Section of Genetics (GEN)

Section head
Dr Paul Brennan

The Section of Genetics (GEN) comprises the Genetic Epidemiology Group (GEP), the Genetic Cancer Susceptibility Group (GCS), and the Biostatistics Group (BST). The work of the Section combines large population-based studies with laboratory and bioinformatics expertise to identify specific genes that contribute to the development of cancer and elucidate how they interact with environmental and lifestyle factors in carcinogenesis. The Section also tries to identify individuals who are at high enough risk of developing cancer that they are likely to benefit from existing risk reduction strategies.

GEN projects usually involve extensive fieldwork in collaboration with external investigators in order to develop large-scale epidemiological studies with appropriate clinical and biosample collections. This typically occurs within GEP, which has a primary interest in the analysis and identification of common genetic susceptibility variants and their interaction with non-genetic risk factors. Genetic analysis comprises either candidate gene or genome-wide association studies (GWAS), as well as sequencing work. GEP studies also assess non-genetic exposures, partly in recognition of the importance of non-genetic factors in driving cancer incidence, and also to facilitate accurate assessment of gene–environment interactions. In contrast, GCS places more focus on identification of uncommon or rare genetic variants that may have a larger effect than common single-nucleotide polymorphisms but that are not sufficiently frequent to be captured by current GWAS genotyping arrays. The GCS approach has been to use genomic and bioinformatic techniques to complement more traditional approaches for the study of rare genetic variants. GCS also uses genomics to explore how the variants may be conferring genetic susceptibility to cancer. Thus, the research programme of GCS complements that of GEP, and also provides a facility for high-throughput genomic techniques and the related bioinformatics to support GEN's large-scale molecular epidemiology projects and other IARC genomics projects. BST interacts at all stages to provide overall statistical support.

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The role of the Biostatistics Group (BST) is multifaceted. It collaborates on projects with the other groups within GEN, exploring new methodologies and ensuring optimal use of existing techniques. BST also works closely with other Sections at IARC with specific methodological needs, as well as with external organizations. In addition, BST is involved in statistical education and facilitation across the Agency in cooperation with statisticians in other Sections.

Increased cancer risk due to paediatric exposure to CT scans

BST played a major role in the analysis of the data from approximately 11 million children and young adults in Australia from a study on cancer risk due to paediatric exposure to computed tomography (CT) scans. The study was led by Professor John Mathews at the University of Melbourne, with Sarah Darby at the University of Oxford. The study demonstrated a 24% increased risk of any cancer after a CT scan before the age of 19 years (Mathews *et al.*, 2013). This risk was evaluated after excluding diagnoses in the year immediately after the scan, but was also seen after excluding the following 5 or 10 years. Moreover, the strength of the effect increased with a larger number of scans. There was also a significantly increased risk for many specific cancers, most strikingly brain cancers, but also for solid cancers of the digestive organs, melanoma, soft tissue, female genital, urinary tract, and thyroid, and for leukaemia, myelodysplasia, and other lymphoid and haematopoietic cancers. The effects were also significantly stronger for younger ages at exposure.

Other radiation-related research occurred in collaboration with the Section of Environment and Radiation and with GCS. These projects focused on the risk of thyroid cancers in Chernobyl clean-up workers (Kesminiene *et al.*, 2012) and the joint effect of radiation and genetic susceptibility, again on thyroid cancer (Damiola *et al.*, 2013)

BST collaborations within GEN

BST has contributed to a variety of studies within GEN, notably combining RNA expression and genomic data to examine risk factors for kidney cancer (Wozniak *et al.*, 2013), and using prior information from the literature to prioritize genetic variants potentially associated with lung cancer (Johansson *et al.*, 2012a). Analysis of data from the Golestan Cohort indicated a strong increased risk of death from all causes associated with opium use (Khademi *et al.*, 2012a).

Other BST research

BST provided important methodological input to other projects. Of note was an effort to quantify the burden of lung cancer attributable to asbestos use, making use of mesothelioma as a calibration factor (McCormack *et al.*, 2012, 2013b), and theoretical work on the development of breast cancer (Dowty *et al.*, 2013).

BST is grateful to the following for their collaboration:

John Mathews, James Dowty, John Burgess, Melbourne, Australia; Francesca Damiola, Pierre Hainaut, Lyon, France; Elisabeth Cardis, Barcelona, Spain; Sarah Darby, Oxford, United Kingdom.

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The Genetic Cancer Susceptibility Group (GCS) investigates genetic susceptibility to cancer through the application of high-throughput genomic techniques (including the related bioinformatics) to the biological samples stored within the extensive GEN biorepositories. In addition to implementing and maintaining genomic techniques to achieve our research goals, we also facilitate access to these techniques by IARC's other research groups through the Genetics Services Platform.

During the 2012–2013 biennium, GCS has studied the contribution of both common and rare variants to cancer susceptibility. We have also focused on the installation and optimization of massively parallel sequencing (MPS) and the development and implementation of bioinformatics tools to complement IARC's scientific activities; for example, IARC's Electronic Notebook programme.

Genome-wide association studies (GWAS)

The genome-wide association studies (GWAS) approach has been very successful in the identification of genetic loci involved with complex genetic traits. GCS, in close collaboration with GEP and BST, is continuing to work within GWAS of lymphomas and kidney, cervical, lung, and nasopharyngeal cancers.

The size of the study appears to be a key factor to the success of a GWAS, with the application of increasingly larger sample sizes identifying progressively more susceptibility loci (Michailidou *et al.*, 2013). In the context of rare cancers, prioritized by IARC, assembling sufficiently large sample sizes for an appropriate GWAS presents a practical challenge. The GCS approach has been to explore the possibility of incorporating additional information to augment the potential of GWAS of relatively modest sample sizes. For example, we have undertaken an oral cancer GWAS consisting of 791 cases and 7012 controls (Johansson *et al.*, 2012a). We developed a Bayesian method (AdAPT) that allows prior probabilities for genetic variants to be considered in the ranking of GWAS results. Automated text screening of the medical literature was used to identify genes that might be more relevant to oral cancers. We placed higher prior probabilities on genetic variants near those genes and used them in the ranking of GWAS results. We then selected the top five genetic variants using the AdAPT ranking approach for validation. Only rs991316, located within the ADH gene cluster, displayed statistically significant association ($P_{replication}$ = 0.003), within a validation series of an additional 1046 oral cancer cases and 2131 controls. As we selected only five variants for validation, and rs991316 was ranked 77th using P-value ranking, we would not have selected this variant using that approach. Furthermore, if sufficient variants were selected for validation to allow the inclusion of rs991316 (more than 77), the statistical evidence in the validation stage would not be considered significant after correction for multiple testing, i.e. Bonferroni correction, P = 0.23 (0.003 x 77).

GCS is now exploring the possibility of incorporating our laboratories' genomics techniques, through gene expression (eQTL) or somatic mutation profiles, as additional information sources for prior probabilities within our genetic studies.

Nasopharyngeal cancer (NPC)

GCS, and the wider GEN Section, has committed to researching genetic susceptibility to nasopharyngeal cancer (NPC). Through studies in Malaysia, Thailand, and Singapore, GEN has assembled almost 2000 NPC cases and 2000 matched controls from South-East Asia. We have completed our first study within these biorepositories; the Thai arm highlighted the importance of tobacco smoking as a risk factor for NPC and the overlap of genetic NPC susceptibility alleles between the Chinese and Thai populations, and suggested the 5p15.33 locus containing the *TERT* gene as a novel NPC susceptibility locus (Fachiroh *et al.*, 2012).

In addition to the case–control studies, we have identified several pedigrees with an unusual reoccurrence of NPC. During the 2012–2013 biennium, we obtained extra-budgetary funds from the United States National Cancer Institute to enable the exploration of the genetic susceptibility to NPC within these pedigrees.

Rare variants and breast cancer susceptibility

An exome sequencing study of families with multiple individuals affected by breast cancer identified two families with mutations in the homologous recombination-related DNA repair gene *XRCC2*, one protein-truncating mutation and one probably deleterious missense substitution (as predicted by in silico tools). To further investigate this gene, 689 families with multiple breast cancer cases were screened for mutations at the University of Melbourne, and 1308 breast cancer patients with an early age of cancer onset and 1120 controls were screened at IARC. The replication phase identified more deleterious variants in high-genetic-risk breast cancers than expected by chance, implicating *XRCC2* in breast cancer susceptibility and demonstrating the potential that MPS, in combination with appropriate study designs, has to discover new cancer susceptibility genes (Park *et al.*, 2012b). We have also investigated other genes in the homologous recombination repair pathway, although we found no evidence for association of rare variants in *RAD51* (Le Calvez-Kelm *et al.*, 2012).

Genetics Services Platform (GSP)

By maintaining and further developing the Genetic Services Platform (GSP) and the related Laboratory Information Management System (LIMS), the GSP, nested within GCS, provides a suite of laboratory services to support multiple IARC genomics projects. The platform integrates several multipurpose liquid handling robots in combination with the use of a LIMS to track the progress of samples as they move through the laboratory workflows. Recent developments of GSP include the installation of two MPS (a Life Technologies SOLiD 5500XLW and an Ion Torrent PGM), and collaborative links have been established with local service providers for IARC researchers to access additional genomic techniques, such as Illumina (HiSeq/HiScan technology).

The main GSP capabilities are:

• Exome and targeted sequencing using massively parallel sequencing;

• SNP genotyping using TaqMan, High-Resolution Melting Curve Analysis, or Illumina microarrays;

• Gene expression, copy number variation, and whole-genome methylation profiling using Illumina microarrays.

GSP coordinates collaborative efforts with IARC Groups (GCS, GEP, Epigenetics [EGE], Infections and Cancer Biology [ICB], Molecular Mechanisms and Biomarkers [MMB]), the Section of Molecular Pathology (MPA), and external partners. Some examples of recent relevant projects are described below:

• Exome sequencing of NPC patients from an extended Malaysian pedigree (GCS);

• Exome sequencing of tumours from lung cancer patients and corresponding germline DNAs (collaboration with GEP);

• Whole-genome expression profiling of tumour/non-tumour renal tissue pairs (collaboration with GEP);

• Exome sequencing within families with a reoccurrence of multiple myeloma (in collaboration with Rockefeller University);

• Whole-genome expression profiling by RNA-Seq of total cellular RNA from Epstein–Barr virus-infected cells with pLXSN, anti-Np73 antisense oligonucleotide, and the sense oligonucleotide (collaboration with ICB);

• Exome sequencing of Schwannoma patients (collaboration with MPA);

• Exome sequencing of formalin-fixed, paraffin-embedded triple-negative breast cancers and corresponding germline DNAs (collaboration with MMB);

• Targeted deep sequencing of circulating free DNA in non-small cell lung cancer (collaboration with MMB);

• Whole-genome methylation profiling using Illumina 450K microarrays on blood samples from hepatocellular carcinoma patients exposed to aflatoxin (collaboration with EGE).

Bioinformatics

During the 2012–2013 biennium, GCS has used a Linux-based, high-performance computing cluster to analyse MPS data produced in our laboratory and elsewhere. Bioinformatics pipelines, composed of pre-existing software packages and in-house custom tools, have been established for genetic variant detection (for Illumina HiSeq/MySeq and Life Technologies SOLiD5500/Ion Torrent) and RNA-Seq (Life Technologies SOLiD5500), allowing the raw sequencing data to be analysed to yield biologically exploitable results.

A total of 102 exomes and 15 RNA-Seq data sets have been generated by our SOLiD 5500XL sequencer and analysed in GCS; 18 of these exome analyses are GCS-related projects, and 84 exome analyses and RNA-Seq experiments are collaborative projects (GEP, MMB, MPA, ICB, EGE, and Centre Léon Bérard).

To complement our in-house data, GCS has also become an avid user of in silico data. Throughout the 2012–2013 biennium, we have accessed and analysed almost 1400 exome pairs from The Cancer Genome Atlas consortium (TCGA) for three cancer types (lung, head and neck, and kidney), which we now use to enhance our genetic analysis.

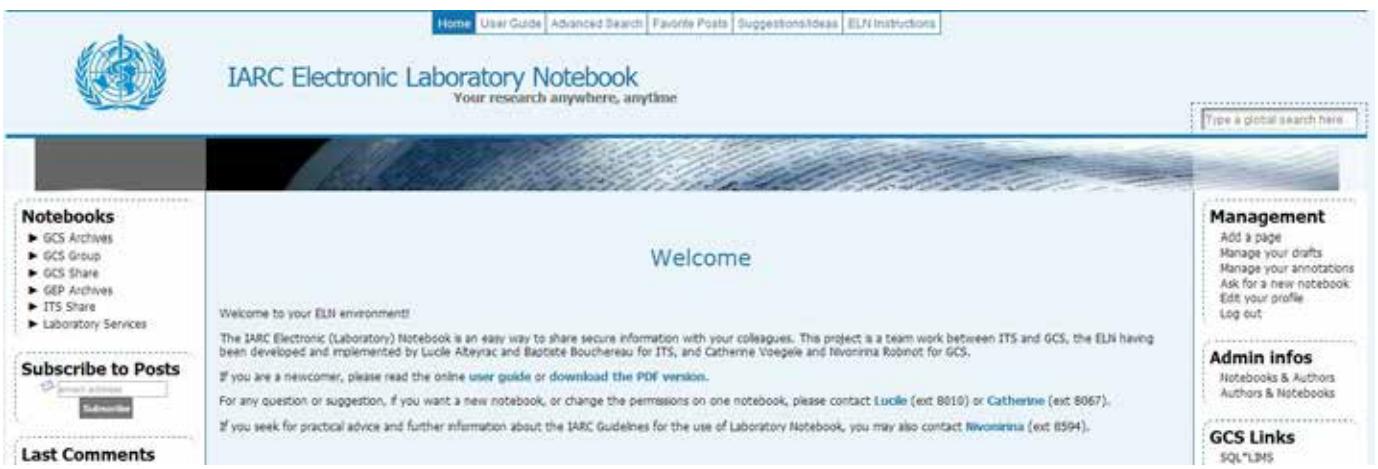
As bioinformatics becomes more important to IARC activities, GCS and ITS have led the formation of the Bioinformatics Steering Committee to monitor and facilitate cooperation among the Agency's bioinformatics and the related IT requirements.

IARC's Electronic Laboratory Notebook (ELN)

Laboratory notebooks remain crucial to the scientific activities of research communities. With the increase in generation of electronic data within both wet and dry analytical laboratories, Electronic Laboratory Notebooks (ELN) are a practical tool to record experimental data while maintaining the legal recording functions of a paper laboratory notebook. Coupled with newer technologies, an ELN has the additional potential to provide more efficient means of communication and higher flexibility for data entry, record linkage, storage, and retrieval.

In recognition of this potential, GCS has worked with ITS on the implementation of an ELN tool adapted to the Agency's multidisciplinary research and adequate for data recording (as advised by IARC's

Figure 1. Interface of IARC Electronic Laboratory Notebook.



Laboratory Steering Committee and according to international standards). A prototype was developed by ITS and, after extensive piloting and refinement, was adopted Agency-wide in January 2013. IARC now has more than 100 users keeping track of their work using the ELN. In addition to laboratory staff, the ELN is also being used by epidemiologists, statisticians, and bioinformaticians (Voegele *et al.*, 2013).

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The overall goal for the Genetic Epidemiology Group (GEP) is to identify genetic susceptibility variants of various cancer sites and study their interaction with environmental and lifestyle factors. An additional objective is to develop accurate risk prediction models that take both demographic information (e.g. age and sex) and biomarkers (genetic and non-genetic) into account. GEP focuses specifically on cancers related to tobacco use and alcohol consumption, as well as rare cancers (e.g. nasopharyngeal cancer). Our main activities involve fieldwork with the goal of recruiting large numbers of cases and controls, comprising extensive questionnaire information and biological samples. Genetic analyses usually include a genome-wide approach initially, with subsequent large-scale coordinated replication studies in diverse populations. This latter aspect is aided by the development of international consortia in which GEP takes a leading role. Confirmed susceptibility loci are investigated in more detail with a variety of techniques, including in silico, expression, and sequencing studies, which are often conducted in collaboration with other IARC Groups. In addition to studies of genetic factors, GEP is conducting a wide range of studies involving non-genetic factors, including evaluations of circulating biomarkers such as human papillomavirus (HPV) antibodies for head and neck cancers, cotinine for lung cancer, and dietary biomarkers for multiple cancers. GEP also performs extensive evaluations of questionnaire data, particularly for data that have been collected during fieldwork.

Lung cancer genetics

Genome-wide data are available on more than 15 000 lung cancer cases and 25 000 controls from eight different study groups (with IARC studies contributing about 25% of the data). A meta-analysis has provided increased support for previously identified risk loci at 5p15 ($P = 7.2 \times 10^{-16}$), 6p21 ($P = 2.3 \times 10^{-14}$), and 15q25 ($P = 2.2 \times 10^{-63}$) (Figure 2). Furthermore, we demonstrated histology-specific effects for 5p15, 6p21, and 12p13 loci. Subgroup analysis also identified a novel disease locus for squamous cell carcinoma at 9p21 (CDKN2A/p16INK4A) (Timofeeva *et al.*, 2012).

Figure 1. Manhattan and quantile–quantile (Q–Q) plots for the meta-analysis of lung cancer genome-wide association studies (GWAS). (A,B) Manhattan plot and Q–Q plot for lung cancer overall. (C,D) Manhattan plots restricting to lung adenocarcinomas and squamous cell carcinomas, respectively. Source: Timofeeva *et al.* (2012), by permission of Oxford University Press.

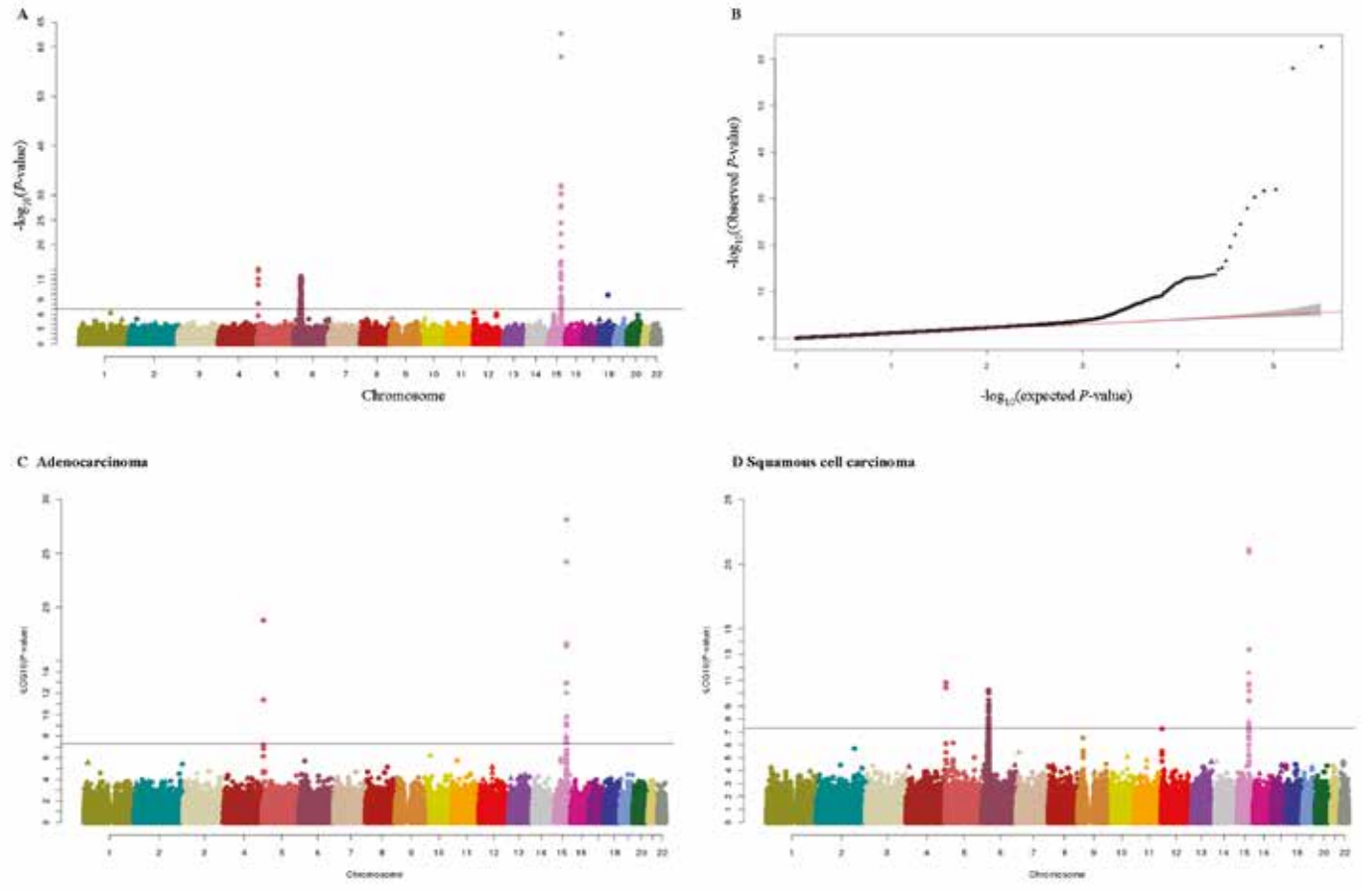
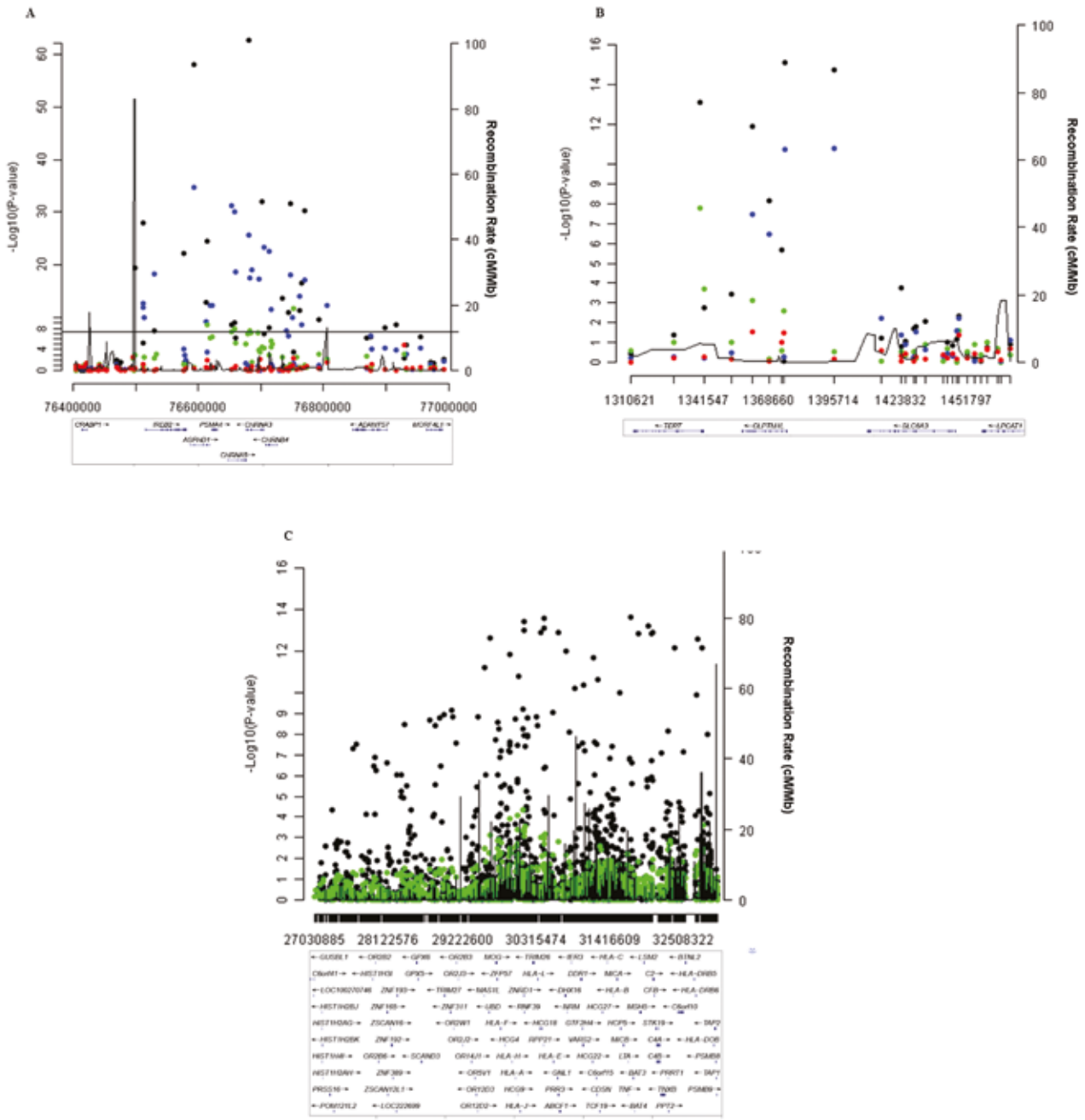


Figure 2. Associations between lung cancer and genetic variants within the (A) 15q25, (B) 5p15, and (C) 6p21 susceptibility loci. Source: Timofeeva *et al.* (2012), by permission of Oxford University Press.



Genetics and genomics of renal cell carcinoma

The continuing recruitment of renal cell carcinoma cases and healthy controls in central and eastern Europe has been very successful. With the collaboration of seven centres in four countries (the Czech Republic, the Russian Federation, Romania, and Serbia), we have enrolled 2500 cases and twice as many controls who donated blood samples for genetic research. Tumour tissue samples were collected for the majority of cases and non-tumour renal tissue for approximately half of the cases. This represents a very large and comprehensive RCC biorepository with detailed questionnaire and clinical data. Follow-up of cases for disease outcome is performed biannually, and pathological characterization of the renal samples is under way.

This biorepository participates in a large genome-wide scanning effort co-led by GEP scientists and the United States National Cancer Institute (US NCI). GEP scientists have coordinated the genotyping of the IARC biorepository together with other study collections (the French CeRePP study; the European EPIC study; the Swedish COSM, SMC, and Umea studies; and the Australian MCCS study), and the US NCI has led the United States component. Genotyping using very dense marker chips is under way, with a goal of reaching 10 000 cases and 16 000 controls in early 2014.

In parallel, we have performed whole-genome expression profiling of tumour/non-tumour renal tissue pairs. Through our initial analysis based on 100 sample pairs collected in the Czech Republic, we identified 630 upregulated and 720 downregulated genes, showing a large overlap with our analysis of the United States public data available for 65 cases (Wozniak *et al.*, 2013). This work is continuing with a plan to correlate expression profiles of 800 cases with germline polymorphisms.

GEP also has a central role in the CAGEKID study (part of the International Cancer Genome Consortium), which has whole-genome sequenced 100 tumour/germline DNA pairs collected through the IARC study and in the United Kingdom. The interpretation of whole-genome data is being finalized, and the replication in 400 cases from the same centres has started. Whole-genome sequencing data are complemented by an examination of gene expression through RNA sequencing and epigenetic changes. CAGEKID represents the renal component of the International Cancer Genome Consortium and, as such, data will soon be available to the scientific community.

Head and neck cancers and human papillomavirus infection

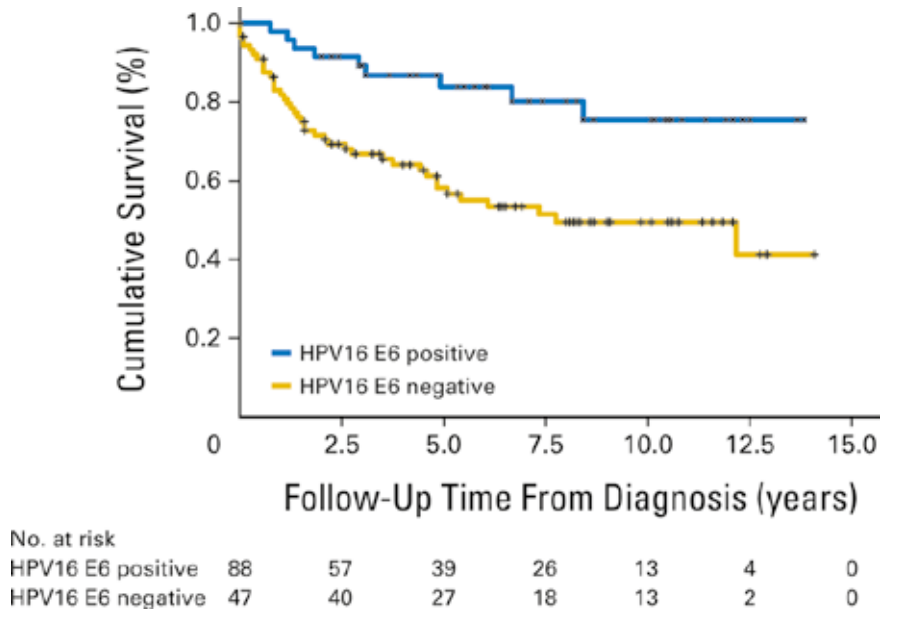
GEP will continue to investigate the role of human papillomavirus (HPV) in head and neck cancers, and potential genetic modifiers. Recently, in a large western European study, we found that HPV16 E6 antibodies were specific to HPV16-related cancer (present in 30% of oropharyngeal cancers, compared with < 1% of 1400 controls) (Anantharaman *et al.*, 2013). Subsequent analysis in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort demonstrated that HPV16 E6 antibodies were detectable 10 years before diagnosis in 35% of cases, again with very few false-positives (< 1% of controls were positive) (Kreimer *et al.*, 2013). Subsequent survival analysis also showed that HPV16 E6 seropositive oropharyngeal cancers had approximately 3 times better survival rates than those that were negative (hazard ratio, 0.3; 95% confidence interval, 0.13–0.67). In particular, 5-year survival rates were 58% among HPV16 E6 seronegative cases and 84% among seropositive cases (Figure 3). We plan to extend our findings within the large cohort consortium, currently being set up, to examine the utility of circulating antibodies to HPV16 as a predictive biomarker for head and neck cancer. GEP is also leading Work Package (WP) 4 of the HPV-AHEAD consortium, which is supported by a major grant from the European Commission (FP7; coordinator, Massimo Tommasino, IARC). The aim of this WP is to investigate the epidemiology of HPV-positive and -negative head and neck cancer, and, as part of this initiative, tumour samples are being retrieved from the previously completed western Europe study. In addition, GEP is also coordinating a multicentre cancer case–control study in South America (InterCHANGE). These new initiatives will help clarify the sensitivity and specificity of HPV16 E6 antibodies, as well as the association of viral infection with cancer response and relapse. Centralized assessment of a large series of samples from Brazil, the USA, and Europe is under way to further evaluate the geographical differences in HPV prevalence.

Large population cohorts

Research conducted within prospective cohorts constitutes an important part of the scientific activities within GEP. These studies focus on risk predictors that require measurement before diagnosis to establish robust associations, with complementary genetic work used primarily to establish causality along the lines of Mendelian randomization, as well as in risk prediction modelling. In the past, these studies were typically conducted within the EPIC cohort, but over the past year we have expanded to also include multiple additional European and non-European cohorts.

We will also continue to assist in the coordination of two large population cohorts that GEP initiated in collaboration with other non-IARC scientists. The first is a prospective cohort of 200 000 adults from three cities in Siberia, Russian Federation, in collaboration with the Cancer Research Centre, Moscow, and the Clinical Trials Services Unit, Oxford, United Kingdom. Analysis has focused on the role of alcohol consumption on all-cause mortality. The second is the Golestan Cohort study of 50 000 individuals from north-eastern Islamic Republic of Iran, being conducted with colleagues from Tehran and the US NCI. Analyses within GEP are focused on the effects of opium, obesity, and hypertension on all-cause and cause-specific mortality.

Figure 3. Cumulative survival of oropharyngeal cancer cases by prediagnostic HPV16 E6 serostatus. Source: Kreimer *et al.* (2013). Reprinted with permission. © 2013 American Society of Clinical Oncology. All rights reserved.



The European Prospective Investigation into Cancer and Nutrition (EPIC)

EPIC remains an important focus for GEP, in terms of both governance and research projects. The Group head, Paul Brennan, and a staff scientist, Mattias Johansson, are members of the EPIC steering committee, and Mattias Johansson is also leading the lung cancer working group within EPIC. Notable scientific highlights include the above-mentioned study of HPV serology in head and neck cancer (Kreimer *et al.*, 2013). Other examples include several studies on circulating vitamins in renal cell carcinoma and head and neck cancers. Of note is a study of renal cell carcinoma where subjects with elevated levels of vitamin B6 had a clearly higher incidence, as well as improved survival after diagnosis (see further details below).

The Lung Cancer Cohort Consortium (LC3)

As a comprehensive follow-up on a previous lung cancer study, we initiated the Lung Cancer Cohort Consortium (LC3) in 2011 and received support from the US NCI. The project aims to conduct biochemical and genetic analyses on more than 5000 case–control pairs from 24 prospective cohorts recruited in Europe, the USA, Asia, and Oceania. The first 2 years of the project have been committed to gathering biosamples, laboratory analysis, and administration. Scientific results are expected in early 2014. Similar projects are planned to follow up the EPIC studies on HPV and head and neck cancer, as well as vitamin B6 and renal cell carcinoma.

The European Biobanking and Biomolecular Research Infrastructure-Large Prospective Cohorts (BBMRI-LPC)

GEP is a leading partner of the BBMRI-LPC project, which is supported by a major grant from the European Commission (FP7; coordinator, Markus Perola, Finland). The overall aim is to join prospective cohorts across Europe and facilitate collaborative transnational studies. The specific aim of WP 10 is to coordinate calls for scientific proposals and select proposals that will receive financial and administrative support to access biosamples and data from multiple European cohorts.

Novel analysis on one-carbon metabolism biomarkers

We have recently expanded our work on biomarkers of the one-carbon metabolism, with a particular focus on renal cell carcinoma and head and neck cancers. For example, the renal cell carcinoma analysis conducted within the EPIC study strongly indicated that subjects with higher concentrations of vitamin B6 had substantially lower renal cell carcinoma risk, as well as reduced mortality after diagnosis. Subjects with plasma vitamin B6 in the top quartile had less than half the risk of renal cell carcinoma than those in the bottom quartile. In addition, elevated plasma B6 was also related to reduced all-cause mortality in EPIC. The associations between vitamin B6 and risk of renal cell carcinoma, as well as mortality, were subsequently validated in the independent Melbourne Collaborative Cohort Study (MCCS). A manuscript outlining these preliminary results is currently being reviewed. Plans are under way for additional analysis within the context of a large-scale consortium in collaboration with cohorts participating in the US NCI cohort consortium.

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