

# International Agency for Research on Cancer

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## IARC Interim Annual Report 2010

## Foreword

In 2010 the Agency published estimates of the global cancer burden in GLOBOCAN 2008. This analysis provides a definitive set of statistics on worldwide cancer occurrence. The estimates highlight the increasing toll that cancer will exert on society in the coming decades, and as such provide an important backdrop to the high-level UN Summit on Non-communicable Diseases to be held in New York in September 2011.

GLOBOCAN 2008 revealed an estimated 12.7 million new cases of cancer worldwide in 2008 and approximately 7.6 million deaths. The majority of both new cases and deaths occurred in the lower-resource countries. Projections based on demographic changes alone indicate that in 20 years time the total number of cases of cancer worldwide will be 21.4 million, with around 13.2 million deaths. This burden will fall increasingly on the developing countries. These estimates assume no underlying change in the incidence rates of cancer; increasing tobacco consumption and a more westernized lifestyle (dietary change, physical inactivity, changing reproductive patterns, obesity) would result in the current projections being underestimates.

The Agency defined its Medium-Term Strategy and Implementation Plan (2010–2014) over the last year, and this was approved by the Governing Council in May 2010. The organizational structure of the Agency in Sections and Groups matches the priority areas in the plan. The strategy itself is designed to respond to the increasing cancer incidence, particularly in low- and medium-resource countries, described above. It focuses not only on providing data on the global occurrence of cancer to inform policymakers and health professionals for the purposes of planning cancer control, but also on identifying the causes of the disease. Major effort is being placed on understanding the roles of nutrition and metabolism, infections, environmental factors, occupation and genetics in the development of cancer. The Agency will continue to evaluate the evidence for carcinogenicity of various agents through its Monographs series as a first step towards cancer prevention.

The strategy places great emphasis on interdisciplinary research. The Agency is investing in new technologies such as next-generation DNA sequencing and mass spectrometry in its laboratories. This will enable a new understanding of the mechanisms of carcinogenesis to be translated into biomarkers to improve exposure assessment and identify susceptible individuals and groups, and into more refined disease definition in epidemiological studies. There has arguably never been a greater potential for advances to be made by combining laboratory research and epidemiology in understanding cancer causation and prevention; the Agency must remain equipped to take advantage of these opportunities.

Research into cancer prevention, both primary and secondary, is also a strong element of the medium-term strategy. The Agency will continue to evaluate prevention strategies that can be applied in low- and medium-resource settings such as vaccinations against hepatitis B virus and human papilloma viruses, and screening for cervical, breast, oral and colorectal cancer. There are increasingly opportunities to conduct observational studies in order to evaluate public health interventions.

Many examples of the ongoing research of the Agency in the above areas are detailed in this Interim Annual Report. The high quality of scientific output remains the foundation for the Agency's activities; a complete listing of 2010 publications is detailed in the Annex. Building on its research foundation, the Agency is able to train and equip the next generation of cancer researchers through its courses, fellowships and research collaborations. Education and training was reinforced in 2010 by the establishment of a

dedicated group, led by a senior professional staff member, to coordinate and develop various initiatives, including those in partnership with national and international organizations. Of particular note was the establishment of an IARC-Australia post doctoral fellowship supported by Cancer Council Australia. It is hoped this may become a model for additional bilateral cooperation with other IARC Participating States.

The Agency continues to provide training in areas of its expertise. In addition to a successful Summer School held in Lyon, a workshop on cancer registration was held at Stellenbosch University in Cape Town, South Africa, and included almost 60 participants from cancer registries in 11 African countries. Such regional training will be a key part of developing cancer registration in the coming years in areas of the world where coverage and quality by registries is currently limited.

A strategy is hollow without excellent researchers. This year has seen the Agency add to its existing strengths by recruiting a number of key senior leaders. Drs Forman and Bray have joined as Head and Deputy Head of Cancer Information; Dr Isabelle Romieu arrived as Head of Nutrition and Metabolism, and was joined in the Section by Dr Augustin Scalbert as Head of the Biomarkers Group; Dr Joachim Schüz was recruited to head the Section of Environment and Radiation. It was also encouraging to see IARC scientists successfully competing for leadership positions, with Dr James McKay appointed as the new Head of Genetic Cancer Susceptibility. In addition to these senior appointments a number of excellent mid-career recruitments were made. The strength of applicants for scientific positions at IARC is a strong positive indicator of the performance of the Agency in 2010.

The year ahead promises to be an exciting one for the Agency. The scientific strategy and structure are in place and the Agency has a near-full complement of scientific staff, providing increasing opportunities for collaborative research internally and externally. The laboratory-base has been strengthened to permit IARC to take greater advantage of the advances in interdisciplinary research. These changes should place the Agency in a strong position to compete for extra-budgetary funding in a difficult international economic climate. The positive support of the Scientific and Governing Councils is also providing a vital foundation for the future. In addition, the IARC continues to develop close working relationships with the WHO and with other international partners including the Union for International Cancer Control (UICC), with the UN Summit on Non-communicable Diseases providing a focal point in the coming year.

Finally, I would like to express again the sadness of all colleagues at the Agency in relation to the loss of Dr Elaine Ron of the Division of Cancer Epidemiology & Genetics, Radiation Epidemiology Branch of the United States National Cancer Institute. Elaine was a great supporter of the Agency, served on the Agency's Scientific Council for four years and was Chairperson of the 44<sup>th</sup> Session of IARC's Scientific Council in 2008. She provided vital support through this period, and we will miss her greatly.

Dr Christopher Wild  
IARC Director

## Section of Cancer Information (CIN)

The Section of Cancer Information was created in 2009, and in March 2010 the two existing Groups within the Section, Descriptive Epidemiology Production (DEP) and Data Analysis and Interpretation (DEA), were amalgamated to constitute an integrated Section to lead IARC activities in descriptive epidemiology. In April 2010, Dr David Forman joined IARC from the University of Leeds, UK to become Section Head, and Dr Freddie Bray joined from the Cancer Registry of Norway as a Scientist within the Section. In October 2010, Dr Bray was appointed as Deputy Section Head. The previous Group Heads, Dr Maria Paula Curado (DEP) and Dr Hai-Rim Shin (DEA), left IARC in July 2010.

CIN has the overall aim of maintaining IARC as the definitive reference source for the provision of information concerning worldwide cancer vital statistics. This aim is accomplished through a series of linked objectives consistent with the IARC medium-term strategy:

- To collect, analyse and disseminate information concerning the global cancer burden and to improve the timeliness of this information;
- To provide support to cancer registries worldwide in terms of development, staff training, promotion of common standards for coding and classification and ensuring effective use of data produced;
- To increase coverage by population-based cancer registration, in particular in low- and medium-resource countries;
- To conduct a programme of research in the descriptive epidemiology of cancer, including geographical analyses, time trends and the estimation of the future burden of the disease;
- To develop the use of new sources of information concerning the burden of cancer and novel methodological approaches in the analysis of registration data;
- To develop online global cancer statistics tools for inclusion within the website *CANCERmondial* ([www-dep.iarc.fr/](http://www-dep.iarc.fr/)).

In June 2010, CIN launched GLOBOCAN 2008 ([globocan.iacr.fr](http://globocan.iacr.fr)), a new online facility that provides standardized incidence and mortality information on 27 cancer types for 185 countries worldwide. Online tools for data analysis compiled in *Cancer Incidence in Five Continents* (CI5) were also published in two formats ([ci5.iarc.fr](http://ci5.iarc.fr)): the *CI5 I-IX* database brings together results from the nine volumes, while *CI5Plus* enables trend analyses of annual data from registries with longer time series. Peer-reviewed publications outlined the methodology of GLOBOCAN 2008 and presented key variations of the global burden (Ferlay et al., 2010), and described 50 years of CI5 including the compilation process and illustrative examples of use of the data (Parkin et al., 2010). CIN staff have presented assessments of the global burden at various international meetings, including the ESMO 2010 congress in Milan, the UICC 2010 World Cancer Congress in Shenzhen and the 32<sup>nd</sup> International Association of Cancer Registries (IACR) meeting in Yokohama.

The *CANCERmondial* website also hosts websites dedicated to the analysis of cancer mortality series (as part of the WHO mortality databank), as well as websites for the analysis of European and Nordic data respectively, through the European Cancer Observatory (funded by Cancéropôle and the European Union), and NORDCAN (in collaboration with the Association of Nordic Cancer Registries).

A key remit of the Section is to assist and advise cancer registries worldwide in population-based registration systems with a view to expanding the coverage of the world population

with high-quality cancer information. The provision and support for cancer registration training and development initiatives in LMRC is central to this objective. The first module of the IARC Summer School provides training in the principles and methods, and the syllabus is also taught in different world regions to target support for local registries and personnel. A workshop at Stellenbosch University in Cape Town, South Africa included 57 participants from registries in 11 predominantly English-speaking African countries in 2010. Further courses in Mumbai (aimed at Asian cancer registries) and in Africa (for French-speaking participants) are under development.

Training in the use of the CanReg5 registration system is also paramount to the aim. The open-source version was officially launched at the IACR conference in Yokohama, and the software is available for download in several languages (English, French, Russian and Portuguese, with Spanish coming soon). Training workshops have been held in Japan, China, South Africa, Ecuador, Trinidad & Tobago, Morocco and Turkey.

Support is also provided to registries through collaborative research agreements with individual cancer registries within low- and medium-resource countries; the appraisal process is presently being reviewed. There have been recent site visits by CIN staff to review and evaluate registration systems in Russia (Moscow), Oman (Muscat) and Indonesia (Jakarta).

CIN provides the secretariat to the International Association of Cancer Registries (IACR) and the European Network of Cancer Registries (ENCR). One of the drivers of the latter network is the EU-funded EUROCOURSE project, which aims to advance the use of registry data across Europe. CIN has developed a data portal that facilitates data exchange and collaboration with European registries, and contributes to the activities through its work packages. IARC is also a collaborating partner in the EU-funded European Partnership for Action against Cancer (EPAAC) and a member of its Steering Committee. It will lead a work package that will support the core activities of the ENCR. CIN also collaborates in several childhood cancer collaborations, including the EU-funded ENCCA (European Network for Cancer Research in Children and Adolescents) and PanCareSurFup (PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies), and the UICC-coordinated "My Child Matters" project.

A programme of research in the descriptive epidemiology of cancer, with an emphasis on time trend analyses and the estimation of the future burden, is being established.

CIN is also responsible for provision of updates to the International Classification of Diseases–Oncology (ICD-O) now in its 3<sup>rd</sup> edition. Resulting from the adoption of new pathological entities, defined in the WHO Classification of Tumour Series (WHO Blue Books), a number of new ICD-O-3 codes have been proposed for tumours of the central nervous system, digestive system and haematopoietic and lymphoid tissues. CIN is making these new codes available to the cancer registry community.

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## Section of IARC Monographs (IMO)

This Section produces the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. The *IARC Monographs* are a series of scientific reviews that identify environmental factors that can increase the risk of human cancer. Since 1971, one hundred volumes of *IARC Monographs* have been developed, reviewing the scientific literature on more than 900 agents and identifying more than 400 known, probable and possible carcinogens.

During 2010 the Section focused on three major activities: publication of the volumes that had been delayed by the preparation and conduct of six Monograph meetings for Volume 100, streamlining the publication process, and preparing for the three Monograph meetings that will be convened during 2011.

Dr Vincent Coglianò, Head of IMO, left the Agency in November 2010. Dr Kurt Straif was named Acting Head, and the post will be advertised in early 2011.

### Publication of volumes that had been delayed

Thanks to additional resources made available by the Governing Council and by the Director, the Section is publishing all seven delayed volumes during 2010. In addition to publishing each volume as a familiar orange book, the Section is making all volumes freely available on the Internet. The schedule for this activity appears in the following table.

Volume	Title	Available on Internet	Available as a book
92	Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures	April 2010	May 2010
93	Carbon Black, Titanium Dioxide, and Talc	Nov 2010	Jan 2011*
94	Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins	July 2010	Oct 2010
95	Household Use of Solid Fuels and High-temperature Frying	May 2010	July 2010
96	Alcohol Consumption	Dec 2010*	Feb 2011*
98	Painting, Firefighting, and Shiftwork	Oct 2010	Dec 2010*
99	Some Aromatic Amines, Organic Dyes, and Related Exposures	Oct 2010	Dec 2010*

\* Expected. Note: Volume 97 was published during 2009

To take advantage of electronic technology, the Section notifies the experts who developed each volume as soon as it is available electronically. This allows the experts one month to verify the information before it is printed, providing an additional level of confidence in the scientific accuracy of the Monographs.

Scientists in the Section also worked on verifying the scientific accuracy and clarity of the text and tables for Volume 100, which updated and reviewed the more than 100 agents that IARC classifies as *carcinogenic to humans* (Group 1). This activity is expected to be completed in early 2011, eliminating the backlog and allowing the verification of future

volumes to commence soon after each meeting is adjourned. After the last part of Volume 100 is posted on the Internet, all six parts will be sent for printing and distribution.

### **Streamlining the publication process**

The Section undertook a review of its operating procedures. Major changes are being made in the use of desktop publishing software. The Section uses software based on Extensible Markup Language (XML), the state-of-the-art language in the publishing sector, which will facilitate publishing the Monographs in print, pdf, and e-publishing formats. Related software automates reference checking and links to the U.S. National Library of Medicine's PubMed database, facilitating more efficient and accurate listing of references cited in the Monographs.

Other software is being developed to manage the working papers developed before Monograph meetings and to facilitate pre-meeting review and expert collaboration on these manuscripts.

In addition, an electronic database of Monograph results is being developed. This will make it possible to search the agents evaluated by the Monographs programme for evaluation results, cancer sites in humans and in experimental animals, and mechanistic events that are associated with tumour development. It will be possible to use CAS Registry Numbers and ICD codes to link this database to others that contain physical-chemical information on an agent or pathology information on its associated cancer types.

### **Preparations for Monograph Volumes 101–103**

The Section began preparations for the three Monograph meetings that it will convene during 2011, when the programme returns to its usual schedule of producing three volumes per year. The topics of these meetings are as follows.

*Volume 101: Some Chemicals in Industrial and Consumer Products, Food Contaminants, and Water Chlorination By-Products*  
15–22 February 2011

Many chemicals found as additives or contaminants of food, drinking water, and consumer products have recently been shown to cause cancer in experimental animals. This volume will review and evaluate 16 such chemicals for which the available data consist primarily of cancer bioassays and mechanistic studies.

*Volume 102: Non-Ionizing Radiation, Part II: Radiofrequency Electromagnetic Fields [includes mobile telephones]*  
24–31 May 2011

This volume will review the potential cancer hazards of mobile telephones, microwaves, and radar. Use of mobile telephones is nearly universal in many countries, and there is intense interest among national health agencies and among the general public. Pooled results on gliomas and meningiomas from the Interphone multi-centric case-control study were published in May 2010 and will be reviewed along with the many other epidemiological and experimental studies on these types of radiofrequency radiation.

*Volume 103:* Bitumen and bitumen fumes, and some heterocyclic polycyclic aromatic hydrocarbons  
11–18 October 2011

This volume is part of the series of Monographs on air pollution and will review and evaluate bitumen and bitumen fumes, and some heterocyclic polycyclic aromatic hydrocarbons. Bitumen is processed from residues of petroleum refining, and liberates fumes when heated for use as paving materials. Exposure is primarily occupational and is widespread.

Scientists from the Section are exploring several agents that were recommended by an Advisory Group as high priorities for future evaluation to determine whether important studies then in progress are likely to be available for review by the time of the meeting.



## Section of Mechanisms of Carcinogenesis (MCA)

The MCA Section is dedicated to two objectives. First it conducts original laboratory research aimed at elucidating the molecular basis of carcinogenesis. Second, it develops studies for discovery of molecular biomarkers and for piloting their application into molecular epidemiological studies. The two Groups of the Section follow the same strategy of balancing basic research, technical advances and translational projects, with focus on mutation detection (Group of Molecular Carcinogenesis, MOC) and on epigenetics (Group of Epigenetics, EGE). The two Groups share many common research themes (liver cancer, lung cancer, esophageal cancer, regulation of cell proliferation) and run parallel studies in which both mutation and epigenetics biomarkers are applied to the same study designs and specimen series. As a result of the translational dimension of the Section's project, many publications are developed in collaboration with IARC epidemiologists, illustrating the multiple ways in which the Section uses its molecular knowledge to advance research projects developed by other groups.

### Molecular Carcinogenesis Group (MOC)

Mutations are the cornerstone of cell transformation and cancer progression. Inheritance of mutations in tumour suppressor genes causes familial cancer syndromes, which account for 3–5% of all cancer cases worldwide. In sporadic cancers, mutations are acquired somatically, either through defective DNA repair or through extensive mutagenesis caused by environmental factors. Thus, the type and nature of mutations in cancer cells can be informative of exposures and processes involved in cancer causation. Work by the MOC Group focuses on the *TP53* tumour suppressor gene (encoding the p53 protein), its somatic and inherited mutations and their significance for cancer occurrence, progression, prognostic and prediction on therapeutic responses. In addition, the Group investigates the mechanisms by which mutant p53 protein interferes with cell homeostasis and perturbs physiological responses. The Group also maintains and publishes on the web a comprehensive database of all *TP53* mutations published in the literature.

#### ***TP53* mutations in breast cancer: impact on prognosis and on responses to estrogens**

In the largest study to date on *TP53* mutations in breast cancer (BC) we have previously shown that mutations were independent and extremely strong biomarkers of poor prognosis, in particular in estrogen/progesterone (ER/PR)-positive cancers. We have investigated the molecular basis of this phenomenon. Studies published in 2010 show that in normal breast cells and in ER/PR+ BC cells, estrogen levels act as a rheostat on p53 levels and modulate p53-dependent growth arrest responses (Fernández-Cuesta et al., 2011). This observation led us to investigate how p53 affects the responses of cancer cells to anti-hormone therapies. We showed that p53 status influences response to tamoxifen but not to fulvestrant in breast cancer cell lines, suggesting possible strategies to improve the response of tumours with mutant *TP53* to this type of therapy (Fernández-Cuesta et al., 2010). Furthermore, we showed that one of the main p53-dependent mechanisms by which estrogen controls the proliferation of BC is the down-regulation of Focal Adhesion Kinase (FAK/PTK2), a tyrosine kinase that regulates cell adhesion, motility and metastatic capacity (Anaganti et al., 2011). Studies are underway to further assess the predictive significance of *TP53* mutation for responses of BC to different forms of therapy. Additionally, we have initiated a series of studies on BC in low-resource countries including Latin American countries (in collaboration with Isabelle Romieu of NME) and West Africa. As background to this project, we have analysed available data on BC incidence in The Gambian, providing evidence for ethnicity-related variations (Sighoko et al., 2010).

**Mutation patterns and genetic predisposition in lung cancers in relation to tobacco smoke**

After developing detailed analyses of mutation patterns in lung cancers of smokers, we have turned to the impact of factors other than tobacco that contribute to the etiology of lung cancer, with particular focus on adenocarcinoma (ADC). Our work has focused on identifying the contribution of factors other than indirect tobacco smoke or occupational exposures (Clement-Duchêne et al., 2010; Paris et al., 2010). We have also begun to analyse the genetic heterogeneity of lung cancers and we have shown that KRAS mutation status were frequently discordant between primary lung cancers and metastases (Cortot et al., 2010). In terms of mechanisms, we have finalized a study initiated in 2006 in collaboration with Dr Toufic Renno, demonstrating that MyD88, an adaptor molecule in IL1-R and TLR signalling pathways that is often up-regulated in lung cancers of never-smokers, operates as a regulator of the RAS signalling pathways, thus providing a direct link between inflammatory responses, cell-cycle control and transformation (Coste et al., 2010). In collaboration with Paul Brennan of GEN and Zdenko Herceg of EGE, we have investigated the molecular mechanisms accounting for the role of genes encoding CHRNA located on chromosome 15q25 using *in vitro* cell models. Our work shows that CHRNA5, which contains a non-silent polymorphism associated with predisposition to lung cancer, is a critical modulator of calcium influx and bronchial cell adhesion and motility (Brennan et al., 2010). Together, these results contribute to develop a model for the pathogenesis of lung cancer in never-smokers, in which local inflammatory damage and delayed tissue repair may represent precursor conditions.

**Interactions between Hepatitis B and exposure to aflatoxins in liver carcinogenesis**

MOC has made a significant advance in understanding the mechanisms by which mutations induced by aflatoxins (AFB) cooperate with Hepatitis B virus in liver carcinogenesis. The specific TP53 mutant p.R249S, a result of AFB-induced mutagenesis, binds strongly and specifically to the viral oncoprotein HBx and cooperates with HBx to maintain the proliferative capacity of liver cancer cells *in vitro*. In human HCC samples, mutation at codon 249 did not correlate with p.R249S protein accumulation or HBx truncation status. We suggest that p.R249S may contribute to hepatocarcinogenesis through interaction with HBx, conferring a subtle growth advantage at early steps of the transformation process, but that this interaction is not required for progression to advanced HCC (Gouas et al., 2010).

**Germline TP53 mutations and cancer predisposition: identification of a founder mutation in Brazil**

Previous studies in Southern Brazil have shown that familial cancer syndromes are common and are often associated with a special mutation in TP53, p.R337H, detected in about 0.3% of the general population. In collaboration with two oncogenetics groups in Brazil (Maria Isabel Waddington Achatz and Patricia Prolla) and with the GCS Group, we have carried out a detailed haplotyping of TP53 in unrelated cancer families from Brazil and demonstrated that this common mutation was the result of a founder effect that most likely originated in the mid-18th century (Garritano et al., 2010). Analysis of tumour patterns in these families led us to develop the hypothesis that predisposition to early cancer in TP53 mutation carriers was essentially due to defects in the regulation of pools of stem cells during late development and childhood (Palmero et al., 2010). Furthermore, in collaboration with David Malkin (Toronto), we contributed to determine that inherited microdeletions in TP53 may lead to phenotypically distinct syndromes, depending upon the extent of the deletion (Shlien et al., 2010).

### **Mutations in TP53 in cancers of the upper digestive tract: clues for etiology**

Our research is ongoing on mutations in squamous cell carcinomas of the esophagus and of the oral cavity (SCC). In collaboration with Paul Brennan of GEN, we analysed *TP53* mutations in a large series of well-characterized cancer cases from Latin America, and identified distinct mutation patterns in relation to tobacco and/or alcohol exposure (Szymańska et al., 2010). Further extending previous studies on esophageal SCC in Northern Iran, we have shown, in a study using samples from the GEMINI case-control study, that there was a strong association between SCC risk and presence of markers of exposure to polycyclic aromatic hydrocarbons in the esophageal mucosa. This result provides strong support to the hypothesis that PAHs are critical environmental mutagens in esophageal SCC causation (Abedi-Ardekani et al., 2010). Finally, experimental studies on cultured squamous epithelial cells have led us to identify that the *TP53* homolog gene *TP63* plays an essential role in the expression of cell adhesion complexes within the normal and cancer esophageal epithelium, supporting the notion that deregulation of this gene is fundamental in the mechanisms of esophageal carcinogenesis (Thépot et al., 2010b; Thépot et al., 2010a).

### **Regulation of p53 through its common isoforms Delta40p53 and Delta133p53**

In recent years, our work and that of others have shown that p53 could be expressed as distinct isoforms. The major isoforms are Delta40p53 and Delta133p53, lacking, respectively, the first 40 or 133 residues of the full-length p53 protein. These isoforms are now considered to be essential regulators of the dynamics of p53 activation in a variety of physiological and pathological conditions. We have shown that the production of Delta40p53 is dependent upon alternative splicing regulated through a tertiary G-quadruplex structure in p53 pre-mRNA. This structure is located with intron 3, in a domain that is polymorphic in the human genome. There is now growing evidence that this polymorphism is associated with predisposition to cancer, suggesting a plausible link between expression of p53 isoforms and predisposition to cancer (Marcel et al., 2010). On the other hand, we analysed the structure and regulation of an intragenic promoter that controls the expression of Delta133p53. We showed that this promoter is self-regulated by p53, suggesting a novel autoregulatory loop by which p53 controls its own activation in response to diverse forms of stress (Marcel et al., 2010).

### **Leading developments in biobanking**

Over recent years, biobanking has emerged as a critical activity supporting the development of large-scale studies in all aspects of health research. Mastering the complex pre-analytical procedures that produce high-quality specimens and biomolecules is a pre-requisite for the application of novel technologies of the "omics" family, such as genomics, transcriptomics, proteomics and, very recently, metabonomics. Given its role in developing large multicentric studies, IARC has played a leading role in setting and disseminating standards, guidelines and protocols for high-quality biobanking. The MOC Group is involved in many aspects of this task, with in particular technical research aimed at optimizing protocols and streamlining the biobanking process (Voegele et al., 2010). This activity has led to several publications focusing on international standards for large biobanks (Bevilacqua et al., 2010; Hainaut et al., 2011; Vaught et al., 2010; Zatloukal and Hainaut, 2010).

## Epigenetics Group (EGE)

Epigenetics represents a new frontier in cancer research owing to the fact that epigenetic events have emerged as key mechanisms regulating critical biological processes and the development of human diseases. Although the implication of epigenetic events in cancer is supported by both epidemiological and experimental studies, the precise contributions of epigenetic mechanisms and cellular targets of epigenetic alterations in specific human cancers are largely unknown. The intrinsic reversibility and ubiquity of epigenetic changes in virtually all types of human cancer make them attractive subjects for biomarker discovery and strategies for cancer prevention (Herceg, 2007; Lima et al., 2010; Krutovskikh and Herceg, 2010). The Epigenetics Group (EGE) conducts both mechanistic studies and epigenetic profiling to gain a better mechanistic understanding of tumorigenesis and to discover and validate new epigenetic biomarkers.

### **Hepatocellular carcinoma displays distinct DNA methylation signatures with potential as clinical predictors**

We characterized the changes in promoter DNA methylation in a series of hepatocellular carcinoma (HCC) and their respective surrounding tissue, and identified methylation signatures associated with major risk factors and clinical correlates. A wide panel of cancer-related gene promoters was analysed using Illumina bead array technology, and CpG sites were then selected according to their ability to classify clinicopathological parameters. An independent series of HCC tumours and matched surrounding tissue was used for validation of the signatures. We were able to develop and validate a signature of methylation in HCC. This signature distinguished HCC from surrounding tissue and from other tumour types, and was independent of risk factors. However, aberrant methylation of an independent subset of promoters was associated with tumour progression and etiological risk factors (HBV or HCV infection and alcohol consumption). Interestingly, distinct methylation of an independent panel of gene promoters was strongly correlated with survival after cancer therapy. Together, our studies show that HCC tumours exhibit specific DNA methylation signatures associated with major risk factors and tumour progression stage, with potential clinical applications in diagnosis and prognosis (Hernandez Vargas et al., 2010).

We have further established assays for quantitative analysis of DNA methylation levels in a panel of cancer-associated genes and repetitive elements, and combined these assays with a series of HCC tumours associated with major risk factors and collected from two different geographical areas. We found a high frequency of aberrant hypermethylation of specific genes (*RASSF1A*, *GSTP1*, *CHRNA3* and *DOK1*) in HCC tumours as compared to control cirrhotic or normal liver tissues, suggesting that aberrant hypermethylation exhibits non-random and tumour-specific patterns in HCC. Importantly, our analysis revealed an association between alcohol intake and the hypomethylation of *MGMT* and between hypermethylation of *GSTP1* and HBV infection, indicating that hypermethylation of the genes analysed in HCC tumours exhibits remarkably distinct patterns depending on associated risk factors (Lambert et al., 2010). Together, these studies identified aberrant DNA methylation of specific cellular genes in HCC and the major risk factors associated with these changes, providing information that could be exploited for biomarker discovery in clinics and molecular epidemiology.

### **DNA methylation of the HBV genome associated with the development of hepatocellular carcinoma and occult HBV infection**

Recent studies have identified the presence of methylation in the HBV genome and suggested that it may be an important mechanism regulating transcription and replication of the HBV virus; however, it remains unclear whether this phenomenon is associated with

occult hepatitis. To better understand epigenetic regulation of the HBV genome in infected liver cells, we investigated methylation profiles of HBV DNA in liver samples of different stages of HCC development and in *in vitro*-infected human hepatocytes. We found discrete CpG sites in the HBV genome that are recurrently hypermethylated in cancer and not in chronic hepatitis tissue (Kaur et al., 2010). Our findings argue that hypermethylation of the HBV genome resulting from deregulated DNA methylation in malignant cells may contribute to the disease phenotype, although it is unlikely to be responsible for the occult status.

### **Aberrant DNA methylation links cancer susceptibility locus 15q25.1 to apoptotic regulation and lung cancer**

Nicotinic acetylcholine receptor (nAChR) genes form a highly conserved gene cluster at the lung cancer susceptibility locus 15q25.1. In this study, we found that the *CHRNA3* gene encoding nAChR3 subunit is a frequent target of aberrant DNA hypermethylation and silencing in lung cancer (Paliwal et al., 2010). Treatment of cancer cells exhibiting CHRNA3 hypermethylation with DNA methylation inhibitors caused demethylation of the CHRNA3 promoter and gene re-activation whereas restoration of CHRNA3 levels through ectopic expression induced apoptotic cell death. shRNA-mediated depletion of nAChR3 in CHRNA3-expressing lung cancer cells elicited a dramatic Ca<sup>2+</sup> influx response in the presence of nicotine, followed by activation of the Akt survival pathway. CHRNA3-depleted cells were resistant to apoptosis-inducing agents, underscoring the importance of epigenetic silencing of the *CHRNA3* gene in human cancer (Paliwal et al., 2010). In defining a mechanism of epigenetic control of nAChR expression in non-neuronal tissues, our findings offer a functional link between susceptibility locus 15q25.1 and lung cancer, and suggest nAChRs as therapeutic targets for cancer detection and chemoprevention.

### **Prospective study of DNA methylation changes associated with cancer risk factors and blood levels of vitamin metabolites**

We tested whether genomic DNA from surrogate tissues such as blood cells may be exploited in the discovery of biomarkers of exposure and cancer risk. We quantitatively determined DNA methylation levels in a panel of candidate genes in blood cells of cases and controls from EPIC, and examined the association between lung cancer risk and DNA methylation patterns. We also investigated whether blood levels of vitamin metabolites modify DNA methylation levels in blood cells (Vineis et al., 2011, in press). Our results revealed that DNA methylation patterns in specific genes are associated with the case-control status and that methylation levels are influenced by serum levels of 1-carbon metabolites and vitamin B. Interestingly, these associations were modulated by smoking status. These results are consistent with the notion that blood levels of 1-carbon metabolism markers and dietary/lifestyle factors may modify DNA methylation levels in blood cells, and that blood cells can be exploited for the discovery of epigenetic biomarkers of exposures, providing proof-of-principle on the use of blood samples in the context of prospective studies (Vineis et al., 2011, in press).

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## Section of Molecular Pathology (MPA)

### Molecular pathology of brain tumours

The Section of Molecular Pathology 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 tumour classification and tumour progression. Some highlights of 2010 are described below.

#### *Intratumoral patterns of genomic imbalance in glioblastoma*

Glioblastomas are morphologically and genetically heterogeneous, but little is known about the regional patterns of genomic imbalance within glioblastomas. We recently established a reliable whole-genome amplification (WGA) method to randomly amplify DNA from paraffin-embedded histological sections with minimum amplification bias. We assessed chromosomal imbalance by array CGH (Agilent 105K), using WGA-DNA from 2–5 separate tumour areas of 14 primary glioblastomas (total, 41 tumour areas). Chromosomal imbalances differed significantly among glioblastomas; the only alterations that were observed in  $\geq 6$  cases were loss of chromosome 10q, gain at 7p, and loss of 10p. Genetic alterations common to all areas analysed within a single tumour included gains at 1q32.1 (*PIK3C2B*, *MDM4*), 4q11-q12 (*KIT*, *PDGFRA*), 7p12.1-11.2 (*EGFR*), 12q13.3-12q14.1 (*GLI1*, *CDK4*) and 12q15 (*MDM2*), and loss at 9p21.1-24.3 (*p16<sup>INK4a</sup>/p14<sup>ARF</sup>*), 10p15.3-q26.3 (*PTEN*, etc) and 13q12.11-q34 (*SPRY2*, *RBI*). These are likely to be causative in the pathogenesis of glioblastomas (driver mutations). In addition, there were numerous tumour area-specific genomic imbalances that may be either non-functional (passenger mutations) or functional, but constitute secondary events reflecting progressive genomic instability, a hallmark of glioblastomas (Nobusawa et al., 2010).

#### *Molecular classification of low-grade diffuse gliomas*

The current WHO classification recognizes three histological types of grade II low-grade diffuse glioma (diffuse astrocytoma, oligoastrocytoma and oligodendroglioma). However, the diagnostic criteria, in particular for oligoastrocytoma, are highly subjective. With the aim of establishing genetic profiles for diffuse gliomas and estimating their predictive impact, we screened 360 WHO grade II gliomas for mutations in the *IDH1*, *IDH2*, and *TP53* genes and for 1p/19q loss, and correlated these with clinical outcome. Most tumours (86%) were characterized genetically by *TP53* mutation + *IDH1/2* mutation (32%), 1p/19q loss + *IDH1/2* mutation (37%), or *IDH1/2* mutation only (17%). Tumours with *TP53* mutations only or 1p/19q loss only were rare (2% and 3%, respectively). Only 26 neoplasms (7%) showed no alteration in any of these genes. The median survival of patients with *TP53* mutation  $\pm$  *IDH1/2* mutation was significantly shorter than that of patients with 1p/19q loss  $\pm$  *IDH1/2* mutation (51.8 months vs. 58.7 months;  $P=0.0037$ ). Multivariate analysis with adjustment for age and treatment confirmed these results ( $P=0.0087$ ), and also revealed that *TP53* mutation is a significant prognostic marker for shorter survival ( $P=0.0005$ ) and 1p/19q loss for longer survival ( $P=0.0002$ ), while *IDH1/2* mutations are not prognostic ( $P=0.8737$ ). The molecular classification on the basis of *IDH1/2* mutation, *TP53* mutation and 1p/19q loss has power similar to histological classification of diffuse gliomas. Since this is more objective than histological typing and correlates well with clinical outcome, molecular profiling complements histological typing, particularly of oligoastrocytomas (Kim et al., 2010).



### **WHO Classification of Tumours Series**

The Section of Molecular Pathology is also responsible for the publication of the 4<sup>th</sup> edition of the [WHO Classification of Tumours Series \(WHO Blue Books\)](#). The objective of this project is to establish a histological and genetic tumour classification that reflects recent advances in histopathology and cancer genetics, and which is accepted and used worldwide.

#### *WHO Classification of Tumours of the Digestive System*

This volume is the 3<sup>rd</sup> volume of the 4<sup>th</sup> edition of the WHO Classification of Tumours Series (WHO Blue Books), prepared by more than 100 authors from 22 countries, and edited by Drs Fred T. Bosman, Fátima Carneiro, Ralph H. Hruban, and Neil D. Theise, was published in November 2010. This authoritative, concise reference book provides an international standard for oncologists and pathologists and will serve as an indispensable guide for the design of studies monitoring response to therapy and clinical outcome. The book also provides user-friendly algorithmic approaches to the diagnosis of the major tumours of the digestive tract.

#### *WHO Classification of Tumours of the Breast*

This volume is the 4<sup>th</sup> volume of the 4<sup>th</sup> edition, edited by Drs Sunil R Lakhani, Ian Ellis, Stuart Schnitt, Tan Puay Hoon, and Marc J. van de Vijver. In July 2010, 88 contributors from 24 countries were invited, and the consensus and editorial meeting is scheduled for spring 2011.

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## Section of Infections (INF)

The Section of Infections (INF) comprises two Groups: the Infections and Cancer Epidemiology Group (ICE) and the Infections and Cancer Biology Group (ICB). Both Groups focus on the etiology of infectious agents and cancer, using different scientific approaches. It is the role of INF to contribute, in terms of past scientific productivity and future potential, to the accomplishment of IARC's mission of cancer prevention.

Persistent infection with viruses, bacteria and parasites is responsible for approximately 20% of cancers worldwide, and lower-resource countries shoulder the majority of this burden. However, these infections also represent some of the most preventable causes of cancer through immunization or early detection. These measures present a realistic opportunity to curb certain infection-related cancers even in low-resource countries. This opportunity grows with time as new vaccines and detection methods are introduced.

The research of ICE and ICB focuses on infectious agents and the different aspects of the infection/cancer relationship (Table 1). Some aspects under study are exclusive either to ICB (e.g., transformation mechanisms) or ICE (worldwide distribution and trends of cancer-associated infections). Collaborations on other relevant aspects (the role of innate and acquired immunity, the impact of different HPV variants) are becoming possible with the increasing availability at ICB of tests suitable for large-scale application (Table below).

Regardless of the infectious agent or the aspect under study, one of the great assets of INF is the facility for collaboration on methodological issues. The Groups complement each other very well, with ICB providing advice regarding decisions on INF biological protocol aspects, and ICE providing guidance on statistical matters in INF protocols and publications.

INF has had 53 articles published in 2010. The list of publications covers a wide range of topics and is evidence of the productivity and high quality of projects coordinated. In addition to a large number of international collaborations, projects are also ongoing with other IARC Sections, notably the Sections of Early Detection and Prevention, Nutrition and Metabolism, Genetics, Environment, Molecular Pathology and Mechanisms of Carcinogenesis.

### INF Studies

<b>Aspects under study</b>
<ul style="list-style-type: none"> <li>Worldwide distribution and trends over time of infections associated with cancer</li> <li>Range of tumours associated with infection, and strength of the association</li> </ul>
<ul style="list-style-type: none"> <li>Transformation mechanisms</li> <li>Meaning of viral variants</li> <li>Role of innate and acquired immunity</li> <li>New virological and bacteriological tests for epidemiological studies</li> </ul>
<b>Agents included</b>
<ul style="list-style-type: none"> <li>Mucosal and cutaneous human papillomavirus (HPV) types</li> <li>HIV, in combination with other viruses associated with cancer</li> <li><i>Helicobacter</i> species</li> <li>Hepatitis B and C virus (HBV/HCV)</li> <li>Epstein Barr virus (EBV)</li> <li>Merkel cell polyomavirus</li> </ul>

## **Infections and Cancer Biology Group (ICB)**

The main goal of the ICB Group is to evaluate the potential role of infections in human carcinogenesis. In particular we are focused on double-stranded (DS) DNA viruses, i.e. mucosal and cutaneous human papillomaviruses (HPVs), Epstein-Barr virus (EBV) and hepatitis B virus (HBV). Two complementary strategies are currently followed:

- (i) Functional studies using *in vitro* and *in vivo* model systems to characterize the biological properties of specific infection agents; and
- (ii) Epidemiological studies to determine the presence of specific infectious agents in benign and malignant human lesions.

The functional studies were focused on characterizing the ability of the viral oncoproteins to target key events in virus-mediated carcinogenesis, and resulted in the identification of novel mechanisms to evade the innate immunity and inactivation of cellular tumour suppressors. In addition, we extended our studies to non virus-induced cancers and discovered that the functionality of the same cellular proteins inactivated by the oncogenic viruses can be lost in virus-negative cancer cells.

Regarding the epidemiological studies, we have established several novel assays for the detection of approximately 100 DS DNA viruses. These diagnostic assays are based on Luminex technology and have high throughput, sensitivity and specificity.

Future plans of the Group include (i) extending the functional studies to emerging oncogenic viruses, e.g. human Merkel cell polyomavirus and related viruses; (ii) developing novel detection assays for additional infectious agents; and (iii) expanding the epidemiological studies in collaboration with groups from IARC and other institutes, including institutes from low-resource countries.

### **Cutaneous HPV types**

The skin-tropic human papillomavirus (HPV) types from the genus beta of the HPV phylogenetic tree, also known as Epidermodysplasia verruciformis (EV) HPV types, are strongly suspected to be involved in non-melanoma skin cancer (NMSC). However, their direct role in human carcinogenesis is not yet fully proven. In addition, it is not yet known whether, similar to what has been observed with the mucosal HPV types, beta HPVs may be sub-grouped in low- and high-risk HPV types. To address these questions, we have initiated the characterization of the biological properties of the main oncoproteins, E6 and E7, from several beta HPV types. Several experimental models have been used, ranging from primary keratinocytes to transgenic mice.

Our data show that certain beta HPV types (i.e. HPV24, 38 and 49) display transforming activities in comparison to other beta HPV types (i.e. HPV14, 22, 23 and 36), supporting the existence of low- and high-risk HPV types (Gabet et al., 2008; Bouvard et al., ongoing study). Studies on HPV38 have resulted in the identification of a novel viral mechanism of inactivation of p53. Unlike HPV16, HPV38 does not induce p53 degradation but rather promotes accumulation of a potent inhibitor of p53 transcriptional functions,  $\Delta$ Np73 $\alpha$  (Accardi et al., 2006). HPV38 E6 and E7 expression in the skin of transgenic (Tg) mice using K10 promoter induced  $\Delta$ Np73 $\alpha$  accumulation, cellular proliferation, hyperplasia and dysplasia in the epidermis (Dong et al., 2005; Accardi et al., 2006; Dong et al., 2008). These functional studies support the putative role of certain beta HPV types in human carcinogenesis.

### **Mucosal HPV types and toll-like receptor signalling**

Establishment of a chronic infection is a key event for virus-induced carcinogenesis. Several prospective studies, in which HPV-positive women have been followed-up for many years, have shown that HPV16 is able to persist much longer in the host than the other mucosal high-risk HPV types. Thus, the high carcinogenicity of HPV16 may be explained by its better efficiency than the other mucosal high-risk HPV types in evading the immune system. We observed that the expression of a key player in innate immunity, Toll-like receptor 9 (TLR9), which senses double-stranded (Ds) viral DNA, is strongly impaired by HPV16 E6 and E7 oncoproteins in several *in vitro* experimental models (Hasan et al., 2007). Accordingly, immunohistochemical analyses revealed weak TLR9 expression in HPV-positive malignant cervical lesions, while strong TLR9 staining was detected in normal cervical tissues (Hasan et al., 2007; ongoing studies). E6 and E7 from other mucosal high-risk HPV types, including HPV18, are less efficient than E6 and E7 from HPV16 in down-regulating TLR9 expression, while the mucosal low-risk HPV6 E6 and E7 do not interfere at all with TLR9 transcription. Thus, the ability of the different HPV types to down-regulate TLR9 expression appears to correlate with their ability to persist. Based on these data, we have extended our studies to cutaneous beta HPV types and other cancer-associated viruses to target the TLR9 signalling pathway.

### **Prevalence of HPV infections in human specimens from different anatomical sites**

We have developed a novel assay for the detection of three different groups of HPV, namely (i) mucosal high-risk HPV types (n=19), (ii) mucosal low-risk HPV types (n=18) and (iii) beta and gamma cutaneous HPV types (n=31) (Gheit et al., 2006; Gheit et al., 2007; Gheit et al., ongoing study). Due the high sensitivity and versatility of our HPV detection assay, we were able to perform several epidemiological studies to evaluate the ability of HPV types (i) to infect a specific anatomical site and/or (ii) to promote carcinogenesis (Dai et al., 2007; Cazzaniga M et al., 2009; Rollison et al., 2008). In addition, some of the cancer case studies aimed at determining the prevalence of specific mucosal high-risk HPV types in populations that have not previously been analysed (Gheit et al., 2009; Sideri et al., 2009).

### **Role of DOK1 tumour suppressor in non-virus and virus-associated cancer**

The *Downstream of tyrosine kinase* (DOK1) is an adaptor tyrosine kinase substrate with tumour suppressive activity. The *DOK1* gene can be mutated in chronic lymphocytic leukemia (CLL); DOK1 mutated in CLL is a nuclear protein, in contrast to wild-type DOK1 which is cytoplasmic. In addition, nuclear DOK1 with a mutated nuclear exclusion site is impaired in inhibiting cell proliferation. Nuclear mislocalisation of DOK1 has also been found in HPV-immortalized keratinocytes. Thus, the subcellular localization of DOK1 correlates with its tumour suppressive activities. Further studies revealed that the expression of the *DOK1* gene is repressed through hypermethylation of its promoter in the majority of head and neck cancer (HNC) lines analyzed, as well as in primary human neoplasms including solid tumours (93% in HNC, 81% in lung cancer) and hematopoietic malignancy (64% in Burkitt's lymphoma). In addition, an inverse correlation was observed between the level of DOK1 gene methylation and its expression in tumour and adjacent tissues. Studies are ongoing to evaluate the potential role of *DOK1* as a prognostic marker in HNC and other cancer types.

### **Ongoing additional studies**

In addition to the studies described above, we are involved in (i) characterization of the molecular mechanisms of HBV-mediated carcinogenesis, and (ii) identification of host and viral factors that influence the establishment of chronic infections.

## **Infections and Cancer Epidemiology Group (ICE)**

ICE is a multidisciplinary group that includes epidemiologists of different backgrounds (medical, biological and statistical) from many countries. Its goal is to elucidate the contribution of infectious agents, such as human papillomavirus (HPV), human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV, HCV), Kaposi sarcoma herpes virus (KSHV), and *Helicobacter pylori* (*H. pylori*), to the etiology of cancer, with a focus on lower-resource countries. In 2010, ICE has strived to maintain certain elements of study continuity, and to tackle new research issues.

### **HPV**

The study of HPV, the necessary cause of cervical cancer, has been the main focus of ICE in the past year. If HPV vaccines and HPV-based screening are to be successful, accurate knowledge of the infection burden and type-specific distribution of HPV types in different parts of the world must be available. To fill existing knowledge gaps, ICE has carried out new population-based HPV prevalence surveys among women with and without cervical cancer (Raza et al., 2010; Sherpa et al., 2010). HPV testing is also in progress for additional study sites in Fiji and Vanuatu. Pooled analyses on factors such as seroprevalence have also been published (Vaccarella et al., 2010), and meta-analyses of women with and without cervical cancer continue to be updated (Li et al., 2010).

In 2010 ICE started work on the new priorities that have arisen following previous findings and the introduction of HPV vaccines. They include studies to further explore the existence of populations in which HPV prevalence does not diminish in middle-aged women, and the monitoring of HPV prevalence in vaccinated populations.

Finally, some of the work that ICE has supported in Uganda on HPV and conjunctival cancer has now come to fruition (Ateenyi-Agaba et al., 2010).

### **International Collaboration on Cervical Cancer**

ICE is continuing to exploit data from the International Collaboration on Cervical Cancer. Current work aims to explain the known association between early age at first sexual intercourse and cervical cancer risk as a duration effect of HPV infection as predicted by the multi-stage model of carcinogenesis.

### **Bayesian models applied to cancer etiology**

Multiple HPV infections in the IARC HPV Prevalence Surveys have been analysed using multi-level models to investigate the tendency of some HPV types to cluster together (Vaccarella et al., 2010). These models revealed diagnostic artefacts in early versions of the GP5+/6+ primer-mediated PCR test for HPV. This work is expanding to include other large collections of HPV prevalence data.

### **HIV/AIDS**

Cancer risk in people with HIV/AIDS (PWA) is a subject of great importance to ICE now that highly active antiretroviral therapy (HAART) has improved survival in PWA. In the past, ICE has used record-linkage and cohort studies in Switzerland and Italy to achieve both an adequate study power for uncommon neoplasms and accurate information on markers of immunity and use of HAART. An update of this exercise in Switzerland showed that increases in the incidence of selected non-AIDS-defining cancers (anus, liver, non-melanomatous skin, and Hodgkin lymphoma) after the introduction of HAART were largely accounted for by increases in age of PWA (Franceschi et al., 2010).

A second line of research has focused on the way HIV infection modifies the cancer potential of HPV infections in countries at very high risk for both infections (i.e. Kenya and South Africa) (De Vuyst et al., 2010). Although access to HAART is widespread, cervical screening among HIV-positive women needs to be improved. Indeed, support for the use of HPV testing to screen HIV-infected women has been provided for the first time. Screen-and-treat using HPV testing was demonstrated to be as feasible, safe and efficacious in HIV-infected women as it was in HIV-uninfected women. The number of CIN2+ prevented was actually greater among HIV-infected women (11.9/100) than among HIV-uninfected (3.1/100) women. Determining the way to distinguish the many transient HPV infections from long-duration cancer-inducing infections, however, is currently the most important priority for improving HPV test-based screening regardless of HIV status.

### **HBV/HCV**

ICE continues to explore the link between hepatitis and cancer, following the meta-analysis published in 2007. This meta-analysis will be updated this year, and ICE is developing projects on hepatitis viruses in high-risk populations such as Mongolia (Dondog et al., 2011), where HCV infection may well overtake HBV infection in the near future, and where dual infections are also common.

### ***Helicobacter* species**

A comparison of testing methods for *H. pylori* was published this year, showing that histopathology is an accurate tool for *H. pylori* detection in most individuals, but PCR has higher sensitivity in advanced precancerous lesions (de Martel et al, 2010). ICE now turns its focus to other *Helicobacter* species and their possible role in gallbladder cancer. Ongoing pilot studies should lead to larger studies in areas at high risk for the disease, such as Chile.

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## Section of Environment and Radiation (ENV)

The Section of Environment and Radiation is one integrated Section headed by Dr Joachim Schüz, with Dr Ausra Kesminiene as Deputy Head. The Section covers a broad spectrum of possible risk factors, from environmental exposure to pollutants, occupational risk factors, lifestyle-related factors such as smoking and alcohol consumption, and environmental and medical exposure to ionizing radiation and non-ionizing radiation. During the past year, activities focused on smoking, occupational risk factors for lung cancer, lifestyle-related risk factors of head and neck cancers and esophageal cancer, low dose ionizing radiation, and use of mobile phones.

The recent scope of work on lifestyle factors was aimed in particular at smoking and alcohol drinking, two well-established major causes of cancer, and therefore new studies better characterized dose-response relationships with alcohol consumption, addressed other forms of tobacco than from cigarettes, e.g. cigars and pipes, and elucidated the benefits of quitting smoking or drinking alcohol. In respect to occupation and cancer, occupational risk factors of lung cancer were investigated, and initiatives started to investigate cancer in relation to asbestos and to shift work. For specific cancers, several investigations addressed risk factors of head and neck tumours and of esophageal cancer. A large initiative was started to study work-related pesticide exposure and cancer risk.

The scope of the work on radiation encompasses both ionizing and non-ionizing radiation. Ionizing radiation is a model carcinogen for risk assessment, and studies of its effects are important for elucidating mechanisms of carcinogenesis. Results of these studies serve as the scientific basis for radiation protection of the general public, patients and occupationally exposed populations. Although current radiation protection standards are generally judged to be acceptably robust, there remains considerable scientific uncertainty, particularly with regard to health risks at low doses and low dose rates. Recent years have seen an unprecedented increase in the number and diversity of sources of non-ionizing electromagnetic fields (EMF), technologies that have made our lives easier although they have brought with them concerns about possible health risks.

A major effort in 2010 was the preparation of Volume 14 of the IARC Handbooks of Cancer Prevention series on the evidence for the effectiveness of tax and price policies in tobacco control. From 17–22 May 2010, 21 invited scientists and policy experts from 12 countries met in Lyon to review and evaluate the relevant literature. The evidence was organized into the following domains: overview of tobacco taxation; tobacco industry pricing strategies and tax related lobbying; tax, price and aggregate demand for tobacco; tax, price and adult tobacco use; tax, price and tobacco use among young people; tax, price and tobacco use among the poor; tax avoidance and tax evasion; and the economic, and health impact of tobacco taxation. The handbook will be available in print in 2011.

With respect to smoking, a recent analysis using the European Prospective Investigation into Cancer and Nutrition (EPIC) confirmed that cigar and pipe smoking is not a safe alternative to cigarette smoking; the lower cancer risk of cigar and pipe smokers as compared to cigarette smokers was explained by a lesser degree of inhalation and lower smoking intensity (McCormack et al., 2010). Further, LCA carried forward proposals to study effects of smokeless tobacco in regions of high use, particularly Qat chewing, as widely practiced in Yemen and Ethiopia.



Further investigations of head and neck cancer risk revealed that quitting tobacco smoking for 1–4 years resulted in a 30% risk reduction compared to current smokers, with the risk reduction after  $\geq 20$  years reaching the level of never-smokers; for alcohol use, a beneficial effect was only observed after  $\geq 20$  years of quitting (Marron et al., 2010). Recent meta-analyses confirmed that oral and pharyngeal cancers are strongly related to alcohol drinking (Turati et al., 2010), and alcohol drinking versus non-drinking was associated with an approximately doubled risk of laryngeal cancer (Islami et al., 2010); additional meta-analyses on esophageal cancer and colon cancer have been submitted. An inverse association between caffeinated coffee drinking and risk of cancer of the oral cavity and pharynx was observed, whereas tea intake was not associated with head and neck cancer risk (Galeone et al., 2010). Several sexual behaviours were associated with cancer risk at the head and neck cancer sub-sites that have previously been associated with HPV infection, namely cancer of the oropharynx, cancer of the tonsil and cancer of the base of the tongue (Heck et al., 2010). Ongoing analyses in this project investigate the role of marijuana in oropharyngeal cancers.

Investigating occupational risk factors for lung cancer using European multicentre datasets showed that exposure to polycyclic aromatic hydrocarbons (PAH) did not appear to substantially contribute to the burden of lung cancer in Eastern Europe (Olsson et al., 2010a). A study of European asphalt workers found no consistent evidence of an association between indicators of either inhalation or dermal exposure to bitumen and lung cancer risk, while a sizable proportion of the excess mortality from lung cancer relative to the general population is likely attributable to high tobacco consumption, and possibly to coal tar exposure (Olsson et al., 2010b).

Further projects were completed in Golestan, Iran; the cohort profile was recently described (Pourshams et al., 2010) and the validity of causes of death by verbal autopsy confirmed (Khademi et al., 2010). A review of findings in this high-risk area for esophageal cancer suggests cigarettes and hookah smoking, nass use, opium consumption, hot tea drinking, poor oral health, low intake of fresh fruit and vegetables, and low socioeconomic status to be associated with a higher risk (Islami et al., 2009).

New activities include a feasibility study for a mortality follow-up of workers employed in the asbestos mines and processing factories in the town of Asbest, Russian Federation, a mining site for chrysotile since 1885. The inhalation of asbestos fibres can cause lung cancer and mesothelioma, as also further investigated by the IARC working group on asbestos, but there are still some open questions with regard to the carcinogenic potency of pure chrysotile (IARC Monographs Vol. 100c). The risk of breast cancer as it relates to shift-work, classified as probably carcinogenic (IARC Monographs Vol. 98), will be further investigated within a cohort study in China. Further, a workshop was held in conjunction with the Occupational and Environmental Epidemiology Branch of the US National Cancer Institute to discuss how to pool agricultural cohort studies from several countries, to increase sample size for investigation of the relationship between pesticides and cancer; the meeting of over 20 participants representing 13 cohort studies took place 19–21 October in Lyon. Further activities on pesticides include participation in a pesticide working group using data of the International Childhood Cancer Consortium, I4C (Brown et al., 2007), and a collaboration with the Centre Léon Berard in Lyon in a study on pesticides and testicular cancer. Further planning is underway for a workshop on carrying out an epidemiological study on cancer risk in relation to engineered and adventitious products of nanotechnologies.

The growing use of relatively high-dose diagnostic imaging techniques, in particular such as Computer Tomography (CT) and interventional procedures, became a topic of concern in radiological protection, especially in children and adolescents. The Section conducted the Child-Med-Rad project in eight European countries (Denmark, Finland, France, Germany, the Netherlands, Spain, Sweden and the United Kingdom) to assess the feasibility of establishing trans-national cohorts suitable for long-term follow-up evaluating possible health risks from CT scans in this sensitive population. Given that current concerns about possible health effects related to CT exposure in childhood have become an important public health issue, the study group concluded that a combined retrospective-prospective cohort study with prospective follow-up is the best approach to providing meaningful results in a relatively short time (5–7 years) and informing decision making on the application of CT technology. Scientists from other countries (Australia, Canada, Israel, Japan, Korea, and the USA) and from the WHO (Geneva) are also involved to ensure that the European cohort study, which will start in 2011, is fully harmonized with other existing or planned activities around the world.

Despite numerous studies, the exact consequences of the Chernobyl accident remain a matter of debate, and the future direction of health research has been subject to wide differences of opinion. With support from the European Commission, an international group of experts and advisors within the Agenda for Research on Chernobyl Health (ARCH) project reviewed the health consequences of exposure to radiation from the Chernobyl accident and provided advice on the studies needed in the future. The ARCH group recommended a Strategic Research Agenda (SRA) that outlines a reasoned long-term plan for research into the health consequences of radiation from the Chernobyl accident, and set out proposals for long-term funding, similar to the action taken some years after the atomic bomb exposures. The proposed studies address the ongoing thyroid cancer problem, the apparent rise in breast cancer, inherited molecular-genetic alterations, and various cancers, cataracts and other non-cancer diseases in liquidators and in the general exposed population.

The Section conducted the GENE-RAD-RISK project to formally evaluate if subjects with pathogenic alleles in DNA repair and damage recognition genes may have an increased risk of breast cancer following exposure to ionizing radiation, even at low doses. A multinational study (France, Italy, the Netherlands and the United Kingdom) of pre-menopausal breast cancer risk was conducted in populations chosen on the basis of high prevalence of radiation exposure (childhood cancer and Hodgkin lymphoma survivors) and/or high prevalence of known mutations in susceptibility genes (*BRCA1* and *BRCA2* mutation carriers). The study demonstrated that exposure to diagnostic radiation before the age of 30 years was associated with a 2-fold increased breast cancer risk in *BRCA1/2* mutation carriers, with a significant dose-response trend. Data analyses of other study cohorts have been completed and are expected to be published in 2011. There is a need for epidemiology studies, including the GENE-RAD-RISK, for a better evaluation of doses due to different types of radiographic examinations, especially in the past. A study to collect and review historical literature discussing radiation dose to the breast was carried out to assess the dose likely received by the breast during mammography examinations.

With regard to non-ionizing radiation, 2010 saw the publication of the main results of the Interphone study, a case-control study on mobile phones and brain tumour risk in 13 countries (INTERPHONE Study Group, 2010). In this study, 2708 glioma and 2409 meningioma cases and matched controls were interviewed about their past mobile phone use. Overall, no increase in risk of glioma or meningioma was observed with use of mobile phones. There were suggestions of an increased risk of glioma at the highest exposure levels, but biases and error prevent a causal interpretation. As the case ascertainment in

Interphone was during 2000 and 2003, there were still only relatively few heavy longer-term users of 10 years or more in the study population, explaining the scientific uncertainty in this high exposure group. Further activities will include participation in measurement surveys of environmental exposures to radiofrequency electromagnetic fields (Viel et al., 2009a,b) and analysis of the risks in relation to acoustic neuromas.

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## **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-resource countries (e.g. Latin America), and exposures in fetal life/early infancy are not well studied.

Thus, the main objective of the recently-created Section of Nutrition and Metabolism (NME) is to address these issues by evaluating the association between 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, this Section plays a leading role in the coordination and maintenance of European Prospective Investigation into Cancer and Nutrition (EPIC), a large on-going 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 Section.

### **Nutrition 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)**

The Group is active in several cancer site-specific EPIC working groups. For colorectal cancer, major recent publications include a study of blood vitamin D levels and risk of colorectal cancer, showing a strong inverse risk association (Jenab et al., 2010), and blood levels of parathyroid hormone, which show a positive risk association at very high levels (Fedirko et al., 2010a). For liver cancer, biomarker and data analyses are ongoing for several studies exploring dietary, lifestyle and hormonal determinants of risk. Preliminary findings indicate a positive risk association for intake of simple sugars, and an inverse association with dietary fibre consumption (Fedirko et al., 2010b). For breast cancer, studies are exploring the role of fatty acids, folate, glycemic load/index and polyphenols, and the effect of physical activity on hormone levels.

Other recent Group publications relate to inflammation and risk of colorectal cancer (Aleksandrova et al., 2010); B vitamins and risk of colorectal (Eussen et al., 2010a; Eussen et al., 2010b), lung (Johansson et al., 2010) and gastric cancers (Eussen et al., 2010c); and phytanic acid and prostate cancer risk (Price et al., 2010).

#### **Studies in low- and middle-resource settings**

Breast cancer 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 multicenter case-control studies to identify the role by which diet, physical activity, obesity

and metabolic disorders affect breast cancer incidence and survival. The Group is collaborating with the National Institute of Public Health (INSP) and the National Institute of Cancerology (INCAN) in Mexico on a breast cancer case–control study (CAMA) of Mexican women and a large cohort of Mexican teachers (EsMaestras) selected in nine Mexican states. As a first approach, determinants of mammographic density, a strong breast cancer risk factor, are being evaluated.

Also, the Group is developing a multi-country study (Brazil, Chile, Colombia, Costa Rica and Mexico) of molecular subtypes of premenopausal breast cancer in Latin American women, with the objective of evaluating the distribution of specific molecular cancer subtypes and identifying the role and mechanisms of diet, physical activity, obesity and metabolic disorders in breast cancer incidence and survival.

The Group is conducting a feasibility pilot study on establishing a large-scale study on dietary/lifestyle factors and esophageal cancer risk in Kashmir, India, a high-risk region. A dietary questionnaire and a validation study design have been formulated and will be applied shortly.

### **Gene-nutrient interactions**

Exploration of gene-nutrient interactions is of interest for the Group. Recent activities include involvement in the Micronutrient Genomics Project, an international collaboration on micronutrient genomic studies. Studies are currently ongoing on body iron status, hemochromatosis gene mutations and risk of colorectal cancer. The interaction of folate with alcohol and folate metabolism genes, particularly for breast cancer, is also an area of active study.

### **Alcohol and cancer**

The Group is continuing its contribution to a programme of systematic meta-analyses on alcohol consumption and risk of various cancers. Recent results show a dose-response increased risk for colorectal (Fedirko et al., 2010a), laryngeal (Islami et al., 2010) and esophageal cancers (Rota et al., 2010).

### **Determinants of healthy aging**

The Group leads the cancer-specific work package as a partner in the European project entitled Consortium on Health and Ageing Network of Cohorts in Europe and the United States (CHANCES). The project brings together 13 international cohorts and aims to conduct pooled analyses of determinants of cancer risk and survival in elderly populations.

### **Nutritional metabolomics**

Recently, the Group has integrated metabolomics as a key future horizon for the field of dietary biomarkers (Jenab et al., 2009) and is leading a large collaboration to explore metabolomic profiles specific to dietary patterns and lifestyle habits. The Group is also involved in conducting nested case–control studies of NMR metabolomic analyses for pancreatic and liver cancers in collaboration with a leading centre in Lyon.

### **Early life and metabolic disorders**

Fetal and early life appear to be major determinants of health later in life. Currently, a consortium of Latin American birth cohorts is being developed to evaluate the effects of maternal nutrition and early nutritional status on biological and metabolic profiles in children and as predictors of disease status at different life stages.

## 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 standardized dietary methodologies to monitor changes in dietary exposures and improve their integrated analyses in relation to diseases, particularly in international study settings. These activities rely on multi-disciplinary internal and external networks and collaborations (e.g. EPIC, EFSA, EuroFIR, WHO headquarters, WPHNA, local IT companies) to support the dissemination and the implementation of the DEX dietary methodologies in existing and new cohorts and monitoring surveys in collaboration with NME and BMA.

### *Improved and new international methodologies for dietary exposure assessment*

A comprehensive web-based platform, the EPIC-Soft Methodological Platform (EMP), for use and dissemination of an interview-based standardized 24-hour dietary recall, will soon be completed. At the same time, the adaptation of the EPIC-Soft program for conducting standardized 24-hour dietary recalls in future pan-European monitoring surveys is about to be accomplished (EFCOVAL project).

Additional software solutions are also under development or planned through recently-granted projects, including:

- 1) A data entry version of EPIC-Soft (PANCAKE project) that is more user-friendly and 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) and increases the comparability of collected data between different age groups; and
- 2) An EMP module for matching food consumption data with nutrient and other occurrence databases. The conceptual specification of this new module will be developed by the DEX Group within the recently funded EU project EuroFIR Nexus.

The development of new dietary tools also includes the enrichment of the standardized EPIC Nutrient Databases (ENDB) developed by the DEX Group (Slimani et al, 2007). A new folate database has been compiled based on an in-depth inventory and evaluation of the available concentration data (Bouckaert et al., 2010) (ongoing WCRF grant). A first database on flavonoids was also prepared in collaboration with Spanish colleagues, and 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 recently finalized IDAMES project to evaluate measurement properties of dietary assessment tools and the applicability of new dietary assessment technologies for large-scale epidemiological studies.

The main outcomes of the Group's methodological activities described above are improved dietary methodologies for use in international nutritional settings and a series of related papers currently under review or in preparation.

### **Applying DEX methodologies in international monitoring and epidemiological studies**

Two main European projects are already under discussion to make use of the improved EPIC-Soft methodology: first, in the first pan-European monitoring survey involving the 27 Member States (direct contract between EFSA and IARC to support a preparatory/feasibility phase) and second, in a repeat measurement on a large sub-sample of the EPIC cohort (n=37 000) (project proposal approved by the EPIC Steering committee). Using the EPIC-Soft 'bridging' methodology will provide an historical

opportunity to obtain comparable cross-discipline dietary data in Europe, open new avenues for cancer and other research and facilitate translation of scientific evidence into public health, legislation and other actions.

The development of Brazilian and Mexican versions of the EPIC-Soft software for research and monitoring purposes is also under discussion to support new NEP research projects and provide more insights on dietary changes in countries in nutritional transition (DEX activities in collaboration with NEP and BMA).

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 NEP and BMA researchers within or outside the NME Section (see list of publications). These studies complement previous publications (incl. special issues) on these DEX research activities.

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

In parallel to the improvement and standardization of dietary methodologies, dietary pattern analyses appear to be a promising approach for depicting the complexity of diet and for a better understanding of its association with diseases, particularly cancer. However, there is still a lack of reference multivariate methodologies enabling comparisons and interpretation of dietary patterns across countries and taking into account specific features of large international nutritional settings (e.g. heterogeneity, calibration, measurement errors). Thus the DEX Group, in close collaboration with the IARC 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 (ongoing grant), breast cancer (submitted WCRF grant) and diabetes (Interact project). As a starting point of these activities, the diversity of nutrient patterns in the EPIC study at the population level has recently been published using a multi-dimensional graphical representation of the patterns (Freisling et al., 2010).

The Group also contributes to a series of other research activities and international conferences as invited speakers to disseminate results and knowledge (see selected papers below).

### **Biomarkers Group (BMA)**

The Biomarkers Group has been newly created and is currently under development. The major objectives of the Group are to develop new biomarkers to improve assessment of diet, metabolism, and exposure to environmental risk factors including food contaminants, hormonal status, and to apply these biomarkers to large cohort and case–control studies in relation to cancer risk (in closed 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 endpoints at cellular and physiological levels. Special emphasis will be given to metabolomic research, establishing an in-house research capacity in collaboration with external partners.

Within the Group, research projects on hormones and food contaminants, and fatty acids (diet and metabolism) in relation to cancer risk are already underway; therefore only projects related to these activities will be reported here.

Over the last year, the laboratory for hormone analyses has focused on the validation of commercially available assays for measurements of hormones (especially growth factors and sex steroids) for large-scale epidemiological studies. A reference method for the analyses of Bisphenol A in human blood and urine samples has also been established and validated, and analyses on blood cord samples have been performed in collaboration with the Hopital Neurocardiologique, Bron, France. Further studies are currently being mounted to study the validity of serum and urinary Bisphenol A concentrations as biomarkers of exposure, and to evaluate the exposure of the European population and the principal sources of contamination (EPIC and EFCOVAL studies).

The Group is undertaking case-control studies nested within EPIC to study the association between endogenous hormones and cancer risk, including one on cervical cancer risk. The Group is also coordinating the activities of the EPIC thyroid cancer working group (in collaboration with Dr Silvia Franceschi, ICE), and is leading a study on obesity, reproductive factors, thyroid hormones and thyroid cancer risk. Group scientists are also involved in several cancer-related EPIC working groups (breast, ovary, endometrial, colorectum and prostate) in close collaboration with the NEP Group. The Group has a special interest in exploring the relationship between environmental risk factors, including physical activity, and endogenous hormones (sex steroids, growth factors, insulin, cytokines), and is currently investigating this relationship within the EPIC cohort, in subjects who were recruited as controls in nested case-control studies on endogenous hormones and cancer risk.

As described above, the Group developed a special interest on biomarkers of dietary fatty acids and fatty acid metabolism in relation to cancer risk. Several studies on the association between biomarkers of fatty acids and cancer risk are ongoing and planned within the EPIC cohort (ongoing studies on breast, prostate, gastric cancers) and within the EsMaestras and CAMA cohorts in Mexico. In this context, the Group will deploy a new-generation gas chromatography system in order to develop and validate new biomarkers of lipids and related compounds in biological systems, and to apply these biomarkers in large cohort studies in relation to cancer risk. A major focus of the Group is to better understand the interaction between biomarkers of dietary intake with specific genes and pathways in relation to gene methylation and cancer outcomes. Currently, a study is also being developed within EPIC to evaluate the role of folate and other B vitamins involved in one carbon metabolism and different enzymatic pathways on global gene methylation and the risk of breast cancer.

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## Section of Genetics (GEN)

The Genetics Section 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). Dr James McKay was appointed as the new Head of GCS from September 2010.

GEP is mainly involved in coordinating large population-based epidemiological studies and analysis of multiple common genetic variants in order 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 cancers. The genetic services platform, nested within the GCS group, aims to put in place cutting-edge genomics techniques and to make that technology, along with technical expertise and support, available to all IARC groups. Finally, BST provides biostatistical and bioinformatics support to the range of Section projects, as well as across the Agency.

### Genetic Epidemiology Group (GEP)

GEP develops each of its studies taking into consideration the global or regional burden of a particular cancer and the extent to which it is under-studied by other national or international groups. This has led to a range of cancer types being investigated, including common yet relatively under-studied cancers (e.g. lung cancer), intermediate-risk cancer types (kidney and aerodigestive tract cancers), and rare cancers (nasopharynx and rare childhood embryonal tumours).

#### Genetic susceptibility of lung and upper aero-digestive tract cancers

The principal GEP project in the last few years has been a study of the genetic susceptibility of both lung and aero-digestive tract cancers. In 2007 GEP launched a joint project with the Centre National de Genotypage (CNG: Evry, France) to undertake a large genome-wide study of lung cancer. In 2008 we reported four susceptibility loci, located in 15q25, 6p21, and 5p15, which include genes that regulate acetylcholine nicotinic receptors and telomerase production. These results were recently re-examined by ethnicity and histological groups (Truong et al., 2010), and a review bringing together all recent genetic epidemiology studies of lung cancer has recently been published by Lancet Oncology (Brennan et al., 2010).

Using similar methods, we have initiated a genome-wide study of upper aero-digestive tract (UADT) cancers. Three variants were identified in the alcohol dehydrogenase (*ADH*) gene cluster on 4q23, one in an extended linkage disequilibrium region at 12q24 that contains the aldehyde dehydrogenase 2 (*ALDH2*) gene, and a fifth one near DNA repair-related genes *HEL308* and *FAM175A* at 4q21. These results further highlight the importance of alcohol metabolism in UADT cancer susceptibility, and also implicate a new chromosomal region.

#### Genetic susceptibility and genomics of renal cancers

Based on a series of studies including a large case-control study from central Europe coordinated by GEP scientists and other case-control and cohort studies, and in collaboration with the US NCI, we identified three novel susceptibility loci for renal cancer including *EPAS1* on 2p21, which encodes hypoxia-inducible- factor-2 alpha, a transcription

factor previously implicated in RCC development. This finding was notable in former and current smokers but not in non-smokers.

In addition to this genome-wide genotyping initiative, GEP has been acting as a central coordinating partner for a new project of Cancer Genomics of the Kidney (CAGEKID) launched in March 2010. The project is proposing a comprehensive investigation of genetic (including whole-genome re-sequencing) and epigenetic changes and resultant downstream proteomic changes in the most common form of kidney cancer, renal cell carcinoma (RCC). The discovery phase, which will generate a primary set of genome-wide genomic data on 100 tumour/non-tumour pairs of RCC samples, has been launched successfully, with ten initial cases included.

### **Genetic susceptibility to lymphomas**

GEP is additionally investigating genetic susceptibility to lymphomas. Within our ongoing collaboration with the CNG, GEP is performing a genome-wide association study of 1200 Hodgkin lymphoma case-control pairs from eight European countries. Genome-wide genotyping and initial statistical analysis has been completed, and further exploration of multiple strongly associated variants is currently ongoing. Notably, multiple independent variants across 6p21 have been identified.

GEP has also collaborated in genetic studies of non-Hodgkin lymphoma through participation in candidate gene-based studies (Skibola et al., 2010) as well as ongoing large genome-wide approaches (Conde et al., 2010).

### **Non-genetic risk factors and gene-environment interactions**

GEP is also investigating non-genetic risk factors of lung and UADT cancers. Serum analyses of four B-vitamins (B2, B6, folate and B12), methionine and homocysteine in a nested case-control study of 900 cases and 1800 controls showed a striking association between low levels of B6 and/or methionine and an increased risk of lung cancer (Johansson et al., 2010).

Another example of non-genetic work conducted in GEP includes the investigation of HPV infection in association with UADT and lung cancer risk, and to what extent the association vary with respect to other lifestyle factors and known genetic associations.

In addition, GEP is involved in two large cohort studies in which lifestyle risk factors have been the main component so far. These include a 200 000-individual cohort in Siberia, Russia, and a 50 000-individual cohort in Golestan, Iran (Khademi et al., 2010; Islami et al., 2009). Analyses are currently underway.

### **Ongoing field work**

GEP continues to actively invest time and resources in field-work activities. Current large ongoing case-control studies include an international study of rare childhood embryonal tumours (recruitment of case-parent trios and unrelated healthy controls in 12 countries planned for the next two years), a multicentre kidney cancer study in central and eastern Europe (Czech Republic, Romania, Serbia and Russia), a large lung cancer study in Moscow, Russia, and a nasopharyngeal cancer study in south-east Asia. For these recent initiatives, we have incorporated a collection of high-quality tumour tissue collection (and healthy marginal tissue when possible), a comprehensive pathological review, and a follow-up of cases for outcome.

## Genetic Cancer Susceptibility Group (GCS)

Only a small amount of the cancer risk attributable to genetic factors can be explained by the susceptibility genes identified to date. A category of rare variants in intermediate-risk susceptibility genes, exemplified by *CHEK2* in breast and lung cancer, *MC1R* in Melanoma and *ADH1b* in head and neck cancer, may explain a proportion of this missing heritability. GCS has developed an *in-silico*-driven analytical strategy to assess such intermediate-risk susceptibility genes, and has applied this approach to examine the contribution that these make to cancer susceptibility.

### The breast cancer case-control mutation screening project

The main approach of the project is to carry out full open reading frame mutation screening of carefully selected candidate genes from a series of over 1250 breast cancer cases and controls from population-based breast cancer family registries (BCFRs).

*In-silico* assessment is used to categorize variant carriers based on the degree of dysfunction that is likely to be caused by the variant. To assess the contribution of rare missense substitutions, we adapted *in-silico* assessment of missense variants of uncertain clinical significance in *BRCA1/2* (Tavtigian et al., 2008; Tavtigian et al., 2009). The core idea was to stratify rare missense substitutions into a series of grades *a priori* ordered from least to most likely to be evolutionarily deleterious, and then use a logistic regression test for trend to compare the frequency distributions of the graded missense substitutions in cases versus controls.

Full mutation screening and statistical analysis has been completed for the *ATM* and *CHEK2* genes in the BCFR series. The *ATM* study clearly indicated strong evidence that a subset of rare missense variants confer an increased risk of breast cancer in addition to the risk attributable to clearly deleterious *ATM* loss-of-function mutations (i.e. truncating or splice site mutations) (Tavtigian et al., 2009).

The *CHEK2* study stands as a methodological replication and showed that this gene harbours multiple rare, pathogenic sequence variants, a substantial proportion of which are missense variants. The risk estimate for the most severe grade of *CHEK2* missense is approximately equivalent to that of *CHEK2* protein-truncating mutations.

GCS aims to extend the bioinformatics-driven analysis strategy developed on breast cancer genes to other cancer sites. For example a case-control mutation screening of the melanoma susceptibility gene *MC1R* has been undertaken to characterize novel likely dysfunctional sequence variants in the EPIC series, where 1346 sporadic melanoma cases and the same number of matched controls from 10 European populations have been identified.

### Differential allelic expression study of cancer susceptibility genes

GCS has also set an assay based on High-Resolution Melting analysis to assess whether cancer susceptibility genes are subject to differential allelic expression in lymphoblastoid cell lines. This approach may complement high-throughput mutation screening projects aiming to identify dysfunctional regulatory variants in candidate genes.

### Contribution of dysfunctional sequence variants at loci identified by genome-wide association studies of tobacco related cancers

Genome-wide association studies within the GEP Group have identified associations between lung cancer and common genetic variants at 15q25 and 5p15.33. The GCS Group

has begun to explore the extent to which rare variants affecting the coding sequence of genes located at 15q25 and 5p15.33 may additionally contribute to lung cancer susceptibility. Full mutation screening has been completed in the 5p15.33 gene *TERT* in 384 lung cancer patients. *In-silico* assessment of these variants is being carried out and further assessment being undertaken within an additional 2000 lung cancer case-control pairs.

### **The genetic services platform (GSP)**

The GSP aims to employ cutting-edge genomics techniques and make that technology, along with technical expertise and support, available to all IARC groups. Each laboratory workflow is also integrated into the Laboratory Information Management System (LIMS) platform to ensure high quality control standards are met (Voegelé et al., 2010). Optimization of the mutation screening workflow used in the GCS study of *ATM*, *CHEK2* and other breast cancer related-genes continued in 2010, as did the set-up and validation of laboratory processes of the Illumina bead array platform to enable whole genome expression (from both frozen and FFPE material), methylation profiling and genotyping using both GoldenGate and Infinium technologies.

In collaboration with interested IARC groups, new genomics applications are now piloted prior to the implementation of collaborative projects to ensure the suitability of the technique to the research question and its scalability of the techniques to IARC's large population-based studies.

### **Biostatistics Group (BST)**

The Biostatistics Group was relocated to the Genetics Section in March 2010 and its role re-defined. Its purpose is twofold:

1. To develop statistical methods for use in genetics, particularly studies carried out within the Genetic Epidemiology (GEP) and Genetic Susceptibility (GCS) Groups;
2. To foster a professional environment for the various statistical personnel at IARC.

### **Research activities**

This has been a transition year for BST, with projects remaining from its previous role to be finished in addition to re-focussing on genetics.

#### *In-silico classification of genetic variants*

With the departure of Sean Tavtigian, this work has now diverged into two distinct directions:

- a. Development of study designs and simulation-based sample size estimates for studies in the genetics of melanoma, with Dr Fabienne Lesueur; and
- b. Development of high-throughput methods of classification. Current techniques of *in-silico* classification (SIFT, MAPP, AlignGVGD) are not well adapted to application to very large numbers of genes. AlignGVGD in particular is sensitive to the quality of multiple sequence alignment provided to it. However, the advent of next-generation sequencing will require the analysis of whole exome data: applying current manual curation methods to 22 000 genes is not possible. A joint project with Dr James McKay (head, GCS) and Manon Delahaye (PhD student, GEP) addresses both the informatic and statistical issues inherent in automating the protein alignment process.

### *Dietary Nutrient Pattern Analysis*

The development of methods for analysis of patterns of diet with DEX has continued. This project sought to exploit methods of multivariate data-reduction (Principal Components Analysis, PCA) to analyse high-dimensional observation data on diet and nutrient consumption. A particular challenge has been to apply PCA to heterogeneous data generated within different centres of the EPIC cohort: data from different centres are not directly comparable, and it was necessary to evaluate various options for combining or stratifying data. *Inter-alia*, it was necessary to develop methods for comparing principal components defined from different data sets.

This work, jointly undertaken with Nadia Slimani (DEX), Aurélie Moskal (DEX) and Amandine Coquillat (BST), is now mostly completed. The results were presented at an EPIC methodology workshop organized by the MRC Biostatistics Group in Cambridge, and a methodological paper is in preparation. A striking result was that PCA is surprisingly insensitive to variations between centres, provided at least five or six components are retained. Remaining work in this field will be in collaboration with Dr Pietro Ferrari, who has taken up a post as Statistician in the NME section.

### *Breast Cancer Screening Evaluation*

This study of breast cancer screening was a joint effort with Dr Jari Haukka, previously in CIN and now at the University of Finland. Using Swedish mortality data we used a mathematical modelling approach to separate effects of improved treatment from those of mammographic screening *per-se*. A paper has been prepared and is ready for submission.

### *Radiation Dose Estimation*

BST is continuing collaboration with the Radiation Epidemiology group of Dr Elizabeth Cardis at the Centre for Research in Environmental Epidemiology (CREAL) in Barcelona. This aims to refine methods for analysing radiation exposure data while allowing for high levels of uncertainty in the reconstructed doses.

### **Biostatistics environment**

BST is also charged with ensuring a professional environment for Biostatistics at IARC, which is also related to issues of education, training and career development.

Several activities were undertaken in this role:

- The Biostatistics Consultative Committee was formed and held its first meetings. This is an advisory committee comprising senior statisticians at IARC: Freddie Bray (CIN), Pietro Ferrari (NME), Richard Muwonge (EDP), Martyn Plummer (INF), Joachim Schüz (ENV) and Salvatore Vaccarella (INF).
- Graham Byrnes presented a series of four lectures and a practical class as an Introduction to Biostatistics in the IARC Summer School.
- Meetings of statistically interested technical staff and fellows were held. Two principal requests came from these meetings: establishing a web-based statistics forum to enable cross-agency sharing of ideas and questions; and to repeat the Summer School Biostatistics lectures for staff within the agency. The web forum has been established with the assistance of ITS, while the lectures will be given in collaboration with ETR once a suitable time can be found.

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## **Section of Early Detection & Prevention (EDP)**

Cancer prevention and early detection are very important approaches to controlling cancer, provided that the causes are known, affordable and effective early detection approaches are available to detect disease in the precancerous or preclinical phase, effective treatment is available for early-stage disease, and systematic delivery of effective and affordable interventions can be equitably accessed by all segments of the population through well-organized and optimally-financed health systems. The Section aims to make significant contributions to the development of cost-effective and resource-appropriate public health policies, as well as evidence-based and quality-assured strategies to further augment cancer prevention and early detection programmes and services globally, with particular emphasis on low- and medium-resource countries (LMC). Significant efforts are being made to introduce and strengthen quality assurance in the context of national cancer screening programmes, particularly in Europe and in LMC, by developing and updating evidence-based, multidisciplinary guidelines for quality assurance in breast, cervical and colorectal cancer screening programmes. The Section also addresses the integration of HPV vaccination and early detection strategies as part of global cervical cancer control initiatives. There is a continuing emphasis on developing, updating and expanding training resources to catalyse augmentation of human resources for cancer prevention and early detection initiatives. A unique aspect of the studies is that once the research questions have been answered, they ensure continuing and scaled-up prevention and early-detection services by contributing to the development of local health systems within the limitations of the research studies.

### **Screening Group (SCR)**

The studies conducted by the Screening Group (SCR) aim to address the accuracy, reproducibility, acceptability, safety, efficacy and cost-effectiveness and service delivery aspects of different screening and early clinical diagnosis interventions for breast, cervical, colorectal and oral cancer control in low- and medium-resource countries. These studies will also explore 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 in countries, 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. There is a heavy emphasis on collaboration and resource sharing with the national institutions and government health services in the countries where these studies are carried out. The ultimate objective is to help in the development of resource-stratified screening policies and health systems to deliver services.

#### **Cervical cancer prevention and screening**

A cluster-randomized controlled trial to evaluate the efficacy of two doses of HPV vaccine versus the conventional three doses administered over six months in preventing cervical neoplasia, involving 20 000 unmarried girls aged 10–18 years, is ongoing in India. We have vaccinated 17 722 girls fully as per protocol or partially until 8 April 2010, following which vaccination was temporarily suspended in compliance with the instructions from the Government of India, in view of alleged ethical violations and four deaths unrelated to the vaccine in another HPV vaccination demonstration project in India. More than 95% of invited girls received vaccinations; there were no serious adverse events and mild adverse events were observed in 8% indicating excellent vaccine acceptance, safety and compliance in our study. We anticipate re-initiating vaccination in our study by December 2010.



### **Publications highlights**

SCR is continuing to document cervical cancer incidence and mortality among the 230 000 women in the Osmanabad and Dindigul district cervical screening trials in India, addressing the impact of single round of screening with HPV testing or cytology or visual inspection with acetic acid (VIA); follow-up is now in its 11<sup>th</sup> year, and the updated results will be published in 2011. We have also reported on the performance of visual screening in detecting cervical cancer precursors and the ability of the health services to treat women with lesions in Angola and Tanzania (Muwonge et al, 2010; Ngoma et al, 2010) and on the role of cytology and HPV testing as triaging tests among VIA-positive women in Mumbai, India (Pimple et al, 2010). A descriptive evaluation of the national VIA screening programme in Bangladesh (Nessa et al, 2010) and the Thailand national cytology screening programme indicated the need to improve coverage, programme databases and data capture for proper evaluation of the inputs and outcomes. Results of a newly developed rapid HPV test, careHPV, in detecting cervical neoplasia will be reported. The 5-year survival rates from cervical cancer in populations in the Gambia and Uganda were less than 22% and varied between 47–52% in India and the Philippines (which have no population-based screening programmes) and between 63–79% in the Republic of Korea, Singapore and Thailand, which do have national screening programmes, indicating the impact of inequities in early detection, clinical stages and health services development and accessibility to ensure treatment and follow-up care between these countries (Sankaranarayanan et al, 2010). The Group also conducted training courses in cervical cancer screening, colposcopy and management of cervical neoplasia in Porto Alegre, Brazil; Chengdu, China; and Trivandrum, India.

### **Breast cancer screening**

The results of the first round of clinical breast examination (CBE) screening in the randomized controlled trial involving 116 000 women in Trivandrum, India indicate significantly improved early detection of node-negative and <5 cm early breast cancers as compared to routine care (Table 1). The results will be published in 2011. The second round of screening is continuing, with more than 90% of the women invited being screened and around 70% of screen-positive women being reported for diagnostic investigations. New cross-sectional studies involving around 10 000 women evaluating the accuracy of alternative imaging techniques such as near-infrared light imaging and ultrasonography have been organized in Chennai and Trivandrum, India; and Chengdu and Xian, China. Efforts are underway to initiate randomized trials to evaluate breast cancer awareness and a blood-based gene detection test in the early detection and control of breast cancer.

**Table 1: Early results from the Trivandrum breast screening study (TBCS) (2006-2009)**

Criterion	Intervention (CBE) group	Control group (usual care)	
Participating women (30-69 years)	55 844	59 808	
Proportion of households with monthly income <40 USD	55.3%	56.3%	
Mean age in years	46	46	
Proportion of postmenopausal women	35.3%	34.3%	
Women screened with CBE	50,366 (90%)	-	
CBE positive women	2880 (6%)	-	
Incident breast cancers (Age standardized breast cancer incidence rate/100 000 women)	80 (36.6)	62 (26.7)	
Proportion of breast cancers with stages I-IIA (<5 cm)	35 (43.8%)	16 (P=0.034)	(25.8%)
Proportion of cancers <2 cm	4 (6.5%)	15 (P=0.033)	(18.8%)
Patients with negative regional nodes in histopathology	22 (35.5%)	40 (P=0.084)	(50.0%)

### Oral and colorectal cancer screening

We reported a 34% reduction in oral cancer mortality in a randomized trial after three rounds of visual screening at three-year interval. Oral cancer incidence and mortality among the 200 000 participants are being carefully monitored for the 15<sup>th</sup> year of follow-up. Meanwhile, four rounds of oral visual screening in the intervention group and a single one for the control group (in view of the benefit of screening in reducing oral cancer mortality) have been completed, and the long-term results are currently being analysed. A reference manual for early clinical diagnosis of oral neoplasia has been finalized and is in press.

Colorectal cancer incidence and mortality rates are rising in several medium-resource countries due to lifestyle changes. The wide range in survival (4–52%) in low- and medium-resource countries indicates the significant opportunity to improve outcomes by early detection and treatment (Sankaranarayanan et al, 2010). SCR is providing technical assistance to implement a population-based, organized colorectal cancer screening programme in Lampang province, Thailand, providing 150 000 people aged 50–65 years with an immunochemical faecal occult blood test (iFOBT). Those positive on iFOBT are triaged by colonoscopy. The objective of this project is to evaluate the acceptability, feasibility, organization, implementation, monitoring and evaluation of population-level CRC screening in Thailand by integrating the programme within existing public health services, to inform and guide the eventual broadening of CRC screening to cover the entire country. Recruitment has started for this study, and preliminary results indicate that more than 90% of the invited population participate in screening, and iFOBT positive levels are around 2%.

### Quality Assurance Group (QAS)

The aim of screening as a tool for cancer control is to lower the burden of cancer in the population by discovering latent disease in its early stages and treating it more effectively than if diagnosed later when symptoms have appeared. As such, screening is a commendable method to reduce the burden of disease. However, population screening targets a predominantly healthy population, and should therefore only be conducted after a careful consideration of both harms and benefits (Lansdorp-Vogelaar & von Karsa 2010). Cancer screening programmes are an increasingly common tool of cancer control in high-resource countries. Efforts are underway to develop screening strategies appropriate to medium- and low-resource countries (World Cancer Report 2008).

The screening process comprises complex activities extending from invitation of the eligible population to performance of a screening test, assessment of detected abnormalities and, if necessary, treatment. Even in countries with relatively small target populations, quality-assured introduction of nationwide screening programmes may take 10 years or more due to the substantial experience and technical and organisational capacity required for feasibility testing and planning, piloting and quality-assured rollout of services across the regions served by a programme. International exchange of experience and scientific and technical collaboration has therefore become a key factor in avoiding excessive delays for successful implementation of quality-assured screening programmes (von Karsa et al., 2008, von Karsa et al., 2010).

Achieving and maintaining high quality at every step in the screening process requires an integrated, population-based approach to programme implementation. The population-based approach is essential to giving all eligible people an equal chance of benefiting from screening. The population-based approach to programme implementation is also recommended because it provides an organizational framework conducive to effective management and continuous improvement of the screening process, such as through linkage with population and cancer registries for optimization of invitation to screening and for evaluation of screening performance and impact. Nationwide implementation of population-based screening programmes of appropriate quality generally makes high-standard services accessible to the entire population, not just those persons eligible to attend screening. Large numbers of professionals undertake further specialization and training in order to meet the screening quality standards. Consequently, these nationwide efforts also contribute to widespread improvement in diagnosis and management of cancers that are detected outside of screening programmes. Implementation of cancer screening programmes of appropriate quality therefore has the additional potential to improve the entire range of cancer care (von Karsa et al., 2008; von Karsa et al., 2010).

During the current reporting period, the activities of the QAS Group have been focussed on multi-national collaborative projects for developing, updating and implementing guidelines for quality assurance in breast, cervical and colorectal cancer screening, primarily in Europe. Updates of the EU breast and cervical cancer screening guidelines, and new EU colorectal cancer screening guidelines (European Commission 2010), have been prepared with financial support of the European Communities, the American Cancer Society and the Centers for Disease Control and Prevention, and the Public Affairs Committee of the United European Gastroenterology Federation. These activities will be pursued in the future within the framework of the recently established European Partnership Action Against Cancer (EPAAC), in which the QAS Group provides technical and scientific support for the work package on screening. A direct collaboration has started with the WHO and the National Cancer Institute in France on updating the WHO guide to essential practice on Comprehensive Cervical Cancer Control (WHO 2006). Financial and scientific support was provided for the planning of population-based breast and cervical cancer screening programmes in Poland, Albania and other countries in Eastern and South-Eastern Europe. The latter activities were conducted in cooperation with WHO Headquarters and in cooperation with and with financial support from the WHO Regional Office in Albania. These multidisciplinary activities also involve extensive collaboration with external experts and several IARC groups.

The comprehensive European cancer screening Guidelines (European Commission 2006; European Commission 2008; European Commission 2010) have been developed to inform policymakers, public health specialists, and any other interested parties about the essential issues, guiding principles, standards and procedures of quality assurance and best practice

that considered in establishing cancer screening programmes. Although the examples of best practice explained in the European quality assurance Guidelines do not always apply to low- and medium-resource settings, the same principles are valid and appropriate approaches should be developed, tested and piloted for quality-assured implementation of screening programmes in other resource settings.

Due to continuous expansion, the current volume of cancer screening in publicly mandated programmes in the EU is likely to substantially exceed 500 million examinations over a ten-year period (von Karsa et al., 2008). Europe therefore offers a unique opportunity to deal with the challenges of implementation of population-based cancer screening programmes on a scale that is unlikely to be encountered in other regions of the world until at least a decade from now. Colleagues from around the world have therefore been invited to collaborate with European experts in the efforts of the QAS Group. Fruitful discussions were conducted at large network meetings held in Warsaw in May 2010 in cooperation with the work package on cancer screening in the EURO COURSE project (<http://www.eurocourse.org/>) and in Barcelona in October 2010 in cooperation with the UEGF and the International Digestive Cancer Alliance. In addition, a planning meeting on the future direction of the International Colorectal Cancer Screening Network (Benson et al., 2008) was held in Lyon in September 2010 in cooperation with the American Cancer Society, the Centers for Disease Control and Prevention, the Universities of Oxford, Taiwan and Turin, and Imperial University in London.

A truly effective approach to quality assurance in implementation of secondary prevention should be based on comprehensive efforts to control cancer and other chronic diseases. During the current reporting period, Group activities have also focussed on expanding the evidence base to improve implementation of primary prevention strategies that are complementary to cancer screening. These include, for example, vaccination against HPV infection to prevent cervical cancer, as well as strategies to effectively promote a healthy lifestyle by updating the messages on cancer prevention in the European Code Against Cancer 2003 (<http://www.cancercode.org/code.htm>). These projects have also been supported through co-financing provided by the European Communities.

## **The Gambia Hepatitis Intervention Study (GHIS)**

The Gambia Hepatitis Intervention Study is a randomized controlled trial to determine the efficacy of childhood vaccination against hepatitis B virus for prevention of liver cancer in a region with a high incidence of hepatocellular carcinoma. The study is in the period of long-term follow-up using the population-based national cancer registry as the main instrument for case identification. Based on current data, the final outcome of this trial will be measurable between 2015 and 2020.

The Agency continues to provide logistical and scientific support to the field operations in The Gambia in order to maintain, develop and expand the coverage of the national cancer registry, support clinical and laboratory activities aimed at improving identification and diagnosis of chronic liver diseases and liver cancer, optimize the linkage between cancer cases and the trial participants, and maintain a laboratory facility for collection and processing of specimens.

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## Laboratory Services and Biobank (LSB)

The Laboratory Services and Biobank Group provides a number of core generic services and resources used by the laboratory and epidemiology groups across the Agency. This newly created Group incorporates the functions previously carried out by the Laboratory Infrastructure and Resources (LIR) team, and the biobanking resource in the IARC Biological Resource Centre (IARC BRC).

The creation of this new structure was completed and the Group became fully operational in October 2010 with the appointment of Dr Maimuna Mendy to the post of Laboratory Manager. The Laboratory Manager is responsible for the day-to-day management and supervision of the LSB operations and staff. The coordination of the LSB activities is supported by two newly created structures, the Laboratory Steering Committee (LSC) and the Biobank Steering Committee (BSC), which assist in optimizing LSB's operational procedures and setting long-term priorities in line with the IARC Medium-Term Strategy. The oversight provided by these committees presents an opportunity for the research Groups at the Agency to shape the future of the Agency's laboratory support services.

The LSB activities are broadly divided into two areas:

- the provision of centralized basic laboratory services, including histology services, glass-washing service, store of laboratory consumables, biological/hazardous waste collection and all operations related to the control and implementation of laboratory safety;
- the management of storage and access to the large collections of human biological specimens in the IARC Biobank through a laboratory platform for quality control, specimen processing (including DNA extraction) and distribution.

The efficient operation of the IARC Biobank service is of major importance to the Agency and to the wider cancer research community; the large collections of well-characterized human biological specimens in the IARC Biobank provide a key resource for the exploration of the complex relationship between the environment, genetics and cancer.

## **Education and Training (ETR)**

Education and training has always been a core activity of the Agency, and in 2010 this activity was reinforced by the establishment of dedicated group, led by a senior professional scientist, in order to coordinate the various IARC initiatives and give renewed emphasis to these tasks. Priority is given to students from, or with a research interest relevant to, countries with limited resources for the control of chronic diseases in general and cancer in particular. There are two main programmes: Courses and Fellowships.

### **Courses**

The main activity of the courses programme continues to be the IARC Summer School on Cancer Epidemiology, organized in Lyon during June and July each year. This provides the opportunity for students to spend a short time at IARC and enjoy ready access to its scientists. In 2010 over 200 applications were received, of which 61 were accepted and 30 were funded (travel and living expenses in Lyon). Additional financial support for the course came from the US National Institutes of Health–National Cancer Institute (NIH-NCI) and the Fondation Léa et Napoléon Bullukian.

IARC also organizes training courses elsewhere in the world in partnership with other organizations, such as a cancer registration course held in South Africa and a cervical cancer screening course held in India. IARC brings training to the regions, particularly in low- and medium-resource settings, actively building and maintaining relationships with diverse and numerous key players in the field of cancer research, including past fellows, course attendees and course faculty. Cancer registration training leads to increased capacity in registries that contribute to the Agency's collation of global cancer data, and training in cancer screening techniques is applied in subsequent research projects with high impact for public health. In this way, training has helped create subsequent opportunities for conducting high-quality research in a cost-effective manner, as well as providing an important mechanism for recruiting scientists to cancer research.

### **Fellowships**

IARC Fellowships provide excellent training and experience in an exceptional multi-cultural and international environment to deserving post-doctoral fellows from around the world. On completion of their training, over 80% of Fellows return to their home country and remain active in cancer research, often started by a modest research return grant. This high retention rate has ensured the development of cancer research in many countries. The candidates selected undergo a strong peer-review process conducted through the IARC Fellowship Selection Committee, which includes scientists both from the Agency and externally. In 2010, additional funding came from the EC-FP7 Marie Curie Actions-People-COFUND programme.

In 2010, seven new fellowships were awarded, and four fellows were extended for a second year. Fellows came from Colombia, the People's Republic of China, Germany, India, Indonesia, the Republic of Korea (2), Nigeria, Portugal and the Russian Federation. Additionally in 2010, doctoral Fellow Dr Farhad Islami (Iran) successfully obtained his Ph.D. from Kings' College London, and two Ph.D. fellowships were extended: Miss Yayun Dai (People's Republic of China), tenable jointly with Innsbruck University, Austria and Mr Mohannad Alnsour (Jordan), tenable jointly with Glasgow University, UK.

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 2010 was granted to Dr Jia Chen from the Department of Preventive Medicine, Mount Sinai School of Medicine, New York, USA.

Education and training is an integral part of research at IARC, providing as it does the opportunity to build a new generation of cancer researchers worldwide with the motivation and skills to tackle the global cancer burden. The ETR Group will place renewed emphasis on this task, drawing on partnerships where appropriate and using modern technology to transfer its knowledge base to the individuals and organizations where it will have the most impact.



## **Governing Council and Scientific Council**

The International Agency for Research on Cancer (IARC) was established in May 1965 through a resolution of the XVIII<sup>th</sup> 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 2010–2011, the IARC Governing Council voted a regular budget of €37 911 000. A number of projects are also funded by extrabudgetary sources, both national and international. In the 2008–2009 biennium, 31% of the Agency's overall expenditure was financed by extrabudgetary funds.

**Participating States and Representatives at IARC Governing Council  
Fifty-second Session, 13–14 May 2010****Norway**

Professor Lars E. Hanssen, *Chairperson/Président*  
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Oslo

Mr Geir Bukholm  
Deputy Director General, Norwegian Knowledge Centre for the Health Services  
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Dr Henrietta Blankson  
Senior Adviser, The Research Council of Norway  
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**United Kingdom of Great Britain and Northern Ireland**

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Chief Medical Officer, Department of Health and Ageing  
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**Austria**

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**Finland**

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**France**

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Directrice générale, Institut national du Cancer (INCa)  
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Dr Rosemary Ancelle-Park  
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Federal Ministry of Health  
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**India**

No Representative/ *Pas de Représentant(e)*

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**Outgoing Chairperson, Scientific Council**

Dr Harry Comber

**Incoming Chairperson, Scientific Council**

Dr Edgar Rivedal

**International Union Against Cancer**

Mr Cary Adams

Executive Director, International Union Against Cancer (UICC), Geneva

**External Audit**

Shri J.N. Gupta

Additional Deputy Comptroller and Auditor General of India

New Dehli, India

## **Scientific Council Members (2010)**

Dr Harry Comber (**Chairperson**)  
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## Annex

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