in lung cancer risk, comparing highest exposure versus unexposed, and a significant exposure–response relationship, adjusted for smoking habits (Olsson *et al*., 2011).

**Studies on the carcinogenicity of asbestos**
Quantifying the asbestos-related lung cancer burden is difficult due to this disease’s multiple causes. Researchers led by ENV explored two methods to estimate this burden using mesothelioma deaths as a proxy for asbestos exposure, using published data from the follow-up of 55 asbestos cohorts. Ratios varied by asbestos type, but all types of asbestos fibres kill at least twice as many people through lung cancer than through mesothelioma, except for crocidolite (McCormack *et al*., 2012). For chrysotile, widely consumed today, asbestos-related lung cancers could not be robustly estimated.

A retrospective cohort study of employees at the world’s largest currently operating chrysotile asbestos mine and the affiliated processing mills, situated in the town of Asbest, Sverdlovsk Oblast, Russian Federation, has recently been initiated. The overall aim of the study is to more precisely characterize and quantify the risks of cancer mortality associated with exposure to this particular asbestiform mineral. Although the carcinogenicity of chrysotile asbestos is established, this study seizes the opportunity to further characterize its carcinogenicity using a unique, relevant, and – due to its comprehensive study base of job details and historical dust measurements – informative setting.
International paediatric CT scan study (EPI-CT)

Diagnostic radiation represents an indispensable tool for modern medicine. Physicians see benefits of using CT scanning in their daily clinical practice. The growing use of CT technology raises concerns in radiological protection. Children are generally more sensitive to the carcinogenic effects of ionizing radiation than are adults. In addition, they may receive even higher radiation doses from a CT procedure than adults. The long-term risk of radiation-induced cancer or other health effects after CT scanning has not been directly assessed. EPI-CT, coordinated by ENV, involves 18 centres from 11 countries cooperating in this project to enrol approximately 1 million patients.

Risk of thyroid cancer in clean-up workers after the Chernobyl nuclear accident

A collaborative case–control study nested within cohorts of Belarusian, Russian, and Baltic liquidators after the Chernobyl nuclear accident in 1986 was conducted to evaluate the radiation-induced risk of thyroid cancer. The study included 107 cases and 423 controls. A statistically significant dose–response relationship was found with total thyroid dose. Although recall bias and uncertainties in doses could have affected the magnitude of the risk estimates, the findings of this study contribute to better characterize the risk of thyroid cancer after radiation exposure in adulthood (Kesminiene et al., 2012).

Mobile phone use and the risk of brain tumours

Scientific evidence on whether use of mobile phones is associated with an increased risk of brain tumours is still controversial. The question has been addressed using three different epidemiological study designs that complement one another: case–control, cohort, and incidence time trend studies. An update of the largest study led by ENV, i.e. a Danish nationwide cohort study of mobile phone subscribers, did not show any association with brain tumour risk (Frei et al., 2011; Schüz et al., 2011); although this was reassuring for overall mobile phone use, no information was available on amount of use, leaving open the possibility that heavy use of mobile phones still poses a risk. Indeed, such a risk increase has been reported from the largest and most comprehensive case–control study series in 13 countries, INTERPHONE, coordinated by ENV; a 40% risk increase was observed in the 10% heaviest users of mobile phones for glioma (INTERPHONE Study Group, 2010) and likewise for acoustic neuroma (INTERPHONE Study Group, 2011). Due to reliance in case–control studies on self-reported use of mobile phones and high participation, evidence of bias in those studies precluded firm conclusions. The first case–control study on teenagers and adolescents on this topic (CEFALO) also did not show an overall association (Aydin et al., 2011), but questions remain. ENV also conducted incidence time trend studies; while showing that incidence time trends of brain tumours in the Nordic countries were stable (Deltour et al., 2012), and thereby confirming that any large risk increase can be ruled out, they do not allow final judgement on risks restricted to heavy mobile phone users, as the resulting number of excess brain tumours would still be too small.

References


Section of Nutrition and Metabolism (NME)

Diet, nutrition, metabolic/hormonal imbalances, excess energy consumption, obesity, and physical inactivity are thought to be important contributors to increasing cancer incidence rates worldwide. However, the mechanisms of action of these factors remain poorly understood. In addition, the contributing influence of dietary transitions from traditional to Western-type diets, which is taking place in low- and middle-income countries (e.g. Latin America), and exposures in fetal life/early infancy are not well studied.

Thus, the main objective of the Section of Nutrition and Metabolism (NME) is to address these issues by evaluating the association of diet (including dietary patterns), nutrition, physical activity, and energy imbalance with cancer risk in high- and medium-to-low-resource countries using cohort and case-control designs or human intervention studies. Among others, the NME Section plays a leading role in the coordination and maintenance of the European Prospective Investigation into Cancer and Nutrition (EPIC), a large ongoing prospective cohort initiated by IARC. Emphasis is on improving the accuracy, understanding, and interpretation of dietary exposures; developing, validating, and disseminating standardized dietary methodologies relevant to international study settings; applying biomarkers and metabolomics to study cellular, biochemical, and physiological changes; and consideration of gene–diet/nutrient/environment interactions. Ultimately, the translation of findings into public health recommendations and the development of appropriate cancer prevention strategies are of major importance to the NME Section.

Nutritional Epidemiology Group (NEP)

The overall objective of this Group, in close interaction with DEX and BMA, is to determine the role of diet, nutrition (micronutrient deficiency, under/over-nutrition), hormonal factors, physical activity, and energy balance on cancer risk and development, particularly with consideration of biomarkers and gene–diet/nutrient/environment interactions.

Studies in high-resource settings (the EPIC project)

For colorectal cancer (CRC), major recent publications include: increased risk with higher oxidative stress levels (Leufkens et al., 2012); decreased risk with higher concentrations of soluble leptin receptor (Alekandrsova et al., 2012b) and adiponectin (Alekandrsova et al., 2012a); and lower overall and CRC-specific mortality with higher baseline vitamin D concentration (Fedirko et al., 2012). In collaboration with BMA, an analysis of phospholipid fatty acid concentrations and risk of gastric cancer was published (Chajès et al., 2011), as well as an association between obesity and higher risk of differentiated thyroid cancer in women (Rinaldi et al., 2012). For liver cancer, contributions of smoking, alcohol, and hepatitis infection to risk were confirmed (Trichopoulos et al., 2011), as were those of obesity (Schlesinger et al., 2012) and higher simple sugar and lower dietary fibre consumption (Fedirko et al., 2012b). Other analyses in liver cancer are ongoing. For breast cancer (BC), recent efforts have concentrated on risk assessment for molecular subtypes, showing that high glycemic load and carbohydrate intake are positively associated with increased risk of ER– and ER–/PR– cancers in postmenopausal women (Romieu et al., 2012), while higher intake of dietary fibre is inversely associated (Ferrari et al., 2012a). Analyses on fatty acids, folate, polyphenols, and healthy lifestyle index are ongoing.

Studies in low- and middle-resource settings

BC is the major female cancer in developed countries, and its incidence and mortality are rising in lower-resource countries. The Group is using large cohorts and multicentre case–control studies to identify the roles and mechanisms by which diet, physical activity, obesity, and metabolic disorders affect BC incidence and survival. The Group is collaborating with the
National Institute of Public Health (INSP) and the National Cancer Institute (INCan) in Mexico on a multicentre BC case-control study (CAMA) of Mexican women and a large cohort of Mexican teachers (EsMaestras) selected in nine Mexican states. In CAMA, analyses show an inverse BC risk for higher circulating vitamin D (Fedirko et al., 2012c) and higher n-3 PUFA intake, but increased risk for more n-6 PUFA consumption (Chajès et al., 2012). Studies using fatty acid biomarkers are in progress. In EsMaestras, larger silhouettes are associated with high intakes of carbohydrates, sweet drinks, and refined foods (Romieu et al., 2011). A similar study on dietary, metabolic, and hormonal determinants of mammographic density, a strong BC risk factor, is progressing. Efforts are advancing to develop a multicountry study (Brazil, Chile, Colombia, Costa Rica, Mexico) of molecular subtypes of premenopausal BC, with the objective of evaluating the distribution of specific subtypes and identifying the roles and mechanisms by which diet, physical activity, obesity, and metabolic disorders affect incidence and survival. The Group recently published a review paper on the potential role of epigenetics in BC in young women (Teegarden et al., 2012) and is planning studies on the topic in EsMaestras as well as in EPIC.

**Gene–nutrient interactions**
The Group was involved in a successful FP7 application by the Micronutrient Genomics Project to study carotenoid– and vitamin C–gene interactions using existing data. In EPIC, other studies are ongoing on CRC (iron–HFE gene mutations) and BC (folate and alcohol intake and folate metabolism genes).

**Alcohol and cancer**
The Group is continuing its contribution to systematic meta-analyses on alcohol and risk of various cancers, recently confirming that light alcohol drinking is associated with higher risk of oropharyngeal, oesophageal squamous cell, and female BC, but not CRC, liver, or larynx tumours (Bagnardi et al., 2012). Within EPIC, the rs1573496 (ADH7) polymorphism was shown to modulate the alcohol–CRC relationship (Ferrari et al., 2012b). In addition, the group is exploring the application of competing risks approaches to the role of alcohol intake on non-communicable diseases and reanalysing the role of alcohol intake on BC within EPIC in view of a potential interaction with folate status.

**Determinants of healthy ageing**
The Group leads the cancer-specific work package as a partner in a major FP7 project (CHANCES), which brings together 13 international cohorts to conduct pooled analyses of determinants of cancer risk and survival in elderly populations. After 2 years of harmonization of variables, analyses are set to start, with the Group leading efforts on socioeconomic status, and a competing risks approach for alcohol intake.

**Nutritional metabolomics**
The Group is continuing its projects of NMR metabolomic profiling in pancreatic and liver cancers, as well as targeted analyses for a large array of metabolites in close collaboration with the BMA Group.

**Early-life and metabolic disorders**
To study the effects of fetal and early-life exposures on health later in life, a consortium of Latin American birth cohorts has been established. The effects of maternal nutrition and early nutritional status on the child’s biological/metabolic profiles and as predictors of later disease risk are under study.
Dietary Exposure Assessment Group (DEX)
The overall goal of the DEX Group is to improve the accuracy, understanding, and interpretation of dietary exposure (and changes thereof) in studies on diet and cancer and other intermediate diseases. This Group has a leading role in the development of dietary methodologies to monitor changes in dietary exposures and improve their integrated analyses in relation to diseases, particularly in international study settings.

International methodologies and (web-) infrastructure to support nutritional studies
A comprehensive web-based platform, the dietary e-Standardized Methodologies Platform (e-SMP), for use and dissemination of the DEX international research dietary methodologies, is currently being implemented in a stepwise approach. As a key element of the e-SMP, the standardised 24-hour dietary recall program (EPIC-Soft®) initially developed for international epidemiological studies (EPIC) has been adapted for use as a reference instrument in pan-European monitoring surveys within the EFCOVAL project (Slimani et al., 2011). More recently, a data entry version of EPIC-Soft (PANCAKE project) that is better suited for data entry of repeated consecutive days of food consumption data as collected by food diaries among children (but also among the elderly) has also been successfully developed and tested (manuscript in preparation).

Additional software tools and facilities are also under development or planned through recently granted projects, for example an e-SMP module for matching food consumption data with nutrient and other occurrence databases or training and new e-facilities to support distance training.

The development of new dietary tools also includes the enrichment of the standardized EPIC Nutrient Databases (ENDB) previously developed by the DEX Group (Slimani et al., 2007). A new folate database has been compiled (Bouckaert et al., 2011) as well as a database on flavonoids in collaboration with Spanish colleagues, which will be revised and extended through a broader cross-sectional project on polyphenols initiated by Drs Romieu (NEP) and Scalbert (BMA).

The Group was also involved as a task leader in the IDAMES project to evaluate measurement properties of dietary assessment tools and the applicability of innovative e-dietary assessment technologies for large-scale epidemiological studies (Illner et al., 2012).

Applying DEX methodologies in international monitoring and epidemiological studies
In view of the first pan-European monitoring survey involving the 27 Member States in a rolling system where the DEX methodology is used as a reference tool, a pilot study in adults has been launched. Within the two complementary projects, the EMP-PANEU and PILOT-PANEU projects, funded by the European Food Safety Authority (EFSA), the DEX methodology has been successfully implemented in five EU Member States (Bulgaria, Hungary, Finland, Portugal, and Poland) and tested in their respective local feasibility studies. In addition, e-training facilities were developed at IARC and tested under real study conditions.

As an extension of this successful experience in Europe, the implementation of the DEX methodologies for research and monitoring purposes in Latin America is under consideration, starting with Brazil and Mexico as two pilot countries (local and National Institutes of Health grants have been submitted and are still under evaluation). In parallel, collaboration with the Korean National Cancer Centre has been established to develop a Korean version of the DEX methodologies.

Validation and descriptive analyses on dietary exposures and their related biomarkers (e.g. plasma fatty acids, acrylamide/glycidamide haemoglobin adducts, folates) are ongoing or
have already been completed in collaboration with researchers within or outside the NME Section (see list of publications).

**Integrated dietary analyses to study diet–disease associations**

In parallel with the improvement and standardization of dietary methodologies, the DEX Group, in close collaboration with the Biostatistics Group (BST) and other, external partners, initiated a methodological project on analysing nutrient and biological patterns in international study contexts with planned applications to colorectal cancer (granted project), breast cancer (ongoing WCRF grant), and diabetes (Interact project). Two methodological papers that describe the rationale and procedures to derive nutrient patterns and an innovative approach to ease the interpretation and description of the derived nutrient patterns, particularly in an international study context, are in preparation.

To consolidate the future DEX activities worldwide, important collaborations/contacts were established with several EU Member States already using the DEX methodologies in their national monitoring surveys, (cancer) research/public health centres in Latin America and Korea, EFSA, WHO headquarters, FAO, and other key players or networks in these nutritional areas. In addition, an important network of African countries (22 representatives, 35 researchers) was formed to conduct a full inventory on the local situations regarding dietary and physical activity assessment methodologies and infrastructures used/needed. This inventory will serve to develop a road map for prioritizing support infrastructure needed for international nutritional research to be initiated in Africa.

**Biomarkers Group (BMA)**

The major objectives of the Group, created 2 years ago, are to develop new biomarkers to improve assessment of diet, metabolism, and exposure to environmental risk factors, including food contaminants and hormonal status, and to apply these biomarkers to large cohort and case–control studies in relation to cancer risk (in close interaction with DEX and NEP) as well as to small-scale dietary interventions in humans. This approach will allow a better understanding of the mechanisms and metabolic pathways by which biomarkers of diet, food contaminants, and hormones affect cancer and intermediate end-points at the cellular and physiological levels. Special emphasis is given to metabolomic approaches to identify novel biomarkers and to provide more comprehensive measurements of exposure to cancer risk factors in metabolome-wide association studies.

**Establishment of a new laboratory for metabolomics studies**

A new analytical platform has been developed to analyse the human metabolome and has been installed at IARC in two fully renovated laboratories. Novel equipment includes a high-resolution mass spectrometer (QTof 6550 from Agilent) and a tandem mass spectrometer (QTrap 5500 from AB Sciex), both coupled to an ultrahigh-performance liquid chromatography system, a gas chromatograph, and a robot for solid-phase extraction. Computing capacity was developed to allow storage and treatment of metabolomic data. Staff have been trained to run this new equipment, and two young researchers highly skilled in metabolomics have been recruited.

**Metabolomics and discovery of biomarkers of exposure to cancer risk factors**

New research activities have been started to identify new biomarkers of dietary and environmental exposure through metabolomics approaches (grants NutriTech FP7, EXPOsOMICS FP7, EUROCAN). The metabolome is being analysed in urine and plasma samples in large-scale cohort studies and in specifically designed intervention studies to identify biomarkers of intake for a large diversity of foods and of environmental exposure. Databases on food constituents and their metabolites and on biomarkers of dietary exposure are being built to speed up the identification of biomarkers in complex metabolomic profiles.
**Hormones**
A series of hormone analyses have been undertaken within large cohort studies, such as EPIC and the Mexican EsMaestras cohort (led by Dr Romieu). Analyses of thyroid hormones, thyroid stimulating hormone, thyroglobulin, and antibodies against thyroglobulin in serum samples have been finalized in a large case–control study nested within the EPIC cohort on thyroid cancer risk (in collaboration with Dr Franceschi [ICE]; manuscript in preparation). A study on the repeatability of these hormones over time has also been initiated. Measurements of growth factors, adipokines and cytokines, estrogens, and C-peptide have been performed on serum samples from the EsMaestras cohort, to study the relationship between these biomarkers, obesity, and mammographic density in women, in collaboration with the NEP Group (led by Dr Romieu; manuscripts in preparation).

**Fatty acids**
A method has been developed to routinely analyse 60 fatty acids in blood samples. It has been optimized for complete resolution of trans fatty acid isomers from industrial and natural dietary sources. New research activities have been started integrating these measurements for application in large-scale epidemiological studies in relation to cancer risk in low- to high-income countries (Chajès et al., 2011).

**Polyphenols**
A database on all known metabolites of polyphenols, major antioxidants in the diet, has been developed (Rothwell et al., 2012), and an in-depth characterization of all polyphenols detectable in urine and plasma samples from cohort studies is ongoing. A novel method of quantification based on metabolite coding with labelled dansyl chloride is being developed and will be applied to a first nested case–control study to identify polyphenols associated with risk of colorectal cancer (grant from Institut National du Cancer).

**References**


Section of Genetics (GEN)

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

Biostatistics Group (BST)

The BST Group contributed to the design and analysis of various studies throughout the Agency. A selection of these projects is listed below, by collaborating Section and Group.

With the Section of Environment and Radiation (ENV)

**Thyroid cancer risk in Chernobyl clean-up workers**

BST was responsible for evaluating the effects of uncertainties in the radiation exposure measurements (Kesminiene et al., 2012).

**Asbestos-related lung cancer risk**

Mesothelioma was used as a proxy for asbestos exposure, to estimate the attributable fraction of asbestos in lung cancer (McCormack et al., 2012).

With the Section of Nutrition and Metabolism (NME)

**Dietary reporting errors**

Errors in reports of dietary consumption, as judged by physiologically implausible caloric intakes, were found to be strongly associated with body mass index (BMI). This suggests the presence of strong systematic biases in dietary exposure measures (Freisling et al., 2012).

**Body size and differentiated thyroid cancers**

The risk of differentiated thyroid cancer was found to be associated with obesity in women, whether measured by BMI or waist-to-hip ratio. In men, the association was with height, directly and also via leg length (Rinaldi et al., 2012).

With the Genetic Cancer Susceptibility Group (GEN/GCS)

**Optimizing high-throughput classification of rare variants**

It was shown that using a transformed version of continuous measure of variant tolerability produced by the SIFT program can outperform the standard binary classification when applied to multiple variants in a gene (Delahaye et al., submitted).

**Radiation and genetic risk factors for papillary thyroid cancer (PTC)**

In a study of those exposed to radiation subsequent to the Chernobyl accident, several genetic factors were seen to increase the risk of PTC in conjunction with radiation. The effect of radiation and genetic factors appeared to be multiplicative (which may or not be described as an interaction depending on scale) (Damiola et al., submitted).
With the Genetic Epidemiology Group (GEN/GEP)
Opium consumption and mortality – see GEP section below (Khademi et al., 2012a).

Alarm symptoms for upper gastrointestinal tract (UGI) malignancies
An optimal decision tool is being developed for patients presenting with dyspepsia in the context of high rates of UGI malignancy (Khademi et al., 2012b).

Genetic variants, cotinine, and lung cancer risk
Measurements of cotinine were used to calibrate self-reported smoking rates and so obtain modified estimates of the direct effect of 15q25 variants on lung cancer risk (Timofeeva et al., 2011).

Outside IARC

University of Melbourne: Cancer risk of computed tomography (CT) scans of children and young adults
A study of a cohort of 11 million young Australians to estimate risks of cancer resulting from CT scans in the first 19 years of life (Mathews et al., submitted).

University of Helsinki: Trends in breast cancer mortality
A study of breast cancer mortality trends in Sweden, using the staged introduction of screening to obtain an alternative estimate of the benefit of screening (Haukka et al., 2011).

Genetic Cancer Susceptibility Group (GCS)
In 2012, GCS has studied the contribution of rare variants to cancer susceptibility and further exploited the genome-wide association study (GWAS) approach to investigate the contribution of common genetic variants. We have also focused on the installation and optimization of the laboratory and bioinformatics aspects of next-generation sequencing.

Rare variants in XRCC2 and breast cancer susceptibility
An exome (the coding part of the genome)-sequencing study of families with multiple breast-cancer-affected individuals identified two families with mutations in the homologous recombination-related DNA repair gene XRCC2, one protein-truncating mutation and one probably deleterious missense substitution. To further investigate this gene, 689 families with multiple breast cancer cases were screened for mutations at the University of Melbourne, and at IARC we screened 1308 breast cancer patients with an early age of cancer onset and 1120 controls. The replication phase identified eight additional breast cancer cases carrying a protein-truncating or a probably deleterious (as predicted by in silico tools) rare missense variants in XRCC2. This number of variants was more than expected by chance, implicating XRCC2 in breast cancer susceptibility. This is the first breast cancer susceptibility gene to be identified using such an approach. This study demonstrates the potential that massively parallel sequencing, in combination with appropriate study designs, has to discover new cancer susceptibility genes.

Incorporating prior probabilities to assist ranking of a GWAS of oral cancers
We have undertaken a GWAS of oral cancer in 791 cases and 7012 controls. We developed a Bayesian method, AdAPT, that allows prior probabilities for genetic variants to be considered in the ranking of GWAS results. Higher prior probabilities were placed on genetic variants that keyword-based, automated text screening of the medical literature identified as potentially relevant to oral cancers. The top five genetic variants ranked using AdAPT were studied further in an additional 1046 oral cancer cases and 2131 controls. Only one variant, rs991316, ranked 77th by \( P \) value and 3rd using AdAPT, displayed statistically significant association in the replication phase (\( P_{\text{replication}} = 0.003 \)). The rs991316 variant is located in the \( ADH \) gene cluster on 4q23, and appears to be restricted to oral cancers, with little evidence for association with other upper aerodigestive tract cancer sites. The GCS Group is now exploring the possibility of
incorporating additional sources of information to generate prior probabilities within AdAPT, for example genomics information produced by the Genetic Services Platform.

Genetic Services Platform (GSP)
By maintaining and further developing the genetic technical platform and related Laboratory Information Management System (LIMS), the GSP provides a suite of laboratory services to support IARC genomics projects. The platform integrates several multipurpose liquid-handling robots into the laboratory processes in combination with the use of a LIMS to track the progress of samples as they pass through the laboratory workflows. Recent developments of GSP include the installation of two next-generation sequencers (a Life Technologies SOLiD 5500XL and an Ion Torrent PGM) and a high-performance computing cluster.

The main GSP capabilities are:
• Exome and targeted sequencing using massively parallel sequencing
• SNP genotyping using TaqMan, high-resolution melting curve analysis, or Illumina microarrays
• Gene expression, copy number variation, and whole-genome methylation profiling using Illumina microarrays.

GSP coordinates collaborative efforts with IARC Groups (GCS, GEP, EGE, ICB, MPA, MMB) and external partners. Some examples of recent relevant projects are:
• Exome sequencing of nasopharyngeal cancer patients from an extended Malaysian pedigree (GCS)
• Exome sequencing of lung cancer patient tumours and corresponding germline DNAs (collaboration with GEP)
• Whole-genome expression profiling by RNA-seq of total cellular RNA from Epstein–Barr virus (EBV)-infected cells with pLXSN, anti DNp73a anti-sense oligonucleotide and the sense oligonucleotide (collaboration with ICB)
• Exome sequencing of schwannoma patients (collaboration with MPA)
• Exome sequencing of formalin-fixed, paraffin-embedded (FFPE) triple-negative breast cancers and corresponding germline DNAs (collaboration with MMB)
• Whole-genome methylation profiling using Illumina 450K microarrays on blood samples from children exposed to aflatoxin (collaboration with EGE)
• Whole-genome methylation profiling using Illumina 450K microarrays on large series of blood samples from breast cases and controls from the EPIC cohort (collaboration with EGE).

Genetic Epidemiology Group (GEP)
Notable results from GEP in 2012 include the following.

Lung cancer genome-wide analyses
Recent GWASs have identified common genetic variants at 5p15.33, 6p21–6p22, and 15q25.1 associated with lung cancer risk. To identify additional novel risk variants for lung cancer, we have recently performed a meta-analysis of 16 GWASs, totalling 14,900 cases and 29,485 controls of European descent (Timofeeva et al., 2012). This international collaboration, with the analysis hosted at IARC, provided increased support for previously identified risk loci at 5p15, 6p21, and 15q25. Furthermore, we demonstrated histology-specific effects for 5p15, 6p21, and 12p13 loci but not for the 15q25 region. Subgroup analysis also identified a novel disease locus for squamous cell carcinoma at 9p21, which was replicated in a series of 5415 Han Chinese. This large analysis provides additional evidence for the role of inherited genetic susceptibility to lung cancer and insight into biological differences in the development of the different histological types of lung cancer.
Renal cancer genome-wide analyses
Along with colleagues from the United States National Cancer Institute and MD Anderson Cancer Center, we have extended our previous GWA analysis of renal cancer, published in 2011 (Purdue et al., 2011), with an extended analysis that involved an additional 984 cases and 1516 controls (Wu et al., 2012). This analysis resulted in the identification of a fourth susceptibility locus for renal cancers at 12p11.23, implicating the ITPR2 gene. The other primary focus for this year has been to bring together a series of 2000 cases and a similar number of controls, who will undergo dense genome-wide genotyping.

Hodgkin lymphoma genome-wide analyses
In 2012 we finalized a GWAS of 1200 classical Hodgkin lymphoma (cHL) patients and more than 6000 control subjects, with validation in an independent replication series, to identify common genetic variants associated with total cHL and subtypes defined by tumour EBV status (Urayama et al., 2012). Two novel loci associated with total cHL irrespective of EBV status were identified in the major histocompatibility complex region; one resides adjacent to MICB and the other at HLA-DRA, with both results confirmed in an independent replication series. Associations were also found between EBV-positive cHL and genetic variants within the class I HLA region and between EBV-negative cHL and variants within the class II region. Evidence for an association between EBV-negative cHL and the 5q31 region (comprising the IL13 gene – previously linked to psoriasis and asthma) was also observed.

Opium consumption and mortality within the Golestan cohort
The 50 000 individuals of the Golestan cohort, recruited between 2004 and 2008, were followed up to mid-2011, at which point 2145 deaths had been reported. An initial analysis on the role of opium in all-cause mortality was finalized and published in 2012 (Khademi et al., 2012a), reporting a nearly 2-fold increased risk for the 17% of the population who had reported opium use at baseline. Opium consumption was significantly associated with increased risks of deaths from several causes, including circulatory diseases (hazard ratio, 1.81) and cancer (1.61). The strongest associations were seen with deaths from asthma, tuberculosis, and chronic obstructive pulmonary disease (11.0, 6.22, and 5.44, respectively). After exclusion of people who self-prescribed opium after the onset of major chronic illnesses, the associations remained strong with a dose–response relation.

References


Section of Early Detection and Prevention (EDP)

Prevention and early detection are major interventions in reducing the burden of and controlling cancer. The Section of Early Detection and Prevention (EDP) consists of three groups: the Prevention and Implementation Group (PRI), the Quality Assurance Group (QAS), and the Screening Group (SCR). Together, their aim is to make significant contributions through focused research to the development of cost-effective and resource-appropriate public health policies for early detection and prevention, as well as evidence-based and quality-assured strategies to further augment prevention and early detection programmes for breast, cervical, colorectal, oral, and gastric cancers globally, with particular emphasis on less-developed countries. To achieve this objective, the Section investigates various early detection and prevention approaches and addresses the development of quality assurance guidelines and the integration of the different prevention and early detection strategies as part of routine health services. There is a continuing emphasis on developing, updating, and expanding training resources to augment human resources for cancer prevention and early detection initiatives and on the scale-up of prevention and early detection services by contributing to the development of local health systems within the limitations of the research studies.

Prevention and Implementation Group (PRI)

PRI conducts studies to evaluate the efficacy, population impact, and feasibility of interventions aimed at the primary and secondary prevention of cervical, anal, oral, and gastric cancer, particularly in low- and middle-income countries. In addition, we collaborate with public health institutions and governments to implement and evaluate effective interventions for cancer prevention. The main focus of PRI has been the development and implementation of safe and effective vaccines against human papillomavirus (HPV)-related cancers and the evaluation of the potential impact of *Helicobacter pylori* (*H. pylori*) eradication on gastric cancer incidence and mortality. In addition, a multicentre evaluation of methods to triage HPV-positive women in the context of cervical cancer screening is planned, to start in the near future.

Cervical cancer studies in Guanacaste, Costa Rica

The Guanacaste Project (PEG) is a long-term collaboration with the United States National Cancer Institute and Costa Rican investigators to investigate the natural history of HPV infections and associated neoplasia, in addition to new preventive strategies. The Costa Rica Vaccine Trial (CVT) is part of this effort. Between 2004 and 2005, CVT recruited approximately 7500 women aged 18–25 years to participate in a randomized controlled trial of the bivalent HPV vaccine (HPV 16/18) to evaluate its efficacy against cervical infections and cervical intraepithelial neoplasia (CIN2+). The initial 4-year follow-up has been completed, and initial results on prevention of 1-year persistent infections published (Herrero et al., 2011). A report on efficacy to prevent CIN2+ has been submitted to the United States Food and Drug Administration. We observed approximately 80% protection against CIN2+ regardless of HPV type in the according-to-protocol cohort of naive women. The long-term follow-up of the vaccinated cohort continues, mainly to evaluate long-term protection (10 years), safety, immunogenicity, and HPV type-replacement.

Epidemiology and prevention of anal and oral HPV infection

At the 4-year visit in the Costa Rica Vaccine Trial, we obtained anal specimens for HPV testing from sexually active women. We detected 22% of anal oncogenic HPV infection in this group of relatively young women (Castro et al., 2012). Current plans include long-term follow-up of anal HPV-positive women with HPV testing, anal cytology, and anoscopy, to define the natural history of these infections. We have already reported on the efficacy of the vaccine to prevent anal HPV infection 4 years after recruitment (Kreimer et al., 2011), and the long-term follow-up will permit assessment of long-term efficacy. Oral HPV detection was relatively low (1.9%), but we
observed lower prevalence among vaccinated women 4 years after vaccination (unpublished results). Follow-up is under way to investigate the natural history of these infections.

**Multicentre study of HPV screening and triage (ESTAMPA)**
We have put together a group of Latin American investigators to conduct a large multicentre study including more than 50,000 women to evaluate multiple triage techniques among HPV-positive women. Women aged 30–64 years will be recruited at centres in at least seven Latin American countries and screened with an HPV test. All HPV-positive women and a sample of HPV-negative women will be referred for colposcopy, biopsy, and final diagnosis, with follow-up at 18 months. Visual, cytological, and molecular triage methods should allow the definition of specific strategies to select women requiring more intensive follow-up and treatment. The study is in its final phases of preparation.

**Clinical trial of *H. pylori* infection in Latin America**
We have completed the initial follow-up phase of our Latin American randomized clinical trial to evaluate efficacy of three different treatment regimens against *H. pylori* in seven centres in Latin America, conducted in collaboration with the Southwest Oncology Group (SWOG) in the USA. The results of eradication at 6 weeks after treatment have been published (Greenberg et al., 2011), and we have now completed analysis of the 1-year follow-up data. The recurrence/reinfection rate appears larger than expected, and detailed analysis of its determinants is under way.

**Medellin, Colombia, ASCUS trial**
In collaboration with the University of Antioquia, we are participating in a randomized trial to evaluate different strategies for clinical management of women with atypical squamous cells of unknown significance (ASCUS) cytology. The trial is well under way, with close to 1500 women recruited. Recruitment will continue for at least another year.

**Support of HPV vaccination and screening programmes in Latin America**
In the context of the Argentina national screening programme to implement HPV-based screening, extensive political and educational meetings, development of guidelines and educational material, setting up of laboratories, etc., have been completed for the first province to implement the programme (Jujuy). A protocol to evaluate the acceptability and performance of self-collected specimens was recently initiated. Extension to new areas is now being planned. The materials developed and the experience gained should be useful for implementing other programmes in the region. We have participated in meetings with local authorities from Mexico, Costa Rica, Chile, Colombia, Peru, and Paraguay and with the Network of Latin American Cancer Institutes to promote implementation of new cervical cancer screening approaches and HPV vaccination.

**Quality Assurance Group (QAS)**
Quality assurance aims to ensure that a given endeavour leads to the outcome for which it is intended. It is highly relevant to complex systems, such as screening and primary prevention programmes that are designed to lower the burden of cancer in the population. The activities of the QAS Group aim to expand and effectively disseminate knowledge key to assuring the successful implementation of primary and secondary prevention programmes as a tool for comprehensive cancer control. The focus is on programmes and evidence-based interventions for large segments of the population in which the majority of currently preventable cancer cases and deaths occur. The efforts of the Group are particularly relevant to continuous improvement in comprehensive control of cancer. They cover not only primary and secondary prevention but also tertiary prevention, because the process of screening involves diagnosis, treatment, and also subsequent care of patients identified through screening.
The same principles of quality assurance and successful implementation of cancer prevention programmes apply in all cultural and resource settings (see, e.g., Hill and Dixon, 2010; Kania and Kramer, 2011; Hanleybrown et al., 2012; Lyne et al., 2012; von Karsa et al., 2012a). Through coordination of international networks, the Group promotes exchange of experience and collaboration in quality assurance and successful implementation of programmes in Europe and, increasingly, in other regions of the world.

Guidelines for cancer screening
The WHO guidelines on Comprehensive cervical cancer control were published by WHO in 2006. The QAS Group has collaborated with the Department of Chronic Diseases Prevention and Management and the Department of Reproductive Health and Research in a project co-financed by the French National Cancer Institute to update the WHO guidelines.

The fourth edition of the European guidelines for quality assurance in breast cancer screening and diagnosis was published by the European Commission in 2006 (Perry et al., 2006; see also Perry et al., 2008). A full revision of the European guidelines for quality assurance in breast cancer screening and diagnosis is now under way, and the new, fifth edition is planned for publication in 2014 or 2015. In the meantime, supplements to the current, fourth edition have been prepared in a project coordinated by the QAS Group and co-financed by the EU Health Programme. These supplements have been developed to address those fields that the editors felt warranted an earlier update of the standards, protocols, and best practice recommendations, in particular digital mammography and pathology. The supplements also include recommendations on implementation of population-based cancer screening programmes that are relevant not only to breast cancer screening but also to cervical and colorectal cancer screening.

The Group has collaborated with experts in quality assurance and evaluation of breast cancer screening in the preparation and publication of a series of 10 papers based on the results of population-based service screening programmes in the EU (Broeders et al., 2012; Giordano et al., 2012a, 2012b; Hackshaw 2012; Hofvind et al., 2012; Moss et al., 2012b; Njor et al., 2012; Paci and EUROSCREEN Working Group, 2012; Puliti et al., 2012; Zappa and Federici, 2012). The papers elucidate the balance between the key benefits and harms of breast cancer screening and show that the results expected from the randomized trials have been achieved in service screening programmes. Preparation of these publications has been co-financed by the EU Health Programme.

Another series of 13 papers based on the individual chapters of the European guidelines for quality assurance in colorectal cancer screening and diagnosis (Segnan et al., 2010) have been prepared and published (Atkin et al., 2012; Austoker et al., 2012; Halloran et al., 2012; Lansdorp-Vogelaar and von Karsa, 2012; Malila et al., 2012; Minozzi et al., 2012; Moss et al., 2012a; Quirke et al., 2012; Steele et al., 2012a, 2012b; Valori et al, 2012; Vieth et al., 2012; von Karsa et al., 2012b). Adherence to the principles, standards, and recommendations in the guidelines has the potential to enhance the control of colorectal cancer through improvement of the quality and effectiveness of screening programmes and services. Through these publications, the editors hope to promote international discussion and collaboration by making the content of the new EU guidelines known to a wider professional and scientific community. The preparation of the recommendations in the EU guidelines has been co-financed by the EU Health Programme.

The second edition of the European guidelines for quality assurance in cervical cancer screening was published by the European Commission in 2008 (Arbyn et al., 2008; see also Arbyn et al., 2010). Supplements to the current, second edition have been prepared in a project coordinated...
by the QAS group and co-financed by the EU Health Programme. These supplements deal with fields that the editors felt warranted an update (primary screening through HPV testing) or inclusion in the guidelines (HPV vaccination) before preparation of a third edition. The supplements will be published in 2013.

Revision of the European Code Against Cancer
Work has begun on the revision of the European Code Against Cancer (Boyle et al., 2003). The aim of the project, which is co-financed by the EU Health Programme, is to evaluate, revise, and expand if necessary the previous recommendations for key lifestyle and public health interventions that if adopted by average-risk members of the population may result in a reduction in cancer incidence and mortality. The project is coordinated by the QAS and ENV groups and involves several other sections and groups within the Agency (CIN, COM, IMO, INF, PRI, SCR).

EU screening implementation report
The first Report on the Implementation of the Council Recommendation of 2 December 2003 on Cancer Screening was published by the European Commission in 2008. Work has begun on the second report in a project coordinated by the QAS group and co-financed by the EU.

Dissemination of knowledge on successful implementation of cancer screening
In addition to the above-mentioned guidelines publications, in bilateral projects the Group has provided advice to the programmes and responsible authorities involved in breast and cervical cancer screening in Belarus; in breast cancer screening in Estonia; and in breast, cervical, and colorectal cancer screening in Turkey. The ongoing expert support to Belarus is provided in collaboration with WHO (headquarters, WHO Regional Office for Europe, and country office). The Group has also played a key role in the EUROMED project, providing advice in capacity building in early diagnosis and training in quality assurance and implementation of cancer screening programmes to 18 countries in the Mediterranean region, including the Middle East and Northern Africa. This project is co-financed by Italy, France, and Spain and is jointly coordinated by the Ministries of Health and Finance in these countries in collaboration with the WHO headquarters (Department of Chronic Diseases Prevention and Management) and IARC (QAS).

A two-week course on planning, management, and evaluation of population-based cancer screening programmes has been developed, and piloting will begin in November 2012. This project is co-financed by the EU Health Programme through the European Partnership for Action Against Cancer and the EUROMED project.

Screening Group (SCR)
SCR conducts studies to evaluate the performance characteristics, effectiveness, and service delivery aspects of different screening and early clinical diagnosis interventions for breast, cervical, colorectal, and oral cancer control in low- and middle-income countries (LMICs). These initiatives address the development and evaluation of pragmatic and feasible quality assurance inputs, the methods by which screening services could be scaled up through routinely existing health systems, the evaluation of population and service delivery determinants that influence participation in intervention programmes, and the development of different training resources to catalyse and augment trained human resources through close collaboration with the national institutions and government health services in the countries. The Group aims to catalyse the development of resource-appropriate screening, early diagnosis policies, and health systems to deliver effective early services. Technical support is also provided to planned and ongoing national early detection programmes in selected LMICs.
Cervical cancer prevention and screening
As part of efforts to accelerate the introduction of HPV vaccination in low-resource countries, the efficacy of two doses versus three doses of HPV vaccine, administered over 6 months, in preventing cervical neoplasia is being evaluated in a clinical trial. Of the 17729 unmarried girls recruited, 4920 have received two doses and 4337 have received three doses over 180 days or more; the remainder have received either a suboptimal single dose or two doses over 60 days. Preliminary results indicate that the immunogenicity of two doses is non-inferior to the three-dose regimen. No serious adverse events related to vaccination have been reported so far. The study cohorts will be followed up to establish long-term immunogenicity, amnestic response, HPV infection, and cervical neoplasia outcomes following the different dose regimes.

SCR continues to document cervical cancer incidence and mortality among the 230000 women in the Osmanabad and Dindigul district cervical screening trials in India, addressing the impact of a single round of screening with HPV testing, cytology, or visual inspection with acetic acid (VIA). The role of cytology and VIA to triage HPV-positive women is being evaluated in a randomized trial involving 30000 women in India. The effectiveness of different screening approaches in preventing cervical neoplasia in human immunodeficiency virus (HIV)-infected women is being addressed in a cross-sectional study in India (Joshi et al., 2012). A descriptive evaluation of the Thailand national cytology screening programme has been completed, highlighting the need to improve several programmatic aspects, and results have been published (Khuhaprema et al., 2012). Technical support was provided to ongoing programmes in Bangladesh, Guinea, India, Morocco, Republic of Congo, Sri Lanka, and Thailand. An evaluation of cervical cancer screening in health services in Mali was completed (Teguete et al., 2012). A high acceptability of HPV vaccination in the general population of Argentina was established in a qualitative study (Arrossi et al., 2012). An overall assessment of visual inspection methods for cervical screening was completed (Sankaranarayanan et al., 2012a). A meta-analysis of the efficacy of cryotherapy in curing cervical intraepithelial neoplasia was completed (Sauvaget et al., 2012).

Breast cancer screening
The second round of screening by clinical breast examination (CBE) has been completed, and the third round has been initiated in a randomized controlled trial involving 116000 women in Trivandrum, India. A qualitative study addressing the factors influencing participation in the various levels of the screening trial has been initiated. A study of the role of breast awareness in improving early detection and survival of breast cancer patients was initiated in Mumbai in 2012 (Gadgil et al., 2012). We are currently evaluating the performance characteristics of new tools based on near-infrared imaging and tactile imaging in India, China, and Thailand.

Oral cancer screening
Long-term results, after 15 years of follow-up, of the participants in the randomized trial of oral visual screening in Kerala, India, indicate a 25% reduction in mortality among users of tobacco and/or alcohol and a more than 80% reduction in mortality in those who complied with all four rounds of screening (Sankaranarayanan et al., 2012b). We are currently evaluating the inputs and outcome of a “social marketing” increased-awareness-based early detection programme in Sri Lanka.

Colorectal cancer screening
SCR is technically supporting the integration and scaling up of a colorectal cancer screening programme based on immunochemical faecal blood testing and triage colonoscopy in the government health services in Lampang Province, Thailand. It has already covered 50% of the 150000 target population aged 50–64 years and will inform and facilitate large-scale national scaling up in the future.
References


The Gambia Hepatitis Intervention Study Group (GHIS)

The Gambia Hepatitis Intervention Study aims to evaluate the effectiveness of vaccination against hepatitis B virus in infancy for the prevention of cirrhosis and liver cancer in The Gambia. It was initiated in 1986.

The three partners in this long-term project – IARC; the Medical Research Council, The Gambia Unit; and the Government of The Gambia – met in January 2012 to review progress. They endorsed plans for enhanced surveillance of chronic liver disease, including cancer, and re-affirmed their commitment to the study.

Dr Njie, the hepatologist now managing the project, has further developed clinical services for those with liver disease and ensured that all the relevant information is captured by the National Cancer Registry. To further strengthen the registry, one of the senior Tumour Registry Officers attended the IARC Summer School on Cancer Epidemiology in Lyon.

Dr Ervik of IARC visited The Gambia to support the registry and to develop record-linkage methods. The variability in spelling of both forenames and family names is a key issue, particularly since this spelling may have changed between the time when the name was recorded for the infant and now, when that infant is an adult giving their own name. A strategy of generating a complete listing of possible spellings and using this for linkage is now being evaluated. The final linkage is likely to require verification using the foot and palm prints collected both for those in the vaccination study and for all subjects in the appropriate age range recorded by the cancer registry. Once this has been validated, the linkage protocol can be finalized.
Laboratory Services and Biobank Group (LSB)

The biobank arm of the Laboratory Services and Biobank Group (LSB) is responsible for managing biological resources and for providing biobanking services to IARC colleagues and international collaborators. IARC stores more than 7 million biosamples – about 4 million from 370,000 participants in the EPIC study, and the remainder from collaborative projects involving IARC-based scientists. LSB’s other role is to support core laboratory activities at IARC. Together with the Laboratory Steering Committee (LSC), the laboratory services arm of LSB sets priorities for investment in equipment and shared platforms.

Biobank

The main goals of the biobank arm of LSB are to maintain and manage a centralized IARC Biobank in a safe and secure environment; to provide an up-to-date record of IARC’s resources; to provide a reliable pre-analytical sample processing service for sample retrieval, DNA extraction, and shipment according to international guidelines and protocols; and to contribute its resources and services internationally, through established networks. For sample inventory and cataloguing, to date, sample records for 47% of the IARC-based collections have been checked and verified, and more than half of the verified records have been entered into the centralized database (SAMI). A sample access policy has been developed in collaboration with the Biobank Steering Committee (BSC), to provide information on how to access IARC’s resources. In 2012 a review was conducted of the practices and procedures, including the operational costs, of the biobank. As a result, the Material Transfer Agreement (MTA) and sample shipment procedures have been revised in line with international guidelines and protocols and for synergy with the sample access procedures. Through a tender process, a new company has been identified that will provide liquid nitrogen at a much lower cost compared with the previous contract.

Future priorities include working closely with the Section of Support to Research (SSR), LSC, and BSC to develop the new laboratory and biobank infrastructure for IARC, and exploring the possibility of coordinating a biobank network for low- and middle-income countries (LMICs) in collaboration with the United States National Cancer Institute (NCI) and other international societies and organizations. The aim is to work with LMIC partners to address shortfalls in population cohorts and biobanking facilities, which are underdeveloped in resource-constrained settings.

Laboratory Services

The main goal of the laboratory services arm of LSB is to manage the basic laboratory services supporting research. This includes, in collaboration with LSC, coordinating equipment acquisition and maintenance programmes; supervising laboratory safety and safe practice at work across the Agency and providing technical advice to the Occupational Health and Safety Committee; supporting specialized platforms and equipment, such as next-generation sequencing, mass spectrometry, and Biosafety Level 3 facilities managed by specific research groups; implementing and monitoring common quality tools such as the electronic laboratory notebook (ELN) for recording experimental data; and standardization of standard operating practice documents to enhance good laboratory practice for laboratory quality management.

The laboratory services web site, which will be launched at the end of 2012, will serve as a central resource, containing laboratory protocols and providing information on facilities and laboratory equipment. Future priorities include investing in new equipment, such as robotics for sample preparation compatible with popular downstream applications such as qPCR, microarrays, and next-generation sequencing platforms, and continuing to monitor good laboratory and safety practices according to national and international guidelines.
Education and Training Group (ETR)

Education and training in cancer research has been one of the statutory functions of the Agency since its inception in 1966, complementing and supporting IARC’s research activities. Priority is given to scientists from, or with a research interest relevant to, low- and middle-income countries (LMICs). Since its establishment in 2010, the Education and Training Group (ETR) has worked closely with the scientific groups to develop and implement training initiatives, under two main programmes: Courses and Fellowships.

Courses
The activities of the Courses Programme comprise both the IARC Summer School on Cancer Epidemiology and the organization of specialized courses run by the scientific Groups of the Agency.

The Summer School is organized in Lyon each year in June and July. In 2012, more than 160 applications were received, of which 64 were accepted, with approximately 73% of the participants from LMICs. A new Union for International Cancer Control (UICC)-IARC award was successfully launched and will allow one of the most promising participants in the Summer School to return to IARC for a period of 3 months to receive further training and to set up a research collaboration. Additional financial support for the Summer School was provided by the United States National Institutes of Health–National Cancer Institute (NIH-NCI) as well as by the Nordic Cancer Union (NCU).

Specialized courses were also organized by scientific groups, often with the support of ETR. As an example, courses on cancer registration were organized in Egypt (in French), in India (in English), and in Colombia (in Spanish) in the framework of the Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries (GICR). Bringing such training to the regions is supporting the establishment of regional hubs that will provide technical support for cancer registries in the region and the establishment of a regional training programme.

On the distance learning front, renewed negotiations with the Programme of Action for Cancer Therapy/Virtual University for Cancer Control (PACT/VUCCnet) would lead to development of an e-learning module on Cancer Registration in 2013. In addition, two specialized courses, on CanReg5 and EPIC-SOFT, have been run successfully 100% at distance by scientific groups, through a webinar online tool. This approach will be extended to other IARC advanced courses in the future.

Fellowships
IARC Fellowships provide excellent training and experience in an exceptional multicultural and international environment to deserving postdoctoral fellows from around the world.

In 2012, eleven new postdoctoral fellowships were awarded and seven were extended for a second year. Fellows came from Argentina, Australia, Brazil, Colombia, India, Lebanon, Malaysia, Mexico, the Netherlands, South Africa, Spain, Sudan, Thailand, and the USA. One Return Grant was granted to a fellow from China.

Additional funding came from the EC-FP7 Marie Curie Actions-People-COFUND programme. ETR applied for a new EC-FP7 Marie Curie Actions-People-COFUND grant, to contribute to 40% of the postdoctoral fellowship costs for 2014–2019. The proposal was favourably evaluated and is now under negotiation.
In addition, and under the bilateral agreement with the Cancer Council Australia, one IARC-Australia fellowship was awarded in 2012 and one extended for an additional year, and the eligibility criteria for the IARC-Ireland fellowship launched with the Irish Cancer Society have been widened to allow a greater number of applications. Other, similar partnerships are currently under discussion with several institutions in Participating States.

One year after its implementation, the IARC Postdoctoral Fellowship Charter has met with success, allowing a more structured approach to postdoctoral training at IARC, defining expectations and including opportunities for generic training. In this respect, several generic courses were organized at IARC, to equip postdoctoral researchers with essential skills to enhance career prospects: Principles of Oncology, Biomedical Research Ethics, Project Management, and Grant Writing.

The Agency also attracts top international cancer researchers, who spend various periods of time contributing to the Agency’s programmes, making IARC the ideal environment for education, training, and exchange. The Senior Visiting Scientist Award for 2012 was granted to Dr Isabel Dos Santos Silva, London School of Hygiene and Tropical Medicine, London, United Kingdom; Dr Terry Dwyer, Murdoch Childrens Research Institute, Parkville, Victoria, Australia; and Steven Rappaport, Center for Occupational and Environmental Health, University of California, Berkeley, California, USA.
Communications Group (COM)

The Communications Group (COM) consists of several teams: the IARC publications programme, library services, web services, editing and translation services, and the media team. Below are some highlights of COM’s activities in 2012.

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

*IARC Monographs* in PDF online:
Volume 101 (2012) *Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water*

*IARC Monographs* in print:
Volume 100: *A Review of Human Carcinogens* (including a 6-book boxed set):
Volume 100A (2012) *Pharmaceuticals*
Volume 100B (2012) *Biological Agents*
Volume 100C (2012) *Arsenic, Metals, Fibres, and Dusts*
Volume 100D (2012) *Radiation*
Volume 100E (2012) *Personal Habits and Indoor Combustions*
Volume 100F (2012) *Chemical Agents and Related Occupations*

Other books:
*Improving Public Health through Mycotoxin Control*, IARC Scientific Publication No. 158.
*WHO Classification of Tumours of the Breast*, 4th edition.

In 2012, the library team has focused its activity and efforts on developing an open-access policy for the Agency, and that should bear fruit in the next few months. It has prepared key performance indicators for reporting to the IARC governing bodies and contributed the data for the Staff Publications Database implemented by the web team. The Library team also addressed collection preservation and access issues through ongoing weeding and space rationalization projects. A range of library services and information management training sessions were provided for IARC scientists, fellows, students, and staff.

The web team successfully launched an entirely redesigned IARC web site in May. The enhanced web site includes a “Cancer Topics” section, a Search facility for IARC Staff Publications stored in the IARC Reference Manager Database, and a “Who’s Who” section to display detailed profile information about IARC staff. A dedicated effort has been made to align all IARC web sites to the new visual identity. This team has also been developing the IARC Web Strategy, outlining future directions in relation to promoting IARC’s work, and a practical document with policies and procedures for use within the Sections/Groups.

The editing and translation team edited dozens of articles, book chapters, reports, and grants, and translated the official documents from English into French. Training sessions on effective writing were provided for Summer School participants.

The media team issued 51 IARC news items published on the web, and released 7 international news releases. It coordinated media efforts for World Cancer Day in February. It also organized a major press conference on the outcome of the Monographs Working Group evaluation of diesel engine exhaust in June.
IARC Communications Strategy
In 2012, COM has been developing an Agency-wide communications strategy, which focuses on the following as core elements of the dissemination of scientific information to the scientific community and to the wider public.

– The IARC publications programme is being merged with library services to create a Knowledge Management Centre, which integrates relevant services relating to information creation, dissemination, and preservation.

– The web project is improving and introducing new technologies to ensure the dissemination and visibility of the Agency’s research results, and thus a consistent corporate identity throughout the organization’s web sites.

– The editing and translation services have merged, in order to bring similar interests together and offer fast and efficient services to the IARC community.

– The media strategy has been prepared and, as this is considered to be a key area for the Agency’s visibility, the Agency is recruiting a professional Press Officer to help the COM team achieve its medium-term goals: restructuring the Group, ensuring open access to scientific results and literature as much as is possible, making most of IARC’s scientific results available through the media, and developing IARC’s influence in the media.
Governing Council and Scientific Council

The International Agency for Research on Cancer (IARC) was established in May 1965 through a resolution of the XVIIIth World Health Assembly, as an extension of the World Health Organization, after a French initiative. It is governed by its own Governing bodies, the IARC Governing Council and the IARC Scientific Council.

Governing Council
IARC's general policy is directed by a Governing Council, composed of the Representatives of Participating States and of the Director-General of the World Health Organization. It meets every year in ordinary session in Lyon, usually the week prior to the WHO World Health Assembly. The Council elected Dr Christopher Wild in May 2008 to serve for a five-year term; he took office on 1 January 2009. The Chairperson of the Governing Council prepares the meetings together with the Secretariat and advises the Director throughout the year.

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

Budget
For the biennium 2012–2013, the IARC Governing Council voted a regular budget of €39 419 15. A number of projects are also funded by extrabudgetary sources, both national and international. In the 2010–2011 biennium, 28% of the Agency’s overall expenditure was financed by extrabudgetary funds.
Participating States and Representatives at IARC Governing Council  
Fifty-fourth Session, 17–18 May 2012

**Finland**  
Professor Pekka Puska, *Chairperson*  
Director-General, National Institute for Health and Welfare  
Helsinki

Dr Sakari Karjalainen  
Secretary-General, Cancer Society of Finland  
Helsinki

Professor Harri Vainio  
Director-General, Finnish Institute of Occupational Health  
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**United Kingdom of Great Britain and Northern Ireland**  
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Head, International Strategy, Medical Research Council  
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**Switzerland**  
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Collaboratrice scientifique, Office fédéral de la santé publique  
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Chief Medical Officer, Department of Health and Ageing  
Canberra

**Austria**  
Dr Hemma Bauer  
Austrian Federal Ministry of Science and Research  
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**Belgium**  
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No Representative

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Professor Ian Frazer

**Incoming Chairperson, Scientific Council**  
Professor Mads Melbye

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**External Audit**  
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Professor Giulio Superti-Furga (Rapporteur)
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