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COHORT PROFILE

Cohort Profile: The International Childhood Cancer Cohort Consortium (I4C)

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How did the study come about?

Globally, a number of large infant/child prospective studies have been launched to examine environmental and genetic determinants of common diseases of children, such as asthma, developmental delay and behaviour abnormalities, as well as the consequences of early exposure for adult diseases. While several of these studies are relatively very large—over 100 000 subjects—and are adequately powered to examine their principal outcomes of interest, none of the individual studies are of sufficient size to examine the relationship between exposures they are measuring and rare diseases such as childhood cancer. To date, the few established risk factors for specific forms of childhood cancer have largely been identified in case-control studies. Yet, despite many such investigations evaluating postulated risk factors for paediatric malignancies during the past five decades, few consistently established aetiologic factors are known. Recent review papers[1–4] have summarized many promising hypotheses, including pre-natal and post-natal exposure to pesticides, maternal and early infancy dietary factors, paternal pre-conception occupational exposures and smoking, the interplay of maternal or early postnatal immune system handling of common infections, determinants of high birth weight and other factors.

Employment of prospective cohort follow-up of children and adolescents from pregnancy or birth using cohort or nested case-cohort designs, in conjunction with prospective biological sample collection, offers promising opportunities for advancing knowledge of aetiology. This is a result of improved assessment of parental and early life exposures, measurement of biological samples for pre-diagnostic effects, clarification of the temporal relationship between exposure and outcome, reduction of differential recall between parents of cases vs controls and the prospect of understanding the determinants of selection bias.[5]

The concept of bringing the various cohorts of infants and children together in an international collaboration arose during planning for the National Children's Study (NCS), a childhood cohort study in the United States of 100 000 participants.[6] Participants at a 2004 workshop[7] convened to consider whether this cohort would be of sufficient size to include cancer as a feasible outcome; they concluded that this study would have insufficient power for this purpose due to the rarity of all forms of childhood cancer. However, a collaboration of the existing and planned large childhood cohorts globally might provide the power necessary to obtain prospective evidence on potential causes of childhood cancer.[8] This idea was developed further and a proposal was presented to the National Institute for Child Health and Human Development (NICHD), National Cancer Institute (NCI) and the US Environmental Protection Agency (EPA). Along with funding support from the National Institute of Health's Office of Rare Diseases, these organizations held a workshop in 2005,[9] bringing together representatives from 11 cohorts in four continents, accounting for 700 000 children (Table 1), as well as experts in epidemiology, paediatric oncology, genetics, toxicology and other disciplines. Its purpose was to discuss the development of an international collaboration among children's cohort studies to enable investigations of

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Table 1 Summary of Childhood Longitudinal Studies. This table includes cohorts present during the 2005 workshop. Additional childhood longitudinal studies collecting relevant data were either unable to attend the workshop or are in the early planning stages of their study, for example in Canada, Brazil, New Zealand, Mexico, Korea, Japan and Germany

Study	Country	Years of Recruitment	Age at enrolment	Study sample size
Jerusalem Perinatal Study[10,11]	Israel	1964–1976	At birth	92 408 births
Tasmanian Infant Health Survey (TIHS)[12]	Australia	1988–1995	Post-natal (4 days)	10 627 babies
Avon Longitudinal Study of Parents and Children (ALSPAC)[8]	U.K.	1990–1992	Pre-natal	14 541 pregnancies, 14062 live births
Birth Defects Surveillance System for the Collaborative Project China (BDSS-China)[13]	China	1993–1995	Pre-conception, pre-natal	247 831
Danish National Birth Cohort (DNBC)[14]	Denmark	1996–2002	Pre-natal	101 042 pregnancies
Norwegian Mother and Child Cohort Study (MoBa)[15]	Norway	1999–2007	Pre-natal	100 000 planned (77 000 by Oct 2006)[16]
Infancia y Medio Ambiente (INMA)[17]	Spain	2001–2005	Pre-natal	3100 planned (3500 by Oct 2006)[18]
China Children and Families Cohort Study (CCFC)	China	2006–2007	Pre-conception, pre-natal	300 000 planned
Born in Bradford[19]	U.K.	2006–2008	At birth	10 000 planned
National Children's Study (NCS)[9]	U.S.	2008–2012	Pre-conception, pre-natal	100 000 planned
Etude Longitudinale Française depuis l'enfance (ELFE)[20]	France	2008–2009	At birth	20 000 planned

Table 2 Sample sizes needed for a statistical power of 80% to detect associations for an OR of 1.5 and 2.0 with varying exposure rates with acute leukaemia (ALL and AML)

Exposure (%)	Minimum OR detectable	Sample size required
5	1.5	1 180 059
15	1.5	446 633
30	1.5	277 781
5	2	328 992
15	2	125 813
30	2	79 594

the role of various environmental and genetic exposures in the aetiology of childhood cancer.

The first critical determination at this meeting was how many subjects would be needed to evaluate postulated statistical associations between environmental exposures and childhood cancers. Based on age-specific childhood cancer incidence data for 13 geographic areas in the US from 1993 to 2002 from the NCI covering 14% of the population,[21] for every 100 000 study participants followed from birth, 221 total cancers would be expected before age 15. Based on these data, the number of children by cancer type would be in the order of: acute lymphoid leukaemia (ALL): $n = 57$; acute myelocytic leukaemia (AML) or other leukaemias: $n = 14$; central nervous system and brain: $n = 44$; and all other cancers: $n = 106$.

Table 2 summarizes the cohort size that would be needed to reliably detect associations between a given exposure and leukaemia, the most common childhood cancer. These sample size calculations are based on population-based US paediatric cancer rates for the year 2000, standardized to the 2000 US Standard Population.[22] For an exposure affecting 5% of the population, more than 1 million participants would be needed to obtain the power to detect associations in which incidence of acute leukaemia was 50% higher among those exposed [e.g. an odds ratio (OR) of 1.5], while for a more common exposure of 15% the sample required would drop to around 450 000 participants.

Another important question presented at the 2005 meeting was whether it would be possible to pool data from questionnaires developed by each cohort for potentially different purposes. A pilot investigation evaluated data from the Avon Longitudinal Study of Parents and Children (ALSPAC)[8] and the Tasmanian Infant Health Study (TIHS)[15] to assess the feasibility of combining data collected in a somewhat different fashion for selected exposures across studies. We found that despite the independent design and somewhat different wording of questions on the same variables, the data were sufficiently similar to enable the limited data sets examined to be combined. Detailed examination of protocols from several of the larger studies—the NCS,[9] Danish National Birth Cohort (DNBC),[17] and the Norwegian Mother and Child Study (MoBa)[18]—revealed that each had collected or were planning to collect questionnaire data and biospecimens concerning key exposures relevant to childhood leukaemia and that pooling was likely to be feasible.

Following the discussions, workshop participants agreed to establish a consortium of studies referred to as the *International Childhood Cancer Cohort Consortium* (I4C). A steering committee was established comprised of primary investigators of cohorts (NCS, TIHS, DNBC, and the China Family and Children Cohort Study), along with representation from NICHD, NCI and EPA to assist with consortium activities and international collaboration. The experience of the NCI in developing successful consortia, such as the International Lymphoma Epidemiology Consortium (InterLymph),[23,24] provides useful experience and guidance as the I4C proceeds.

A draft policies and procedures manual has been developed based on available models. This manual outlines the consortium's mission, goals, principles and governance such as criteria for membership, data sharing policies publications policies, and process issues. Working groups as well as an advisory committee will be established as necessary. To assist with communication and document management, the NCS has offered their web-based technology to facilitate communication and document management. Finally, the steering committee has been actively engaging investigators involved in conducting studies of other children's cohorts to join the consortium, whether these cohort studies are in the planning phases or already underway.

Figure 1 Geographical locations of the participating longitudinal cohorts

What does it cover?

Leukaemia, including ALL and AML, is the most common type of childhood cancer comprising approximately one-third of all childhood cancers in most Western populations. For this reason, the I4C will initially concentrate on conducting studies on the aetiology of childhood leukaemia.

A number of candidate hypotheses concerning environmental and biological factors with childhood leukaemia, for which there is supporting evidence, were discussed at the 2005 workshop. These factors included birth weight;[25] maternal folate acid intake and polymorphisms in genes controlling the enzyme methylene tetrahydrofolate reductase (MTHFR);[26,27] maternal or early childhood infection;[28] exposure of the mother to specific pesticides during pregnancy;[29] maternal pre-natal[30] and/or paternal pre-conception[31,32] cigarette smoking and chromosomal translocations present at birth.[33] Additional considerations also include parental age,[34–36] specifically paternal age,[37] and exposure to electromagnetic fields.[38]

Who is in the sample?

All large-scale prospective cohort studies examining the effects of the environment or genetics on children's health will be considered for inclusion in the I4C. The criteria for inclusion in the Consortium relate to size and scope of the cohort, type of exposure data collected and ability to ascertain childhood cancer incidence in the cohort. The cohort must ideally collect data from participants no later than the time of birth. They must also be able to ascertain in a complete way occurrence of childhood cancer and to include measures that cover the key hypotheses. The initial participating cohorts are those that attended the 2005 workshop (Figure 1, Table 1),[9] and will be expanded to participants of other cohorts as interest grows.

How often have they been followed up?

Each cohort will adhere to its own unique protocol, depending on their goals, purposes, hypotheses and available funding. Exposure measurements have or will be collected at varying intervals until varying ages. Birth Defects Surveillance for BMD-CDC Collaborative Project China (BDSS-China) had direct contact with participants prior to conception, through gestation, to 6 weeks of age,[16] at 4–6 years and at 10–12 years;[39] TIHS at ages 4 days, 4 weeks and 10 weeks of age;[15] the Jerusalem Perinatal Study through age 1 year;[40] ALSPAC during gestation, birth, 6 weeks, 6 months, 18 months, 3 years and 7 years; [8,41] DNBC at 12–16, 12, 24, 25 and 30 weeks gestation, birth, 6 months and 18 months of age;[17] MoBa at 13–17, 22 and 30 weeks gestation, 6 months, 18 months, 3 years and 7 years.[18] The protocols for the more recent studies are not yet definitive, although they generally plan for multiple points of contact from pre-conception through childhood.

Similarly, outcome assessment has or will occur until varying ages. Ideally, each cohort will be able to follow its participants to the age of adulthood (18 years of age) in order to capture all childhood cancers, and include measures on mothers concerning their pregnancy, on children at birth and during the first year of life, and intermittently thereafter. However, not all cohorts are planning for the same length of follow-up, or cannot be assured funding for decades of follow-up. INMA intends to follow-up the children until they are at least age 4 years,[20] MoBa until at least age 7 years,[18] BDSS-China until at least age 10–12 years,[42] ALSPAC until at least age 15 years,[44] DNBC to age 20 years,[17] and the NCS to age 21 years.[9] The Jerusalem Perinatal Study that began in 1964 has been able to follow up their initial births for up to 39 years of age.[43] The majority of childhood leukaemias occur by age five, so most studies will collect data during the relevant age period.

What will be measured?

The I4C is particularly interested in the association between environmental exposures, defined broadly, and childhood leukaemia. All participating cohort studies in the I4C have or will incorporate a number of exposure measures in their protocols (Table 3). These include: parental health measures (e.g. infection) and occupational, residential and lifestyle exposures (e.g. smoking, drug use, diet); and childhood health measures (e.g. growth and infection) and residential and lifestyle exposures (e.g. diet and chemical exposures). Data relevant to each of these hypotheses is or will be available from each of the largest cohorts and captured via questionnaires administered to mothers and via biospecimen collection from mothers during and after pregnancy and from the infant from birth onwards. Biospecimens collected may include, but will not

Table 3 Questions which pertain to the aetiology of acute child leukaemia from the DNBC, MoBa and ALSPAC birth cohorts

Phase	Measurements
Baseline	Paternal antenatal occupation
	Maternal antenatal occupation
	Paternal antenatal smoking/drug use
	Maternal antenatal smoking/drug use
	Maternal passive antenatal smoking
	Maternal antenatal dietary intake
	Maternal antenatal supplement intake
	Maternal antenatal infection
	Maternal antenatal sun exposure/Vitamin D intake
	Maternal antenatal radiation exposure
	Maternal antenatal pesticide and chemical exposure
Follow-up	Infant anthropometry
	Infant infections up to 1 year
	Infant radiation exposure up to 1 year
	Infant pesticide and chemical exposure up to 1 year
	Infant mixing with other people, siblings, day-care
	Infant sun exposure
	Infant feeding habits
	Infant dietary intake
Ongoing	Maternal postnatal occupation
	Paternal postnatal occupation
	Maternal postnatal smoking/drug use
	Paternal postnatal smoking/drug use
	Child's passive smoking
	Maternal biological samples
	Paternal biological samples
	Child's biological samples
	Child's atopy/asthma
	Maternal atopy/asthma
	Paternal atopy/asthma

be limited to, blood for genetic analysis, serology and chemical analysis, and urine for chemical analysis.

In addition to exposure data collection, a standardized case ascertainment form has been developed in order to collect outcome information from each cohort. This form is based on one recently developed by the International Agency for Research on Cancer.[42] The data will include leukaemia type (e.g. ALL, AML) and molecular subtype (ascertained from tumour tissues), the method utilized for case ascertainment (e.g. regional or national cancer registry, hospital record linkage) and age of onset.

What is the anticipated attrition?

The attrition rate has or will vary depending on the retention plan, funding, community attributes and many other factors of each cohort. While some studies may not have on-going exposure measurements, or study participants may not continue to comply with the exposure assessment protocol, they may still be able to capture cancer incidence on study participants if the country has well-established mandatory cancer registries. Loss to follow up for the Jerusalem study is estimated at 0.7%;[3] BDSS-China has retained 90% of the original cohort;[42] DNBC and MoBa had approximately a 75% response rate at 18 months after delivery;[17,18] ALSPAC about 81% response rate 42 months after delivery[44] and for TIHS, the level of attrition is generally 78–83% by age 7 years, depending on the individual follow-up study.[43] The I4C will encourage and maintain individual cohort's participation in the consortium through coordination, communication and support for the collaborative effort as described above.

What will be the major areas of research?

The I4C will focus on questions that this collaboration can best answer and that require longitudinal data collection in very large samples. Initial studies will use available prospective data to assess exposures postulated to cause specific types of childhood cancer, as suggested by past work based primarily on case-control studies. The first two hypotheses proposed for analysis will examine the relationships between chromosomal translocation present at birth with childhood leukaemia, and folic acid supplementation during pregnancy and childhood leukaemia.

Chromosomal Rearrangements

More than 25% of childhood leukaemia cases exhibit non-random chromosome translocations in the leukaemic cells,[44] and studies of chromosomal translocations in cord blood suggest that the causal pathway may commence *in utero* with evidence that these arise during fetal life.[36,45,46] The ability of the I4C to contribute new information will depend on the type and availability of the relevant biological specimens and a biospecimen audit will be required. For example, suitably stored RNA would be of value. Given that these translocations have been observed to occur 100-fold more frequently than incidence of childhood leukaemia suggests that such translocations are not sufficient as causes of childhood leukaemia, but that (an) additional exposure(s) or host factor(s) are required. The relationship between the presence of translocations at birth interacting with additional exposures post-natally and subsequent leukaemia, have not been examined in epidemiological studies. Therefore, it is important to identify characteristics of children who appear to be at risk of developing cancer associated with a specific chromosomal marker, and whether specific environmental exposures may later trigger the cancer (e.g. delayed early life infection). It would be useful to assess whether the observed international variation in child leukaemia incidence may reflect primarily differences in post-natal events.

The data and biomarkers obtained will potentially provide i) the proportion of subjects with translocations and hyperdiploidy across the cohorts, ii) the incidence of ALL and AML among those with translocations and hyperdiploidy across the cohorts, and iii) the ratio of birth incidence of translocations to age-specific incidence of ALL and AML across the cohorts.

Folic Acid Supplementation and Genetic Polymorphisms

There is suggestive biological evidence that folate may be important in the aetiology of childhood leukaemia.[47] Polymorphisms in genes controlling the enzyme MTHFR may influence folate metabolism, and may play a significant role in modifying risk of childhood leukaemia.[29,30] Some ethnic populations have been found to have a higher prevalence of these MTHFR polymorphisms,[48–50] which may result in a higher incidence of childhood leukaemia. However, epidemiological studies provide only limited direct evidence to support the association between low maternal peri-conceptional folate supplementation and leukaemia in the offspring,[50] and introduction of folic acid into the diets of mothers appears not to have changed population incidence of ALL in infants.[51] Prospective data on large numbers of individuals may provide needed insight into whether maternal folate intake or MTHFR polymorphisms play a role in the development of childhood leukaemia.

What are the main strengths and weaknesses?

Retrospective case-control epidemiological studies have thus far been the principal strategy used to examine the association of environmental exposures with childhood cancer. This is due to the economy of case-control designs in studying rare diseases, such as childhood cancers. Potential problems with case-control studies include differential parental recall for cases compared with controls;[52,53] the prolonged period of recall from the exposure to the outcome;[54] higher participation rates by control parents of higher socio-economic and educational status than case parents resulting in potential selection[55] and response bias;[56] and the limited collection of biospecimens prior to diagnosis.[57]

With a prospective design, some of the inherent limitations of childhood cancer retrospective case-control studies can be overcome. In the cohort design, collection of exposure information occurs prior to onset of serious health outcomes, thus eliminating the differential recall resulting from the effect of a subsequent condition or event, and follow-up studies are needed for all exposures that cannot be reconstructed back in time. Cohort studies of pregnant women or very young children could also provide pre-disease data collection closer to the time period of aetiologic relevance, compared with parents reporting about those time periods years later. The opportunity for collection of biospecimens obtained prior to childhood cancer onset offers an opportunity to assess exposure measures before diagnosis and to compare an objective measure of an exposure with questionnaire responses about the exposure.

Prospective data on a large sample would specifically contribute, for example, to untangling whether the finding (based on self-reported parental pre-natal occupational exposures)[57] that estimated risk for leukaemia varies inversely with the time period between data collection and birth reflects an attenuation of recall over time or reflects the risk of leukaemia from those exposures at different ages. Furthermore, prospectively collected data, under some circumstances, may allow for more accurate analysis of the timing of certain exposures.[5–7] While collecting and analyzing vast amounts of information on all cohort members can be overly expensive and inefficient, this information can also be banked and analyzed in a nested case-control study.[58]

It is difficult to design and implement large longitudinal studies, and collaboration may provide valuable assistance to investigators planning new childhood cohort studies through discussions about new ideas, sharing study forms, providing advice about data collection and management, and preventing mis-steps. Early collaboration can also ensure similar data collection among new cohorts (e.g. CCFC, ELFE), with members of the I4C providing input to encourage common protocol elements to be incorporated to enable new studies to participate in studies of childhood cancer aetiology. Finally, the potential for participating in an international consortium may provide support for those applying for funding to start up a new childhood cohort.

Because the I4C is an international project bringing together ongoing and new cohort studies, a number of challenges will arise. These include variation in available capacity and technology, questionnaire data and biospecimen collection methods, terminology and diagnosis and ethical requirements. Moreover, participating studies are at different stages and thus may not have collected all desired data and biospecimens. Nonetheless, because these studies have or will collect data on the same, key, exposure domains, this collaboration of cohorts from multiple populations may provide valuable insights concerning the causes of childhood leukaemia, and could contribute significantly to the evidence base for the improvement of preventive measures and treatment. Moreover, the consortium holds the promise not only of helping to answer several questions concerning the association between early exposures and childhood cancer but could be a model for other rare childhood outcomes.

Can I get access to the data? Where can I find out more?

Mechanisms for data sharing to enable pooled analyses across different centres are currently being developed. The exact nature of this data repository has not yet been determined, although the data will likely be located at one collaborating site and accessible to all collaborating members. Access to cohort data can be achieved through permission of the I4C Steering Committee.

Only analyses agreed to by the I4C's steering committee can be undertaken using the collaborative data. The process for gaining approval for data analysis for research projects to test specific hypotheses involving I4C member Principal Investigators and other researchers is under development. Institutional review board clearance for accessing data will be necessary if individual identifiers such as date of birth are provided to a researcher; alternatively, data might be provided in the form grouped, rather than individual-level data. The Steering Committee may consider posting a limited data set on the web with a mechanism for access to the more complete data if adequate human subjects protections can be

put in place. Ultimately, the goal is to provide public access to the data with appropriate safety measures to protect confidentiality.

Currently, information regarding the I4C is available online at http://www.nationalchildrensstudy.gov/get_involved/int_involvement.

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