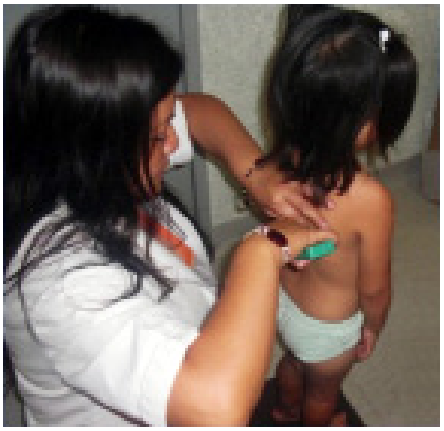
Collaborative Research: examples of multicentre studies

The need for an organization with a worldwide mandate to promote and lead international collaborations in cancer research was one of the main driving forces behind the creation of IARC. Today, the Agency's extensive network of collaborations is widely recognized as one of its major strengths, and the promotion of collaborative research in cancer remains one of the guiding principles for its programmes.



One area where the Agency's contribution has been particularly significant is the coordination of large, international, multicentre epidemiological studies. As epidemiology focuses on identifying risk factors with small effect sizes, one of the requirements is to increase the scale of studies to have the requisite statistical power in the analysis; such scale can, for the most part, only be achieved through large, international, multicentre collaborative studies.

A particular priority for the Agency has been the establishment and coordination of this type of study in low- and medium-income countries (LMICs). These studies are of particular importance as the knowledge of the etiology of cancers more prevalent in these regions is often limited. In addition, they provide the opportunity to study the consistency of effects in different populations, and to test the applicability of approaches for prevention in different socioeconomic and cultural settings. Large-scale collaborative consortia also offer opportunities for designing more efficient studies which optimize the use of limited international, national and local resources.

The remainder of this section describes some of the current examples of multicentre, international, collaborative epidemiological studies and consortia coordinated by the Agency. These include collaborative efforts studying genetic susceptibility or occupational exposures, as well as examples of a new consortia of birth cohorts and the development of laboratory capacity in a LMIC.

Transdisciplinary Research in Cancer of the Lung (TRICL) consortium

Genome-wide association (GWA) studies aim to identify relevant genetic susceptibility variants by genotyping up to 1 000 000 genetic variants (or SNPs). While GWA studies do not require prior knowledge of the functional significance of the variants studied, they do require very large sample sizes, typically thousands of cancer cases and controls.

In 2008 and 2009, multiple independent groups reported results of GWA studies of lung cancer (Hung *et al.*, 2008; Thorgeirsson *et al.*, 2008; Amos *et al.*, 2008). These included studies

coordinated by the IARC GEN Section, MD Anderson Cancer Center (USA), DeCode Genetics (Iceland) and the Institute of Cancer Research (United Kingdom), which jointly comprised over 5000 cases and an even greater number of controls. These studies all provided strong evidence of a susceptibility region in chromosome 15, with an extremely consistent measure of effect between the studies (Fig 1). Two other susceptibility loci were identified in the larger studies, including a region on chromosome 6 (which includes the HLA region that largely comprises immune function-related genes) and on chromosome 5 (including the telomerase gene). Subsequent large studies coordinated by the US National Cancer Institute (NCI), including over 5000 cases and controls, failed to identify further susceptibility loci (Landi *et al.*, 2009).

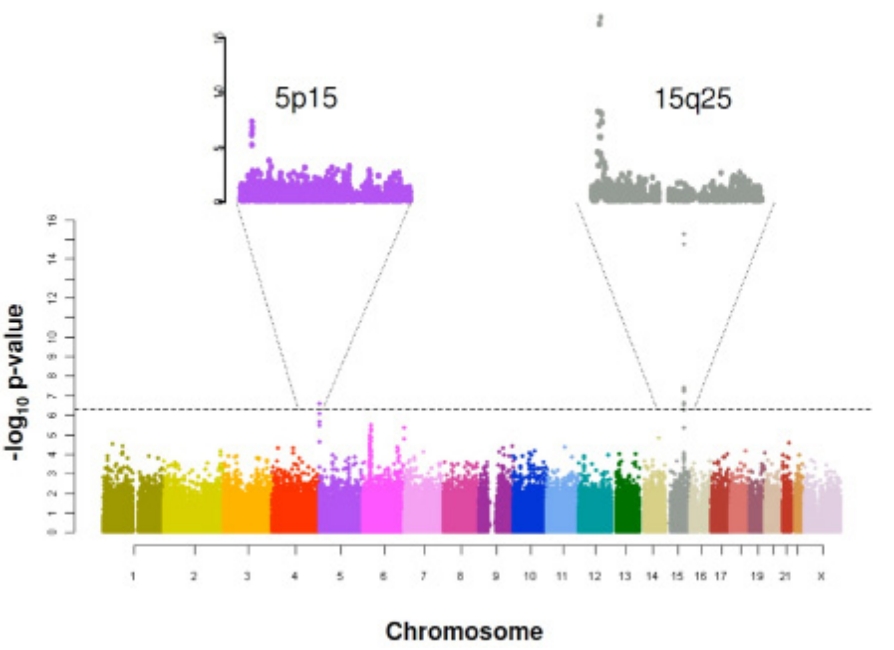


Figure 1. Scatter plot of p-values in –log scale from the trend test for 315 956 variants comparing 2971 lung cancer cases and 3745 controls, showing susceptibility loci in chromosomes 5 and 15

As part of an NCI-led initiative to follow-up on results from GWA studies of cancer, the TRICL consortium was established and started work in 2010. The primary objectives of the consortium are to: further elucidate genetic susceptibility for lung cancer by bringing together all previous studies; follow-up with functional research to help identify causal variants; and identify measures of population risk.

IARC scientists have been instrumental in leading the first objective by bringing together and conducting a meta-analysis of nine separate GWA studies of lung cancer, as well as looking for genetic susceptibility restricted to certain subgroups (e.g. among never smokers or by histological group). The final pooled dataset includes genome-wide results on approximately 15 000 cases and 30 000 controls, of which about 25% originate from IARC-led studies. New potential susceptibility loci have been identified and are being validated in other large lung cancer studies before publication. Other major partners in this initiative include MD Anderson Cancer Center, USA; the Institute of Cancer Research, United Kingdom; and the NCI, USA.

The SYNERGY consortium

A particular challenge in assessing the cancer risk associated with occupational exposures is that few independent studies would be large enough to have the power to correctly assess the joint effect of multiple risk factors.

The SYNERGY project was started in January 2007 to study the joint effects of five selected occupational exposures (polycyclic aromatic hydrocarbons, asbestos, crystalline silica, chromium and nickel) and smoking in the development of lung cancer. The ENV Section of IARC, the Institute for Prevention and Occupational Medicine (IPA, Germany) and the Institute for Risk Assessment Sciences (IRAS, Netherlands) coordinate the project, and IRAS is, in addition, responsible for exposure assessment. Investigators with relevant case-control data on occupational exposures were contacted with the suggestion to pool information.

So far, data from 14 case-control studies from Europe and North America have been pooled. The epidemiological database currently includes relevant demographic information and lifetime occupational and smoking history from 17 705 cases and 21 813 controls, which makes it the world's largest database of its kind. The data were collected between 1985 and 2009, and include around 20% women and 822 never-smoking cases. Another unique feature of the SYNERGY project has been the methodological development of SYNJEM – a country, year and job-specific job-exposure matrix with exposure estimates modelled from extensive quantitative exposure measurements from 21 countries.

The SYNERGY project has developed into a scientific platform for occupational lung cancer research, with main and parallel analyses, as well as for collaboration with other consortia and partners. The results will provide evidence for creating fair compensation schemes for occupational lung cancer and the introduction of more efficient prevention measures.

The Latin American Birth Cohort Consortium on Healthy Growth and Development

The effects of changes in lifestyle and of the rapid nutritional transition from traditional to Western type diets, observed in many LMICs around the world, are fast becoming a major health concern. However, the effects of these changes on children are not well established. Early exposure to poor diet, sedentary lifestyle, tobacco smoke and other environmental factors can alter infants' and children's growth patterns and may result in altered metabolism,

obesity and risk of chronic disease in adulthood.

The Latin American Birth Cohort Consortium on Healthy Growth and Development (BCCHGD) will combine data from established birth cohorts from three Latin American countries – Brazil, Chile and Mexico – with the primary aim of evaluating early life factors associated with optimal growth and developmental patterns and with the prevention of obesity and metabolic disorders.

One of the first activities of the consortium will be to explore the role of maternal anthropometry on the health and growth of offspring. In addition, the Consortium aims to evaluate the effects of maternal and infant nutrition and its interaction with environmental and genetic factors on early markers of cancer risk, epigenetic changes, and on biological and metabolic profiles in children as predictors of disease status at different life stages.

The BCCHGD is being established through a collaboration between scientists from IARC, the 'Centro de Pesquisas Epidemiológicas da Universidade Federal de Pelotas' (CPE-FPel, Brazil), the 'Instituto de Nutrición y Tecnología de los Alimentos' (INTA, Chile) and the 'Instituto Nacional de Salud Pública' (INSP, Mexico).

Establishing HPV serology and genotyping laboratories in Trivandrum, India

Increasingly, epidemiological studies rely on advanced laboratory assays to measure a range of biomarkers to improve disease definition, exposure assessment, or to identify susceptible individuals. The lack of state-of-the art laboratory facilities in many LMICs hinders the development of research led from such regions. The incorporation of capacity-building is a valuable feature of IARC collaborative studies.

Collaboration led by the IARC SCR and ICE Groups, together with the German Cancer Research Centre (DKFZ) and local partners, recently established dedicated HPV serology and HPV genotyping laboratories at the Rajiv Gandhi Centre for Biotechnology (RGCB) in Trivandrum, India. The RGCB HPV laboratories will support the analysis of plasma samples and cervical cells collected from 20 000 participants in the multicentre randomized clinical trial in India evaluating the comparative efficacy of 2-doses versus 3-doses of HPV vaccination in preventing cervical neoplasia.

Figure 2. HPV typing laboratory at the Rajiv Gandhi Centre for Biotechnology in Trivandrum, India

DKFZ trained two staff members from RGCB in HPV serology analyses using a competitive Luminex® immunoassay (CLIA), and provided the technical support for the transfer of CLIA technology to the RGCB. The first trial run of the serology testing facility at the RGCB was carried out in 2011. The assay procedure has been validated and currently large numbers of samples from the study are being processed to evaluate the antibody response following the different regimes.

The ICE Group of IARC trained two staff members from RGCB in the use of a multiplex PCR/APEX assay, a highly sensitive method for the detection and typing of 19 high-risk mucosal HPV types. The use of this methodology at the RGCB has now been validated. The assay will be used for testing the large numbers of cervical cell samples obtained from the participants of the IARC multicentre HPV vaccine trial to evaluate the efficacy of the two different dose regimes in preventing HPV infection. Financial support for this training was provided by the Union for International Cancer Control and IARC.

Publications

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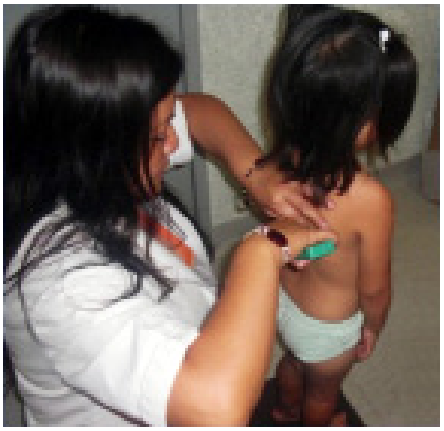

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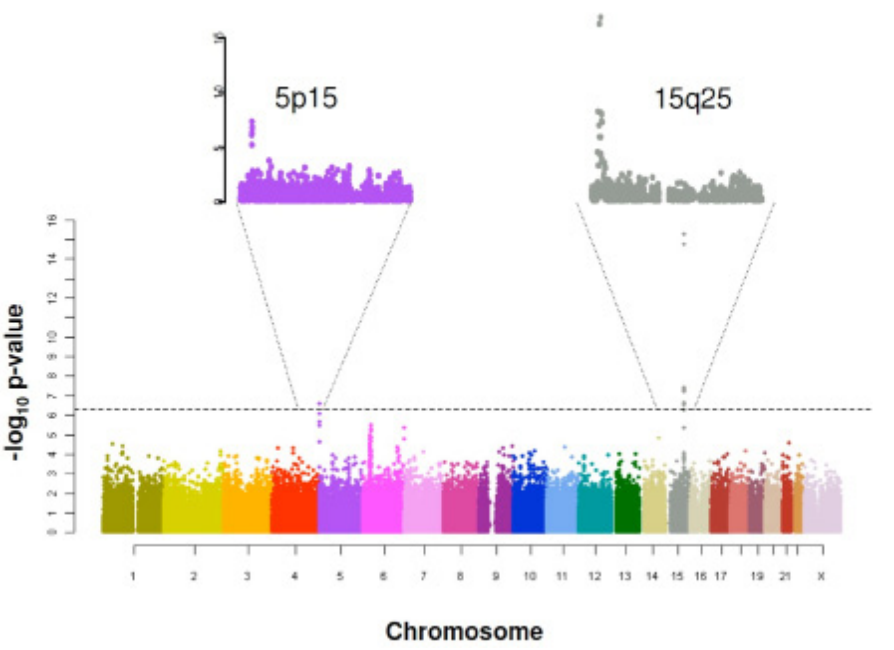

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