International Agency for Research on Cancer

World Health Organization

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CURRENT SCIENTIFIC INITIATIVES

IARC scientific Sections, except the Section of Early Detection and Prevention (EDP) and the Section of Nutrition and Metabolism (NME) which will undergo a separate Review by a dedicated Review Panel in 2013, have been requested to make a presentation on their current scientific initiatives.

Sections have been asked to present one or two areas where the input of the Scientific Council would be valuable. You will find them as follows:

Section of Cancer Information (CIN)

Global monitoring of the WHO '25 by 25' target for cancer

Background

In response to the September 2011 United Nations declaration on Noncommunicable Diseases (NCDs), WHO has put forward a global target of a 25% reduction in premature mortality from NCDs by 2025. Cancer will evidently be a major component of the NCDs and, in several countries, it is likely to be the most important category in the requisite age range (30–69 years). As examples, in Japan, cancer represented 54% of all NCD deaths in 2010, while in the 15 countries for which mortality data are available for 2010, age-adjusted cancer mortality rates ranked above those of cardiovascular disease (CVD) in every country within the age range, with cancer mortality rates two- to three-fold higher than CVD mortality rates in seven of those countries.

The project will evaluate recent cancer mortality trends worldwide against the '25 by 25' target and will deliver a report card on cancer control progress at the national level. Utilizing existing long-term mortality data available (in combination with existing incidence and survival data), IARC will establish the extent to which the targets for cancer (and in the context of the other NCDs) are feasible in each country. This activity thus seeks to quantify (through prediction models) the extent to which the 25% reduction in premature mortality is attainable by 2025 for all cancers combined based on recent sex- and cancer-specific trends. We could then revise the country-by-country 25% target for premature deaths from other NCDs given the predicted changes in premature cancer burden.

Data sources

There are approximately 100 countries for which the exercise is currently feasible (mortality and population data available from 2005 or thereafter, data series of five or more consecutive years, sufficiently large populations). Disaggregation of the trends by cancer type is needed in assessing progress, given the successes or otherwise in cancer control pertain to a combination of changing risk factors, preventive activities, screening programmes and improvements in therapy. Such complexity means that it is necessary to predict the cancer mortality burden for each of the major cancer sites in a given country and aggregate to obtain the all-cancer mortality predictions. Mortality, as an indicator of progress, cannot be utilized in isolation; to pinpoint the multiple reasons for such changes that occur across the cancer control domains, measures of cancer-specific incidence and survival data are also essential. Indeed, the differing but complementary properties and caveats associated with each indicator promote their combined synergy and the utilization of a joint presentation and interpretation of incidence, mortality and survival in a given country, where such data are available.

Methods

The statistical approach is based on long-established prediction modelling methods and the extrapolation of recent trends in cancer mortality rates (last 20 years) by age, period and birth cohort into the future. Where data are available for <15 years, simpler time-linear models will be fitted to derive predictions for 2025.

Expected Outcomes

The 2025 predictions will be presented and interpreted using a number of measures in both graphical and tabular formats. These will include:

Tables

- Mean number of recorded deaths in last five years (circa 2008) vs predicted number of deaths for 2025 by country;
- % increase/decrease predicted in deaths 2025 vs mean number of recorded deaths in last five years, partitioned into changes due to demographic changes (population ageing and growth) vs changing risk (rates), all ages and age group 30–69, by country;
- Age-standardized rates (ASR, world) based on recorded deaths in last five years vs predicted ASR 2025, all ages, and truncated to ages 30–69, by country;
- Cumulative risk of death (up to age 70) based on recorded deaths in last five years vs predicted cumulative risk of death 2025, by country;
- Quantitative assessment of the impact of the predicted change in cancer mortality 2010–25 ages 30–69 on the target for all other NCDs given by country.

Graphics

- Age-standardized rates 1990–2010 and predictions 2011–2025 (years according to availability of data) for all cancers combined and 10 most common causes of cancer death, by sex and for both sexes;
- Numbers of recorded deaths 1990–2010 and predicted number of deaths 2011–2025 (years according to availability of data) for all cancers combined and 10 most common causes of cancer death, by sex and for both sexes.

Other

- Tables and graphics of cancer incidence and survival patterns and trends based on cancer registry data in a given country will augment the above mortality statistics, where available and relevant.

Dissemination

A report will be generated with individual chapters for each country that contain the above tables and graphics, further analysis of incidence and survival, where applicable, alongside a commentary on the major drivers of the current cancer mortality trends and predicted deaths in 2025, the extent to which the '25 by 25' target will be met for cancer based on the analysis, and the extent to which the predicted cancer trends will impact on all other NCDs.

An online menu-driven resource at IARC will be established enabling perusal of the above graphics and tables, with links to the specific chapters of the report and the availability of high quality factsheets by country and region.

Questions for the Scientific Council (CIN)

1) Should this work be restricted to cancer (in theory we would have the data to also examine other NCD categories)?
2) The majority of countries for which adequate mortality data are available are from high- or upper-middle income groups. Low-income countries, especially from Africa, are under-represented. What could be done in estimating the monitoring of the target in these countries?
3) Do we incorporate risk-based models and scenarios e.g. impact of effective tobacco control, cervical screening etc.?

Section of IARC Monographs (IMO)

Future perspectives of quantitative risk assessment for the IARC Monographs

In 1999, developments and perspectives of biologically-based risk estimation were reviewed. The resulting IARC Scientific Publication (Vol. 131, 1999) did not, however, include a consensus statement or recommendations regarding risk assessment for the IARC Monographs.

In 2003, the Advisory Group on Future Priorities for the IARC Monographs discussed risk assessment and noted that the topic was not mentioned in the Preamble. While one option considered inclusion of critical reviews of published risk assessments in future Monographs, it was not envisaged that Working Groups themselves embark on risk assessment. This Advisory Group also noted that there are many different approaches to (quantitative) risk assessment, and that "In the case of epidemiological data an approach to such an assessment would perhaps be feasible."

Whilst there was support for future consideration of this area, some caution was expressed concerning the more policy-orientated and less science-based approaches to risk assessment. It was also stressed that experts with relevant professional training would be required both in the IARC Secretariat and in the Working Groups. It was suggested that 'risk assessment' should be included as a discussion topic in a broad meeting to assess strategic developments of the IARC Monographs Programme.

Two Advisory Groups met in 2005 to recommend an amendment of the Preamble to the IARC Monographs. These two Advisory Groups recommended that, while quantitative information on carcinogenic risks can be useful, a cautious approach should be adopted in including quantitative risk assessment (QRA) in the IARC Monographs. In particular, these Advisory Groups recommended that IARC confine its potential involvement in QRA to areas where unverifiable assumptions are not required or very limited.

The Advisory Groups considered several ways in which the IARC Monographs Programme might implement the cautious approach to QRA recommended above. These include (i) the systematic incorporation of quantitative analysis of carcinogenic risk that do not involve extrapolation outside the range of the available data (this is currently provided for within the Preamble), (ii) the inclusion of a new section in future Monographs that would summarize data on carcinogenic risks (which would focus on results that involve minimal or no unverifiable assumptions, and could include standardized measures of risk for comparison with other carcinogenic hazards such as

summary relative risks from meta-analyses), (iii) the development of a handbook on cancer risk assessment that would provide guidance on practical aspects of QRA and (iv) the use of a separate group of experts to develop a supplement to a specific Monograph that would deal with quantitative risk assessment. These options might be explored more fully in a future Workshop on quantitative assessment of risks for cancer.

Regardless of which of these approaches is adopted, this Advisory Group emphasized that any initiatives taken by the IARC Monographs Programme in the area of quantitative assessment of risks for cancer should be firmly based on science. This Advisory Group also noted that the development of a programme in QRA will require specialized expertise and a significant commitment of resources.

The amended Preamble (IARC, 2006) includes the following guidance on quantitative data:

Objective and Scope: "A Monograph may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment."

Cancer in humans: "Dose–response and other quantitative data may be summarized when available."

Cancer in experimental animals: "Negative findings, inverse relationships, dose–response and other quantitative data are also summarized."

With this history of discussions and recommendations in mind and building on the results from the Volume 100 Workshops on "Tumour concordance" and "Mechanisms of carcinogenicity" IMO is planning to convene an Advisory Group meeting in late 2013 on "Perspectives of quantitative risk assessment for the IARC Monographs: opportunities and potential pitfalls".

Questions for the Scientific Council (IMO)

1) General support of the proposal versus concerns (including questions regarding other key players and potential users);
2) Potential approaches for the IARC Monographs: integration into regular Monographs versus separate meetings on selected agents; restriction to observed exposure–response relationships on cancer in humans versus low dose-extrapolation, between species extrapolation and/or use of mechanistic data to inform such extrapolations;
3) Recommendations regarding participants for this Advisory Group, including scientists from academia and members of national expert groups;
4) Strategic approach for funding: if quantitative risk assessment is recommended by the Advisory Group should this be integrated into the next grant proposal (next five-year proposal to NCI due in summer 2014) or which other funding sources would be suggested?

Section of Mechanisms of Carcinogenesis (MCA)

The overarching objective of the Section of Mechanisms of Carcinogenesis (MCA) is to gain a better understanding of the molecular mechanisms by which genetic and epigenetic alterations resulting from environmental and lifestyle exposures alter critical cellular processes and promote cancer development. Major emphasis is placed on discerning events that precede or drive tumour initiation and progression as opposed to genetic changes that are non-causal or non-functional. Innovative research, development of genomic and epigenomic methodologies applicable to biobanks associated with population-based studies is an important part of the MCA strategy. In collaboration with epidemiology groups, MCA also contributes to the development of translational studies through the discovery and validation of biomarkers of tumorigenesis and environmental exposures. The Section comprises two Groups: the Molecular Mechanisms and Biomarkers Group (MMB, headed by Dr Jiri Zavadil) and the Epigenetics Group (EGE, headed by Dr Zdenko Herceg), both of which work in close collaboration to create synergies and better exploit and further expand unique research tools and expertise. Among several new initiatives, MCA research is currently focusing on (although not limited to) the following projects:

(i) Early molecular ("driver") changes in carcinoma development associated with environmental exposures

The objective of MMB is to identify mutations and molecular events associated with specific environmental exposures that drive tumour initiation and progression, and to distinguish these from non-functional or merely modifying passenger events. MMB focuses on a specific type of cancer caused by aristolochic acid type-I (AA), a "Group 1" human carcinogen (IARC), found in the *Aristolochia* plant species. Dietary exposure to AA leads to aristolochic acid nephropathy (AAN) and tumour formation in the upper urinary tract (UUT). While AAN-associated UUT cancers are potentially preventable as the carcinogen and its sources are known, the true worldwide AA use and the disease incidence remain largely unmapped and underestimated.

The main aim is to identify driver alterations leading to UUT cancers in AAN patient cohorts using advanced genomic and computational approaches applied to samples collected worldwide through a broad international collaboration. A subset of AAN cancer patients develop secondary bladder tumours and MMB will perform mutational screens in these secondary tumours as well, to elucidate their link to the primary effects of AA. While selective identification of AA-induced driver events in human primary tumours is feasible, it remains technically challenging. MMB will thus also apply a temporal genome-wide mutational screen to a mouse model of AA-induced carcinogenesis to identify the earliest molecular events leading to AA-initiated tumorigenesis. The next priority area is the development of microRNAs, and potentially histone modifications (in collaboration with EGE) as non-invasive biomarkers to detect and evaluate the AA exposure and early carcinogenic events in both the UUT and the bladder cancers. MMB has built a database of UUT tumour-specific microRNAs that will be tested for presence in patient urine, plasma and serum by highly sensitive tests such as quantitative PCR. Such tests, if successful, can be applied as a powerful, non-invasive tool to monitor AAN patients who are at risk of developing UUT- or bladder tumours.

Collectively, these studies will facilitate the identification of molecular changes associated with a specific environmental exposure and the discovery and validation of new biomarkers of carcinogenesis. The conceptual framework of the AAN project will be extended to evaluate additional risk factors by analogous strategies and it will enable future studies of mechanistic, molecular aspects of carcinogenesis leading to the development of a translational cancer prevention programme on specific human cancers associated with low-resource countries.

(ii) Identification of epigenetic biomarkers and their environmental determinants

Although epidemiological studies support the role of environmental factors in a wide range of human cancers, the precise mechanisms by which they promote cancer development and progression remain poorly understood. Environmental factors have been proposed to promote the development of malignancies by eliciting epigenetic changes; however, it is only with recent advances in epigenomics that target genes and the mechanisms underlying environmental influences are beginning to be elucidated. While epigenetic changes in tumour tissues have been extensively investigated in previous studies, it remains unclear whether cancer-associated and exposure-associated changes can be detected in surrogate tissues (such as peripheral blood and circulating nucleic acids) and whether they can be used as biomarkers of exposure and cancer risk.

EGE will investigate whether epigenome changes in peripheral blood (such as WBC) can be used as a biomarker of exposure and/or an intermediate biomarker for cancer risk. The principal goal is to analyse the epigenome (methylome) of WBC of cancer cases and controls using a large sample. We will take advantage of a prospective study (EPIC) to identify changes in epigenomes associated with specific dietary and lifestyle factors and new genome-wide technologies for methylome analysis (based on new generation bead-arrays and next generation sequencing). This study will focus on breast cancer (collaboration with the Section of Nutrition and Metabolism (NME)) although other cancer types (lung cancer, in collaboration with the Section of Genetics (GEN)) are also considered. Additional focus will be on specific environmental/lifestyle (alcohol, smoking and obesity/physical activity) and endogenous factors (one-carbon metabolites, hormones). Samples collected several years prior to diagnosis with extensive dietary and lifestyle information and biochemical and genetic data are important strengths of our approach. The results obtained should answer the question of whether significant epigenetic variation among individuals exists, whether such epigenetic variations are caused by endogenous (hormones, one-carbon metabolites) or exogenous (environmental, nutritional and lifestyle) factors, and whether these changes are causally linked to differences in cancer susceptibility. In addition, in contrast to most previous studies (that were retrospective) the prospective design of this study will rule out the possibility that epigenetic changes (biomarkers) are influenced by the disease process ("reverse causality").

Questions for the Scientific Council (MCA)

1) Can we translate the information obtained from animal model systems used to discriminate between "driver" and "passenger" events into a solid understanding of human tumour development?
2) Can we utilize results of these studies to build relevant and efficient preventive measures?
3) Although blood samples are the most available biological material in epidemiological studies that allow the measurement of biomarkers repeatedly over the life course, is this the appropriate surrogate tissue to test whether epigenetic patterns are useful in understanding how cancer risk changes over time?
4) Should we consider additional risk factors for breast cancer and what criteria should we apply in selecting risk factors associated with breast cancer (low-resource vs high-resource settings)?

Section of Molecular Pathology (MPA)

Population-based studies on brain tumours

We have carried out population-based studies on astrocytic and oligodendroglial gliomas (approx. 1000 cases), diagnosed during 1980–1994 in the Canton of Zurich. These studies involved a collaboration between IARC, the Cantonal Cancer Registry Zurich, and scientists at the University Hospital Zurich, Switzerland. For the first time, our research has combined studies on incidence, tumour pathology, genetic alterations, treatment, and survival, and has contributed to defining the genetic profile of gliomas, particularly that of glioblastoma subtypes. The results showed that the prognosis for glioblastoma patients was extremely poor (survival rate 17.7% at one year). We also observed that patients older than 80 years had a particularly low median survival rate of only 1.6 months versus 8.8 months for patients under the age of 50 years. During the study period, surgery and adjuvant radiotherapy were the only treatment options available. During the last decade, adjuvant radiotherapy and concurrent treatment with the alkylating agent temozolomide (TMZ) has been introduced as generally accepted therapy for patients with glioblastoma. Clinical trials have shown that such therapy increased median survival time to 14.6 months and resulted in longer-term survival (>2 years) in approximately 20% of patients in Europe. In Switzerland, this therapy protocol was introduced in 2005, but there are no data on the actual use of radio-chemotherapy with TMZ, nor on the extent to which this treatment has improved clinical outcome at the population level. We are currently carrying out a retrospective population-based study in the Canton of Zurich (approx. 250 patients) diagnosed between 2005 and 2009.

We are also planning to carry out a new prospective population-based study in glioblastoma patients who at the time of diagnosis were resident in the Cantons of Zurich (population, approx. 1 300 000), Basel (population: Basel Stadt, 185 000; Basel Land, 269 000) or Ticino (population, 328 000), during 2013–2016 (estimated total number of cases, approx. 320). Coverage of patients with glioblastoma in the Cantonal Cancer Registries is expected to be > 90%. Patients will be followed up until 2019, i.e. a minimum of three years. We intend to collect samples of frozen tumour tissue and blood from all patients, in order to carry out exome sequencing. These will be

the first next-generation sequencing analyses of glioblastoma at a population level. However, in contrast to our retrospective population-based studies, patients in prospective population-based studies will be initially identified in surgical centres, but not by cancer registries. Thus, identifying all cases at a population level may be challenging, and we may lose a significant fraction of elderly patients if they are not treated in surgical centres.

Questions for the Scientific Council (MPA) – Part 1/2

Does the Scientific Council recommend that IARC carry out a prospective population-based study on brain tumours? What are the questions that cannot be answered using samples collected in clinical trials?

WHO Classification of Tumours series

Since 2007, IARC has been publishing the 4th edition of WHO Classification of Tumours series. To date, four volumes have been published, and two volumes are in preparation. Like the 3rd edition, this book series has been distributed among pathologists and clinicians worldwide (20 000 – 45 000 printed for each volume) and has been accepted as the international standard of histological and genetic criteria of diagnosis of human tumours. However, there are some concerns regarding the speed of publication. In order to deal with recent rapid progress in genetics in human tumours, it is necessary to revise or update the WHO Classification much more frequently than previously. To achieve this goal without increasing resources, one possibility would be to publish the WHO Classification series online only. This is also advantageous since updating would be much easier and faster. Most developing countries now have access to Internet. This modern option has already been adopted by many scientific journals.

Questions for the Scientific Council (MPA) – Part 2/2

Does the Scientific Council support our intention to move to the online option in the near future? What should be the timeline? What additional considerations should the Agency consider in moving forward?

Section of Infections (INF)

The Section comprises two Groups: the Infections and Cancer Biology Group (ICB, headed by Dr Massimo Tommasino) and the Infections and Cancer Epidemiology Group (ICE, headed by Dr Silvia Franceschi).

Infections and Cancer Biology Group (ICB)

ICB's research is focused on the establishment of a causal role of specific infectious agents in human cancer. It is well accepted that infection with certain oncogenic viruses is sufficient to promote the malignant transformation of infected cells. One example is the mucosal high-risk human papillomavirus (HPV) types associated with ano-genital cancers. However, epidemiological studies provide evidence that oncogenic viral infection may also cooperate with environmental factors in cancer development. For instance the incidence of two Epstein-Barr virus (EBV)-induced cancers, i.e. nasopharyngeal cancer and Burkitt's lymphoma, appears to be influenced by

environmental factors restricted to specific geographical regions. In addition, it is well demonstrated that the mycotoxin aflatoxin B1 a secondary metabolite of *Aspergillus flavus*, strongly increases carcinogenesis of the liver mediated by hepatitis B virus (HBV). Recent data from our laboratory showed that aflatoxin B1 favours EBV infection of primary human B cells *in vitro* by altering the expression of specific cellular genes. Interestingly, populations of sub-Saharan regions with high incidence of Burkitt's lymphoma are heavily exposed to aflatoxin B1-contaminated food, providing additional evidence on the possible EBV/aflatoxin B1 interaction.

An additional example of possible cooperation between environmental factors and viral infection in human carcinogenesis is provided by UV irradiation and cutaneous beta HPV types. Both factors appear to synergize in the development of non-melanoma skin cancer (NMSC). Indeed, biological studies in *in vitro* and *in vivo* experimental models indicate that the cutaneous beta HPV oncoproteins E6 and E7 facilitate the accumulation of DNA damage induced by UV irradiation. However, analysis of NMSC specimens in independent studies showed that far less than one HPV DNA copy per cell was present, indicating that the presence of viral genome may not be required in the late stage of carcinogenesis. This may imply a need to consider a hit-and-run mechanism for the role of cutaneous beta HPV in NMSC pathogenesis.

Questions for the Scientific Council (ICB)

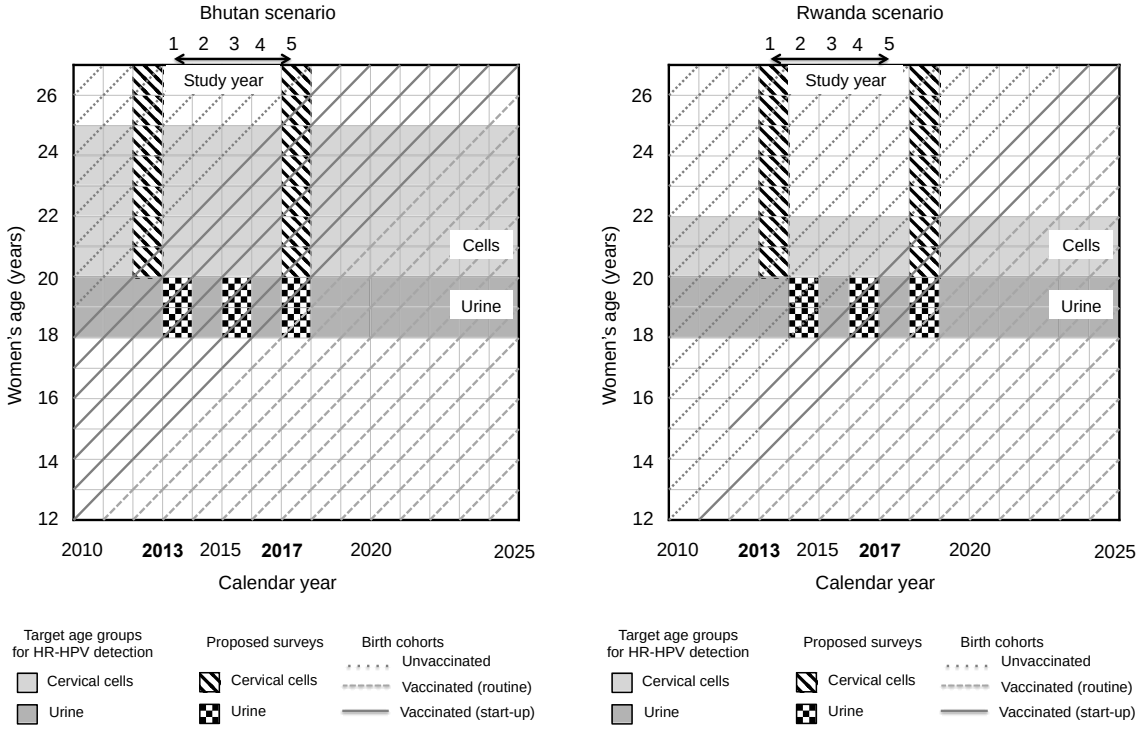
Based on the currently available epidemiological findings, can other hypotheses be envisaged concerning the cooperation of infectious agents with environmental factors in human carcinogenesis? Additionally, what could be the strategies/procedures to evaluate these hypotheses?

Infections and Cancer Epidemiology Group (ICE)

Bhutan and Rwanda are the only two low-resource countries to have been able to transform a quadrivalent HPV vaccine donation into a successful nation-wide vaccination programme. Vaccine coverage exceeded 90% of eligible girls in both countries.

Vaccination programmes are expected to have an important impact on the future burden of cervical cancer, the most common cancer in women in the two countries, but the effect will not be seen on cancer for two to three decades. IARC has, therefore, started a project that will provide useful information on vaccination effectiveness in Bhutan and Rwanda (Figure 1) during the early phase (five years) of HPV immunization. The project will also include support to CareHPV-based screening programmes to benefit older women immediately, and allow long-term vaccine impact assessment in these two model settings. The IARC project has been awarded a five-year grant by the Bill & Melinda Gates Foundation.

Figure 1. Cervical cell- and Urine-based survey implementation: timeline, by age, calendar year and birth cohort. Left panel: Bhutan; right panel: Rwanda.



Identity numbers are being introduced to allow tracing various aspects of population's life and activities (hospital access, revenue taxes, etc.) in both countries. Individual HPV vaccination records, however, are only available on paper in the schools/health centres where HPV vaccination had taken place.

Questions for the Scientific Council (ICE)

Would it be worth investing in the computerization of individual vaccination records?

In other words, how can we identify and follow up individuals and put in place the basis for future record linkage studies?

Section of Environment and Radiation (ENV)

Some agents within the scope of environmental, lifestyle, occupational and radiation-related exposures have already been identified as major causes of cancer, but further characterization of their associated risks is still needed. Ionizing radiation, for example, is a well-known carcinogen although the impact of low-dose radiation on the overall cancer burden is difficult to quantify. When it comes to environmental pollutants and occupational exposures, the attributable fraction of the totality of the cancer burden is also difficult to estimate, but is supposedly smaller than from the above-mentioned lifestyle factors or certain infections. Nevertheless, environmental or occupational risk factors are often modifiable by reduction or elimination of exposure and thus may represent a greater proportion of the realistically modifiable cancer burden. For some cancers with few known risk factors, the contribution from environmental factors might be larger than currently estimated; candidates include testicular and oesophageal cancer, suggested by the descriptive

epidemiology of geographical variation and/or from migrant studies. Also breast cancer, brain tumours or cancers in childhood may have a significant contribution from the environment.

Amongst several ENV activities there are two consortia either recently being established or suggested to be established that relate to programmatic topics of the Section, namely the possible cancer risk associated with the use of pesticides and exposure to low dose ionizing radiation. Yet, strategic decisions are needed to increase the efficiency of these consortia in addressing cancer-related questions.

AGRICOH – a consortium of agricultural cohort studies

AGRICOH is an international consortium of agricultural cohort studies, coordinated by IARC, formed in October of 2010 to encourage and support data pooling to study disease-exposure associations that individual cohorts do not have sufficient statistical power to study. Occupational and environmental exposures to pesticides are common in farming and thus cohorts in AGRICOH offer the possibility to study the role of chronic exposure to pesticides in cancer etiology (and other illnesses: respiratory, neurologic, and reproductive). Participating studies are from the USA (6), Canada (3), Costa Rica (2), France (3), Norway (3), Denmark (1), United Kingdom (1), the Republic of Korea (1), South Africa (2), New Zealand (2), and Australia (2). The studies vary in size, health outcomes studied, time period of enrolment and follow-up, inclusion criteria, in addition to differences in agricultural work practices across countries, requiring substantial data harmonization efforts before pooling.

At present, ENV has a prominent role in the launch of AGRICOH, requiring resources for building up infrastructure. ENV has one member in the nine member Steering Group and the AGRICOH coordinator is an ENV scientist. ENV staff work on data harmonization and putting together a data dictionary of the cohorts of at least common variables and runs the AGRICOH web site.

To date, two projects have been launched within AGRICOH, both led by ENV staff. The first project is to look at cancer incidence and cancer mortality of various agricultural cohorts to measure their cancer burden and to provide an overview of the different cancer risk profiles in the cohorts. In a second step, a more refined analysis will be made to look at different types of farming, in particular by crop farming, cattle farming or both. Out of all cohorts, 10 appear to be eligible and the request for data is currently underway. The second project is to look at haematological malignancies in relation to pesticide use. This project includes cohorts from the US (Agricultural Health Study: ~52 000 private pesticide applicators (farmers) and ~32 000 spouses), France (AGRICAN: ~180 000) and Norway (Cancer in the Norwegian agricultural population: ~250 000 including spouses). This study will use the detailed exposure data from the individual cohort to build up an activity-exposure-matrix, taking into account time period of exposure, country type of farming (crop: grain, soy beans, corn, etc., hogs, cattle, chicken, etc.), pesticide application method and protection measures, and chemical groups or pesticides used to estimate each individual cohort members' cumulative exposure to pesticides. Cancer outcomes will be lymphoma, leukaemia and multiple myeloma, by subtype.

Questions for the Scientific Council (ENV – AGRICOH)

1) Strategic: from the first project being launched it becomes obvious that when cancer is the outcome of interest, less than half of the studies will be able to provide data, either due to their small size or lack of cancer follow-up. The current situation is that all activities are done as one large consortium (data harmonization, meetings, and steering group) to avoid duplication of work. However, an alternative would be to have a stronger focus on outcome groups with ENV restricting its role more to cancer. On the other hand, cohorts may then drop out if only some of the focus groups remain active and it is possible that also smaller cohorts become more valuable in the future. For instance some of them have cohort members of very high exposure and future questions could include investigating genetic changes in small numbers of cancer cases with very high exposures. Should IARC re-consider its role in AGRICOH or/and propose a structure for the consortium that is based on outcome groups?

2) Expansion: so far, most cohorts come from developed countries, particularly sizable ones informative for cancer research; a strategy to open the consortium for more participants from LMICs is to be more inclusive on general population cohorts with a large proportion of farmers. The use of pesticides in some of those countries is less regulated and over-exposure might be common and thus the proportion of cancers attributed to occupational or environmental pollutants might be significant. On the other hand, it would be difficult to include more and more of these cohorts from countries having agricultural cohorts in place. What would be an adequate expansion strategy to LMICs?

Continuation of IARC activities related to the Chernobyl nuclear accident

In 2008–2010, an international group of experts and advisors under IARC leadership carried out the European Union funded project "ARCH: Agenda for Research on Chernobyl Health". ARCH assembled a multidisciplinary group of experts from within and outside the most affected states with considerable experience in the follow-up of the health consequences of the accident. The ARCH group conducted a comprehensive review of the current status of research on the health effects from the Chernobyl accident. Demonstrated health consequences among the liquidators include increases in leukaemia and cataracts, together with well-documented cases of acute radiation sickness in the early recovery workers. Among the general population exposed to fallout the increase in thyroid cancer in those exposed as children is clear, while leukaemia risk in children remains controversial. The on-going thyroid cancer problem requires continued study to determine the extent to which the risk to those exposed in childhood will continue into the future, the risk to adults at exposure, and the continuing change in the molecular findings. ARCH strongly supported the need for well-designed and coordinated long-term studies.

IARC is undertaking a new initiative to build partnerships with the three countries mainly affected, plus Japan, the USA and European countries in order to take the research agenda forward. The purpose of this new investment is therefore to bring together both key scientific players and funding partners to decide on the research priorities and to seek sustainable funding for those priority areas. The European Union launched a call "Trilateral cooperation on Chernobyl: independent assessment of the need to launch studies on the health effects of the Chernobyl accident". In response, IARC submitted a proposal to establish a core team for international cooperation which currently includes several European partners (MELODI, BfS (Germany), STUK

(Finland)) and the NCI (USA). Preliminary agreement has been also reached with the Science Council of Japan.

The specific objectives of this initiative are:

- Identifying key institutions worldwide (authorities and research bodies) willing to commit to future collaboration on Chernobyl research;
- Thorough assessment of existing infrastructures (cohorts of affected populations, dosimetry data bases, biobanks) in terms of their suitability and needs for improvement for setting up future life-span cohorts;
- Identifying the nature and structure of an international coordinating mechanism for future Chernobyl research, including agreements with stakeholders to support the proposed mechanism;
- Development of a long-term research plan based on the Strategic Research Agenda developed within ARCH with agreed research priorities; and
- Identification of seed funding for the pilot phase to implement the agreed coordinating mechanism.

Questions for the Scientific Council (ENV – Chernobyl)

1) The initial proposal of the ARCH group was to establish a coordinating structure similar to the action taken to create the Radiation Effects Research Foundation some years after the atomic bomb exposures in Japan. Centres in Ukraine and Belarus are key partners in this new structure. How much should IARC invest in training and education of researchers of these centres, e.g. for monitoring cancer trends and analysis in the most contaminated areas?

2) The question whether there is an increase in infant leukaemia is still open; one issue is the lack of precise date of birth information in the Belarus childhood cancer registry that hampered calculation of incidence rates to detect presumably small differences. How much effort should be made to either increase the completeness of information in the registry or are there other promising study designs to address the open question?

Section of Genetics (GEN)

The Section of Genetics (GEN) comprises three Groups (Genetic Epidemiology (GEP), Genetic Cancer Susceptibility (GCS) and Biostatistics (BST)) and a range of specialities ranging from classical epidemiology to genomics and bioinformatics. We focus on cancer sites that may be relatively understudied compared to their burden (e.g. lung cancer) or because of their relative rarity (e.g. head and neck, renal and EBV related cancers (nasopharyngeal cancers and Hodgkin's lymphoma)) and have built up exceptional bio-repositories for several of these cancer types by working with colleagues throughout the world. The next generation sequencing (NGS) facility was installed within the Genetic Services Platform of GCS in 2011, and our medium-term plan is focused on opportunities that arise from this. As reflected in the Scientific Council comments in 2011, our projects involve interactions with other Sections and we aim to incorporate genetics into a wide range of Agency projects.

Questions for the Scientific Council (GEN)

Two over-arching questions within the Section include:

1) What types of sequencing studies should we try to initiate, taking into account our access to large bio-repositories but also limited capabilities when compared to other large sequencing centres; and

2) Should we take advantage of other opportunities that arise with NGS, including studies that aim to detect circulating tumour DNA in plasma or serum samples.

These two questions are further developed below:

NGS within highly selected cases from IARC's bio-repositories

NGS can cost effectively characterize the mutation spectrum present within a given tumour. Many of the biological specimens stored in the IARC's extensive bio-repositories are of a quality and quantity conducive to NGS techniques. One promising research area for IARC is NGS of highly informative cases to enable description of their molecular signatures, and how these signatures are correlated with outcome, environmental and genetic exposures.

We propose that rare tumour subtypes, where the large size of the bio-repositories could provide reasonable numbers, maybe a particular niche for IARC's activities.

Some potential subtypes for study include:

- Tumours differing by viral exposure (such as HPV and EBV in head and neck tumours and Hodgkin's lymphoma, respectively);
- Rare histological classes (such as bronchioloalveolar lung carcinoma);
- Tumours that differ by etiological exposures (such as tumours differing by smoking status or other environmental exposures) or geographical region.

We will also use sequencing data from initiatives such as The Cancer Genome Atlas (TCGA) or the International Cancer Genome Consortium (ICGC) to complement in-house sequencing.

Detection of circulating tumour DNA in blood samples as a pre-diagnostic biomarker, and as a measure of disease progression

The presence of cell free DNA (cfDNA) in the blood circulation has been recognized for many decades, with particular high levels being observed in cancer patients. Among cfDNA in cancer patients is a proportion of circulating tumour DNA (ctDNA), typically of short length and thought to be due primarily to apoptosis or direct secretion of tumour DNA into the blood. ctDNA is of much interest given its potential to act as a non-invasive biomarker for a malignancy. Indeed, ctDNA has often been termed a 'liquid biopsy' with potential applications including identifying early stage disease, response to treatment and relapse. The proportion of ctDNA compared to the amount of cfDNA may be high (e.g. above 10%), especially for late stage disease or for large tumours, while for early stage disease this ratio is thought to be approximately 0.1–1%. Recent important developments that are likely to revolutionize this technique include (i) catalogues of gene regions that harbour frequent coding mutations for most common cancers from the TCGA and ICGC

initiatives, and (ii) the potential to conduct ultradeep and accurate multiplex sequencing (e.g. in excess of 5000 fold per base pair coverage) on cfDNA, in order to identify minute quantities of ctDNA (down to 0.02% of cfDNA) along with quality control methods that limit false positive results.

We propose to investigate, for a series of cancers for which we have extensive diagnostic and pre-diagnostic samples, to what extent gene mutations identified in the tumour are also identifiable in cfDNA from blood samples collected (i) at the time of diagnosis, and (ii) collected before diagnosis. Also, if ctDNA are identifiable before diagnosis, how many years prior to diagnosis is this possible? GEN proposals are being developed for lung cancer, renal tumours and head and neck cancers.

External funding is required to undertake these projects, although the input from the Scientific Council would be appreciated on the general design, the competitiveness of such studies, and the utility of ongoing work to build the bio-repositories that allow such studies (including the collection of post-diagnostic blood samples).