I4Cferm - Parental occupation in farming and childhood cancer risk in the International Childhood Cancer Cohort Consortium (I4C)

Scientific description

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I4Cferm objectives

Our overall objective is to investigate if parental occupations in different types of farming and parental use of pesticides are associated with increased risk of childhood cancer in their offspring.

The specific aims are to:

− Evaluate the risk of childhood cancer associated with parental occupation in farming.
  
  o Compare childhood cancer incidence (primarily main sub-types of leukaemia, lymphomas and brain cancer) in the offspring of parents working in field crop farming, livestock (beef, sheep, pig, fur-bearing), dairy, poultry, horticultural, vegetable, and sugar-cane farming, with the incidence among the children born to parents who had never been employed in farming.
  
  o In a nested case-control design, estimate the relative risk of childhood cancer associated with parental occupation in farming, and where possible assess associations separately for different types of farming and specifically of exposure to pesticides.

− Evaluate the risk of childhood cancer associated with maternal and paternal use of pesticides during pregnancy.
  
  o Among mothers and fathers, assess self-reported use of pesticides at home and at work, with details on frequency of use by type of pesticide, and compare with the type and frequency reported in various case-control studies.
  
  o Evaluate the risk of childhood cancer associated with the use of pesticides at home and at work, while adjusting for potential confounders.

− Assess whether the risk of childhood cancer associated with parental exposure to occupation as a farmer and pesticides vary by exposure time-windows (preconception, prenatal, and postnatal)
Originality of the I4Cferm project

The proposed project I4Cferm is a study within the International Childhood Cancer Cohort Consortium (I4C); initiated in 2005 with the explicit objective to obtain prospective evidence on potential causes of childhood cancer, and has for this purpose assembled mother and child cohort studies from around the world (Brown et al. 2007). I4C was established because no individual cohort study is sufficiently large to evaluate the roles of environmental risk factors in the development of different childhood cancers in a satisfactory manner. Retrospective case-control epidemiological studies have thus far been the principal design used to examine the association of environmental exposures with childhood cancer. Potential problems with case-control studies include differential parental recall of cases compared with controls; the prolonged period of recall between the relevant times of exposure to the outcome; higher participation rates by control parents of higher socio-economic and educational status than case parents of lower education resulting in potential selection and response bias. In the cohort design, collection of exposure information occurs prior to onset of the disease, which eliminates the differential recall resulting from the effect of a subsequent condition or event. Thus, with a prospective design and by merging data from many different studies we assemble a sufficient sample size and overcome inherent limitations of retrospective case-control studies in childhood cancer.

Concern that parental pesticide exposure may increase risk of cancer in their offspring is not new and led to the initiation of (i) various case-control studies, particularly in areas with very high pesticide application as in California (Scelo et al. 2009) and (ii) smaller cohorts of heavily exposed populations such as Vietnam war veterans who had been exposed to Agent Orange (Stone 2007). However the findings from these studies, although suggestive of an increased childhood cancer risk associated with parental pesticide exposure, remain controversial. The major reason for this is that although case-control studies do with some consistency show moderate risk increases especially for leukaemia, cohort studies show weaker associations. Reporting bias may lead to inflation of relative risk estimates in questionnaire-based case-control studies. Collapsing broad exposure and cancer sites together through record linkage in cohort studies may cause dilution of associations. I4C now offers the unique opportunity to analyze more detailed exposure data collected in a prospective setting, and I4Cferm will be the first project to make use of data of the I4C consortium comprising more than 500,000 children.

Very few modifiable risk factors for childhood cancer have been established and confirming or refuting the potential association with parental pesticide exposure would lead directly to primary prevention recommendations of a grave disease affecting children and their families.
The I4Cferm project is undertaken by a strong group of scientists with extensive experience in research on childhood cancer and occupational epidemiology, and is fully supported by the I4C steering committee and the sub-group “Environment and childhood cancer” within I4C, see enclosed letters.

**Scientific context**

Childhood cancer is the most common cause of death due to disease and the second most common cause of death in children, second only to accidents in developed countries. Significant advances have been made in the treatment of childhood cancer leading to increases in the five-year survival rate for all childhood cancers from 58.1% in 1975-1977 to 79.6% in 1996-2003. Despite this, the mortality, morbidity, and associated emotional and economic costs are substantial (Savage and Schuz 2011).

The most common types of pediatric cancer are leukaemia (27%) and central nervous system malignancies (18%). Acute lymphocytic leukaemia (ALL) comprises more than 75% of all pediatric leukemia and 21% of all pediatric cancer. The other childhood tumors consist of a heterogeneous group of malignancies including Hodgkin (7%) and non-Hodgkin lymphoma (NHL) (6%), neuroblastoma (5%), bone and soft-tissue sarcomas (11%), germ cell tumors (7%), retinoblastoma (2%), Wilms's tumor (4%) and others (Buka et al. 2007).

In Europe in the 1990s, age-standardised incidence rates were 140 per million for children (0-14 years) and 157 per million for ages 0-19 years. The incidence is slightly higher in males and rates are also higher in children younger than 5 and older than 15 years of age. The incidence rates for the cancer subtypes are quite varied. Hodgkin lymphoma is seen more commonly in developed countries, and within those countries is more common in individuals with higher socioeconomic status. ALL incidence rates are highest in Costa Rica (overall incidence rate of 55 per million person-years), while much lower in Africa (13 per million). The incidence rates of ALL in developed countries are relatively similar (around 40 per million) and in most of them a small increase of less than 1% per year has been observed in the 1990s. ALL occurs more commonly in boys. It has also been found to be more common in white (41.6 per million) than black (25.8 per million) children in the U.S. In contrast, acute myelocytic leukaemia (AML) shows little international variation and no trends in recent time periods (Stelianova-Foucher et al. 2004; Belson et al. 2007; Bunin 2004).

The causes of childhood cancers are to a large extent unknown (Buffler et al. 2005). A few chromosomal and genetic conditions (Down syndrome, Li-Fraumeni syndrome, neurofibromatosis, Gorlin syndrome etc.) and exposure to high-dose ionizing radiation are confirmed risk factors but explain only a small percentage (<10%) of all cases. A number of studies have reported an inverse association between childhood leukemia
and allergies (Dahl et al. 2009), delayed exposure to early childhood infections and daycare attendance (Chang et al. 2009; Greaves and Buffler 2009) and prolonged breast feeding. Promising hypotheses have been studied including history of maternal infections around the time of pregnancy, paternal preconception smoking and postnatal environmental tobacco smoke (ETS), and parental exposure to chemicals, but without conclusive evidence (Kwan et al. 2007; Brown et al. 2007). Residential exposures to low-dose ionizing radiations, extremely low frequency electromagnetic fields, pesticides and traffic exhaust are also suggested as risk factors in childhood leukemia. Very few studies are published on gene-environment interactions yet, but many are in progress. The Childhood Leukemia International Consortium (CLIC) brings together the investigators of case-control studies on childhood leukemia to better analyze and evaluate the various ongoing hypotheses. Works on other tumors are still less developed, although an international case-control study on Embryonal Tumors coordinated by IARC is being set up.

Overall, case–control studies published in the last decade have reported positive associations with home use of insecticides, mostly before the child's birth, while findings for herbicides are mixed (Ma et al. 2002; Menegaux et al. 2006; Metayer and Buffler 2008; Rudant et al. 2007; Rull et al. 2009; Ward et al. 2009). A better characterization of children's exposures to pesticides at home, for example the timing and the location of exposure, is critical to the evaluation of childhood leukemia risk (Ma et al. 2002).

The above evidence comes mainly from case-control studies with inherent potential problems of selection and recall bias. There exist prospective studies of infants and children to study environmental and genetic determinants of diseases in children, such as asthma and behavior abnormalities (Brown et al. 2007). These studies are often large (>100,000 subjects) and adequately powered to examine their main outcomes of interest, but none of the individual studies are sufficiently large to examine the association between exposures and rare diseases such as childhood cancer. One of them is the comprehensive French ELFE study, which has just started, and covers a large a variety of questions on the social, lifestyle, psychological, educational, physical and chemical environments, and many outcomes including growth and health.

It is well recognized that the first step to prevent cancer is to identify its causes so that health agencies can take action to prevent avoidable exposures and people can make conscious choices that will reduce their exposure to cancer-causing agents. It is therefore important to try to replicate the earlier findings from case control studies on the role of parental exposures in different types of agricultural work and residential use and its potential association with the development of childhood cancer.

The International Childhood Cancer Cohort Consortium (I4C) provides a cost-effective opportunity to study parental occupational exposure in different categories of agricultural work and farming in a prospective design and with sufficient power to detect small risks. The proposed study is well in line with AXE 2 : Mise en relation des
expositions et des effets sur la santé; PEST.1 : Identifier des populations vulnérables. It also represents a unique chance to study residential exposures to pesticides using information collected shortly after the exposure, and before the diagnosis of cancer.

**Methodology**

*Study population:* The proposed study is a sub-study within the recently established I4C. Consequently, it is resource-efficient by having access to large studies without the extensive work to conduct the studies and collect the data. The I4C has a Steering Committee and several working groups, notably the Environmental Working Group. The proposed project was introduced to this Committee during a conference call on April 4, 2011, and since the proposed study is the first of many anticipated studies it was agreed that the generic data harmonization and pooling should be carried out by the coordinating bodies of I4C, and with separate funding. Letters from the relevant institutes showing their support for this project are enclosed.

The Danish National Birth Cohort (97,000 children), the Norwegian Mother and Child Cohort Study (108,000 children), the Tasmanian Infant Health Survey (10,600 children), and the Avon Longitudinal Study of Parents and Children (14,000 children) represent smallest set of studies that will be included in these analyses, already large, but the number of studies is most certainly expected to increase substantially. More cohort studies, such as the Jerusalem Perinatal Study (92,000), Spanish Environment and Childhood Research Network composed of seven small birth cohorts (3,000 children), and Birth Defects Surveillance System for the Collaborative Project China (245,000), are expected to join the proposed study. It was the explicit objective when establishing I4C to study risk factors for rare diseases that cannot be studied in individual studies, hence the I4C Steering group and we are convinced every study having eligible data will participate. We believe that the commitment of contributing studies is large as demonstrated by their participation in the 3 I4C meetings, the latest held in 2009 at the International Agency for Research on Cancer (IARC) in Lyon. IARC has longstanding experience of working with large consortia; the common practise is that cohorts that contribute data to a particular project are entitled to scientific involvement and authorship of manuscripts deriving from the study. Investigators are indeed often motivated to participate in such studies by the possibility to publish in journals with higher impact factors than would be possible with results from individual studies.

**Outcomes:** The risk associated with different types of farming will be assessed in relation to the main sub-types of leukaemia, lymphomas, brain tumours and other types of solid tumours, while controlling for potential confounders.

**Exposure assessment:** Different time-windows of maternal- and paternal exposure corresponding to the preconception, i.e. the 3 month preceding the index pregnancy,
the prenatal gestational period, and postnatal periods. The risk associated with parent’s self-reported use of pesticides at home (mainly insecticides) or at work will also be assessed in relation to the main sub-types of leukaemia, lymphomas and brain tumours. In addition, we will compare the types and frequency of use, with data from the case-control studies carried out during same or close periods and countries.

Job and industry classifications differ in the various studies. Two alternatives should be considered: 1) adapt automatic conversion tables from national classification systems to one international classification (ISCO-68, ISIC-rev2) used in the consortiums on occupational exposures, several exist already and others would need to be developed; 2) identify the jobs of interest in each classification and manually recode those jobs to ISCO-68, ISIC-rev2.

In the nested case-control study, we will select all cases and a sub-sample of controls for conducting a detailed revision of self reported use of pesticides at home and at work. The controls should be matched to cases by age, sex and country.

The International standard Classification of Occupations (ISCO-68) was chosen because it allows identifying farmers and agricultural- and husbandry workers, and specialized workers involved in field crop, livestock (beef, sheep, pig, fur-bearing), dairy, poultry, horticultural, vegetable, wheat, cotton, rice, and sugar-cane farming.

The proposed approach could later be applied to other occupations (e.g. painters) and associated exposures (e.g. organic solvents, polycyclic aromatic hydrocarbons).

Parental domestic use of pesticides reported in the participating cohorts will be described and detailed as far as possible in terms of target, frequency and period of use. Its relationship with parental education, occupation, lifestyle and rural or urban housing, size of family and other demographic characteristics will also be described by period and country, before the analysis of its relationships with childhood cancer.

Statistical Power: The power of the study is determined by the prevalence of exposure and the strength of the association. We expect the risk estimate to be <2. The prevalence of exposure varies largely and will depend on which cohorts participate. In one of the on-going projects at IARC (SYNERGY) the prevalence of ever employment in farming ranged between 3% in the United Kingdom and 29% in Hungary and overall was 12.4%. The sample size needed for childhood leukaemia with a statistical power of 80% to detect an OR of 1.5 and with an exposure prevalence of 15% would be ~446,600 children, while an OR of 2 would require only ~330,000 children even with a exposure prevalence of 5%. Thus, this project reaches a sufficiently large sample size to adequately study ALL and AML, even if only the minimum number of cohorts who are also represented in the Steering Group will participate.
Description of collaborators and responsibilities

The proposed study is a prospective pooled cohort study within the I4C consortium. Joining this consortium included a commitment to provide data for such pooled analysis, if approved by the Steering Group which is the case for the present proposal, although the individual investigators will again need separate invitations for each project. I4C investigators will therefore be solicited by e-mail comprising a description of the project, the responsibilities of all collaborators, and the expected results in terms of publications. The e-mail will also contain the list of variables required for the analyses. We will collect data related to the childhood cancer, the child’s birth characteristics, e.g. birth order and breastfeeding, parental education, demographics, smoking habits, occupational and residential histories, pesticide exposure before, during and after pregnancy. A memorandum of understanding (MOU) will be established between the responsible investigator of each cohort and the steering committee of I4C before the data is transferred from the cohorts to MCRI.

IARC and INSERM will undertake conference calls when necessary with the other partners.

The study will be based on already collected data and has therefore all necessary ethical approval and data protection measures in place. Thus, no contract with study subjects or their parents will take place. We will ensure that the project will also be reviewed by the IARC Ethics Committee (IEC).

The analyses will include a descriptive phase. Then childhood cancer incidence between exposed and unexposed children in different exposure time windows will be performed. Nested case-control studies will also be performed so that detailed analyses could be done on smaller samples in parallel to the evaluation of the exposures on the whole cohorts.

One or two manuscripts are foreseen to be published in peer-reviewed journals. All created and harmonized variables will be returned to the I4C consortium, and will be accessible and valuable for forthcoming research proposals in I4C.

The project will strengthen the role of the French partner in the I4C and also the collaboration between INSERM and IARC, particularly since it is anticipated that this project will be followed by further activities within the I4C. The academic and scientific exchange between the leading institutions in France, the US, Australia and Spain will be substantial and providing young researchers opportunities for international networking which is key for the epidemiology of rare diseases.

Here below follows a description of the participating research teams.
**The International Agency for Research on Cancer (IARC)**

IARC’s mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer prevention and control. IARC is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. IARC has a long lasting experience in coordinating international studies and pooling data.

Dr Ann Olsson is scientist in the Section of Environment and Radiation at IARC. Her main interests are occupational cancer epidemiology and exposure assessment and she has been actively involved in the coordination of several large IARC studies in the last years. Dr Olsson has worked in low-income countries in Central America and Africa and has published results from the IARC multi-center study on lung cancer in Central and Eastern Europe, the IARC nested case-control of lung cancer among European asphalt workers, and SYNERGY – a pooling project of large case-control studies initiated for studying joint effects of occupational carcinogens.

Dr Joachim Schüz is Head of the Section of Environment and Radiation at IARC. Throughout his career, Dr Schüz worked also on possible causes of childhood cancer. The topic of his habilitation was “Epidemiology of childhood leukaemia” and included a variety of possible risk factors, including pesticides, and until now three of his PhD students graduated on childhood cancer epidemiology. Dr Schüz became member of the I4C in 2007. In most recent years, Dr Schüz was principal investigator of several childhood cancer studies, including a multinational case-control study on brain tumours in teenagers and adolescents, a Nordic register-based case-control study on birth characteristics and solid tumours in children, a study on broadcast transmitters and childhood leukaemia in Germany, pooled analyses of case-control studies on magnetic fields and childhood leukaemia risk and survival, and a study on space-time clustering of childhood leukaemia in Germany and Denmark.

Dr Kurt Straif is Head of the Section of IARC Monographs at IARC. After six years as a clinical fellow in internal medicine/hemato-oncology and collaboration on several randomized controlled trials on the treatment of leukemias, Dr Straif’s research focused on occupational and environmental risk factors for cancer, first as an assistant professor of occupational and environmental medicine, then as an associate professor and head of a unit of occupational and cancer epidemiology. Dr Straif was principal investigator of several cohort and case-control studies on occupational and environmental risk factors for cancer, including his role of principal investigator of the IARC-coordinated SYNERGY project, a pooling of 15 case-control studies from Europe, North America and Australia. One of the major tasks of this project was the harmonisation of coding of life-time occupational histories as recorded by the individual studies in applying their respective national coding systems. For the last ten years Dr. Straif has also been the senior epidemiologist of the IARC Monographs programme.
IARC will coordinate the proposed study; prepare the e-mails, define and request the relevant data from the cohorts in close collaboration with the I4C steering committee, organize telephone conferences with the other partners as often as needed, and meetings with INSERM at least one time per year. IARC will furthermore conduct the analyses, write up results, and report to ANSES.

**l’Institut national de la santé et de la recherche médicale (INSERM)**

Within INSERM’s, the Center of research in Epidemiology and Population Health, UMR-S1018 Health includes 11 research teams, who cover the epidemiology of several chronic diseases. Team 6 is devoted to environmental epidemiology of cancer.

Dr Jacqueline Clavel is physician and epidemiologist, and Head of the Inserm research team of Environmental epidemiology of cancer since 2006. She has been developing a program on childhood cancers for more than 15 years. She set up and conducts the French national registry of childhood blood malignancies, and carried out several case-control studies on childhood cancer environmental and genetic risk factors. She is responsible of the cancer group in the Elfe study. The group responsible for the evaluation of environmental exposures in Elfe (Céline Boudet from Ineris, Stéphanie Vandentorren and Christophe Declercq, InVS) will also be consulted and associated to the reflexion on residential exposures to pesticides.

INSERM will collaborate closely with IARC in conducting this study, and will supervise the harmonization and pooling of the data related to self-reported pesticide use at home and at work, and write up the findings from that area.

**National Cancer Institute (NCI)**

NCI in Bethesda, MD, is the Federal Government's principal agency for cancer research and training in the US. NCI (Dr Martha Linet) is one of the initiators of I4C, contributes the National Children’s Study, and play an important role in the steering committee and in moving forward the I4C consortium.

NCI is responsible for the harmonization of disease data, as different countries are likely to have used different disease classifications.

**Murdoch Childrens Research Institute (MCRI)**

MCRI in Melbourne, Australia, is playing a key role in I4C and has had a major role in the study concept and planning and is acting as the principle data coordinating centre in I4C. The Coordinating Centre is under the direction of Professor Terry Dwyer and includes Dr Gabriella Tikellis as the Data Coordinator.
MCRI is responsible for establishing the MOU, to receive the data, and to pool most of the core variables; and will re-distribute data as agreed to the other partners.

**Center for Research in Environmental Epidemiology (CREAL)**

CREAL in Barcelona, Spain participates in the steering committee (Professor Manolis Kogevinas) and also contributes with data from two cohorts. CREAL (Dr Martine Vrijheid) is actively involved in the development of the protocols, specifically for environmental exposures and has considerable experience from pooling occupational data in the ENRIECO study.

CREAL is involved in pooling of occupational data in Europe and will collaborate closely with IARC in the re-classification of harmonization and pooling of the occupational data.

**Potential benefits to the subjects and expected results regarding environmental risk management**

The first and necessary step for controlling cancer is to identify risk factors for developing cancer. Until today the causes of childhood cancers are to a large extent unknown. If this study indicates an association between parental exposure in agriculture and childhood cancer, and if there is a pattern with regard to type of farming, country or region, or time period, it could provide indications of what exposure is responsible for the increased risk. Such findings may contribute to an understanding of possible mechanisms for the carcinogenicity in children and how to limit/avoid exposure in the future.

The proposal study will also move forward the I4C consortium as a whole by realizing the pooling of data. This will benefit further research on childhood cancer in general and thereby all children and their parents indirectly.
References


