

**THE INTERNATIONAL CHILDHOOD CANCER COHORT CONSORTIUM (I4C):
A RESEARCH PLATFORM OF PROSPECTIVE COHORTS FOR STUDYING THE ETIOLOGY OF
CHILDHOOD CANCERS**

Gabriella Tikellis^a, Terence Dwyer^{a,b}, Ora Paltiel^c, Gary S. Phillips^d, Stanley Lemeshow^e, Jean Golding^f, Kate Northstone^f, Andy Boyd^f, Sjurdur Olsen^g, Akram Ghantous^h, Zdenko Herceg^h, Mary H. Wardⁱ, Siri E. Håberg^j, Per Magnus^j, Jørn Olsen^k, Marin Ström^g, Somdat Mahabir^l, Rena R. Jonesⁱ, Anne-Louise Ponsonby^a, Jacqueline Clavel^m, Marie Aline Charles^m, Edwin Trevathanⁿ, Zhengmin (Min) Qian^o, Milena M. Maule^p, Xiu Qiu^q, Yun-Chul Hong^r, Silvia Brandelise^s, Eve Roman^t, Melissa Wake^a, Jian-Rong He^{q,u}, Martha S. Linet^v *on behalf of the International Childhood Cancer Cohort Consortium.*

a, Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, UK.

Affiliations

- a. Population Epidemiology, Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, Melbourne, AUSTRALIA
- b. The George Institute for Global Health, University of Oxford, UK
- c. Braun School of Public Health, Hadassah-Hebrew University Medical Center, Jerusalem, ISRAEL
- d. Center for Biostatistics, Department of Biomedical Informatics, Ohio State University, Columbus, Ohio, USA (*retired*).
- e. Division of Biostatistics, College of Public Health, Ohio State University, Columbus, Ohio, USA
- f. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

- g. Centre for Fetal Programming, Department of Epidemiology Research, Statens Serum Institut, Copenhagen, DENMARK
- h. Epigenetics Group, International Agency for Research on Cancer, Lyon, FRANCE
- i. Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA
- j. Centre for Fertility and Health, Norwegian Institute of Public Health, NORWAY
- k. Department of Clinical Epidemiology, Aarhus University, Aarhus, DENMARK
- l. Division of Cancer Control and Population Sciences. National Cancer Institute, National Institutes of Health (NIH), Bethesda, Maryland, USA
- m. Institut National de la Santé et de la Recherche Médicale, Centre for Research in Epidemiology and Statistics Sorbonne Paris Cité, Villejuif, FRANCE
- n. Vanderbilt Institute for Global Health, Vanderbilt University Medical Center, Nashville, USA
- o. College for Public Health and Social Justice, Saint Louis University, Missouri, USA
- p. Cancer Epidemiology Unit, Department of Medical Sciences, University of Torino, Torino, ITALY
- q. Department of Woman and Child Health Care, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, CHINA
- r. Institute of Environmental Medicine, College of Medicine, Seoul National University, SOUTH KOREA
- s. Boldrini Children's Center, Campinas, BRAZIL
- t. Epidemiology and Cancer Statistics Group, Health Sciences, York University, UNITED KINGDOM
- u. Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, UNITED KINGDOM

v. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda,
Maryland, USA

RUNNING TITLE: The I4C: A research platform for studying the etiology of childhood cancers

Corresponding author:

Dr. Gabriella Tikellis

Murdoch Children's Research Institute

The Royal Children's Hospital

Flemington Road Parkville Victoria 3052

AUSTRALIA

Telephone: +61 4 08757251

Email: gabriella.tikellis@mcri.edu.au

Key words: International Childhood Cancer Cohort Consortium (I4C); birth cohort; leukemia;
childhood cancer; lifestyle factors; environmental exposures

Abbreviations

ALL	Acute lymphoblastic leukemia
ALSPAC	Avon Longitudinal Study of Parents and Children
AML	Acute myeloid leukemia
BIGCS	Born in Guangzhou Cohort Study
CATI	Computer-assisted Telephone Interviewing
CC	Childhood Cancer
CL	Childhood leukemia
CLIC	Childhood Leukemia International Consortium
CNS	Central Nervous System
CPP	Collaborative Perinatal Project
DNBC	Danish National Birth Cohort
ELFE	Etude Longitudinale Française depuis l'enfance
GenV	Generation Victoria Cohort
GIS	Geographic Information System
IARC	International Agency for Research on Cancer
IBCC	International Biospecimen Coordinating Center
I4C	International Childhood Cancer Cohort Consortium
ICD	International Classification of Diseases
IDCC	International Data Coordinating Center
IRB	Institutional Review Board
JECS	Japan Environment and Children's Study
JPS	Jerusalem Perinatal Study
Ko-CHENS	Korean Children's Environmental Health Study

MCRI	Murdoch Children's Research Institute
MoBa	Norwegian Mother and Child Cohort Study
NINFEA	Nascita ed Infanzia: gli Effetti dell'Ambiente
TBCS	Taiwan Birth Cohort Study
TIHS	Tasmanian Infant Health Study

ABSTRACT

Background: Childhood cancer is a rare but leading cause of morbidity and mortality.

Established risk factors, accounting for less than 10% of incidence, have been identified primarily from case-control studies. However recall, selection, and other potential biases impact interpretations particularly, for modest associations. A consortium of pregnancy and birth cohorts (I4C) was established to utilize prospective, pre-diagnostic exposure assessments and biological samples.

Methods: Eligibility criteria, follow-up methods and identification of pediatric cancer cases, are described for cohorts currently participating or planning future participation. Also described are exposure assessments, harmonization methods, biological samples potentially available for I4C research, the role of the I4C data and biospecimen coordinating centers, and statistical approaches used in the pooled analyses.

Results: Currently, six cohorts recruited over six decades (1950s – 2000s), contribute data on 388,120 mother-child pairs. Nine new cohorts from seven countries are anticipated to contribute data on 627,500 additional projected mother-child pairs within five years.

Harmonized data currently includes 20+ ‘core’ variables, with notable variability in mother/child characteristics within and across cohorts, reflecting, in part, secular changes in pregnancy and birth characteristics over the decades.

Conclusions: The I4C is the first cohort consortium to have published findings on pediatric cancer using harmonized variables across six pregnancy/birth cohorts. Projected increases in sample size, expanding sources of exposure data (e.g., linkages to environmental and administrative databases), incorporation of biological measures to clarify exposures and underlying molecular mechanisms, and forthcoming joint efforts to complement case-control studies offer the potential for breakthroughs in pediatric cancer etiologic research.

INTRODUCTION

While cancer in children and adolescents is rare worldwide, it remains a leading cause of morbidity and mortality despite notable improvements in survival [1]. Established risk factors include prenatal exposure to diagnostic x-rays [2], genetic syndromes [3], and high birthweight [4] that combined, account for less than 10% of childhood cancer (CC) incidence [5]. More recently, pooled case-control studies of childhood leukemia (CL) suggest modestly increased risks associated with residential painting and pesticide use and pre-labor caesarean delivery [6] [7] [8] and slightly decreased risks from day care attendance, extended breastfeeding, and maternal vitamin and folic acid supplement use [9] [10]. Known and suspected risk factors for CC [2] are briefly summarized in **Appendix A**.

Timing of exposure appears to be associated with variable CC risks, with prenatal and early postnatal periods being particularly vulnerable windows [2] [11]. Increasing recognition of etiologic differences by subtype [2] underscores the need for case-control studies evaluating large numbers of distinct CC entities. While well-designed case-control studies can yield valid estimates, inherent limitations such as recall bias (differential recall of past exposures by case versus control mothers), selection bias (differential participation according to characteristics such as educational level or exposure status of cases compared with controls) and reverse causality may affect risk estimates and interpretation.

To complement and address methodologic limitations of case-control studies, pooling of multiple pregnancy/birth cohorts such as those involved in the International Childhood Cancer Consortium (I4C), could verify case-control study findings, identifying new risk factors and identify mechanisms of carcinogenesis [12,13]. Biospecimens collected

prospectively are an advantage of prospective pregnancy/birth cohort studies for exploring CC etiology, although a few case-control studies have accessed archived pre-diagnostic newborn blood spots [14] or cord blood [15].

Our objective is to report on the progress made by the I4C, furthering the description of Brown et al [16], in developing a platform through a collaborative network that provides access to repeated exposure 'measurement' data and biospecimens. We also describe challenges and future directions including collaborations with a consortium of case-control studies.

METHODS

Overview, structure and operations

The overarching goal of the I4C is to understand the etiology and mechanistic underpinnings of CC by exploiting prospectively collected exposure and biomarker data. The I4C *Steering Committee* includes lead investigators from cohorts, clinicians, pediatric cancer epidemiologists, molecular epidemiologists, exposure assessment experts, and funders (<https://www.mcric.edu.au/research/projects/international-childhood-cancer-cohort-consortium-i4c/i4c-consortium>). An international data coordinating center (IDCC) at the Murdoch Children's Research Institute (MCRI) in Melbourne Australia houses the cohort data, manages data transfers, harmonizes variables, develops pooled datasets and provides scientific input, and ensures the confidentiality, privacy, and security of the data. Additionally, the International Biospecimen Coordinating Center (IBCC) at the International Agency for Research on Cancer (IARC) in Lyon, France, facilitates the pooling of biological samples. The I4C projects are conducted through *annual open scientific meetings and working groups attended by investigators from participating and additional emerging cohorts and other experts.*

Study populations

Eligibility criteria. Cohorts eligible for inclusion in the I4C need to recruit mothers during pregnancy or around delivery. Eligible cohorts must systematically ascertain cases of CC in the offspring and should include questionnaire and/or other exposure data that address key CC etiology-related hypotheses. The specific goals and original outcomes of the individual cohorts (e.g., pregnancy complications and /or serious chronic childhood conditions may vary, but critical data item include parental and offspring demographic, lifestyle, medical,

reproductive, environmental factors, and parental occupational information. **Specific responsibilities of newly joining or participating I4C cohorts include data sharing (and biospecimens- if available) for current and future proposals.**

Currently contributing cohorts. Six cohorts currently contribute data on cancer cases, exposure data and biospecimens (if available) as described in **Table 1a**; more details are available in the published cohort descriptions.

Data sharing

Data sharing and material transfer agreements for the I4C were developed and approved by MCRI Ethics Committee and sent to cohort investigators for approval by their Ethics Committees. Only anonymized data were requested (see **Appendix B**).

Follow-up methods

Strategies and time points for follow-up varied (**Table 1a**). Follow-up methods included postal mailings of self-administered questionnaires (ALSPAC, DNBC, MoBa), phone-administered questionnaires (DNBC, TIHS), letters to primary care physicians requesting medical records (CPP), field staff visits to extract medical record data (CPP, ALSPAC, JPP, TIHS), home visits (TIHS) and/or linkages with hospital and other national registry data (ALSPAC, DNBC, MoBa, JPS, TIHS). **Follow-up response rates for the six participating cohorts were around 60-70% for most cohorts ≥ 7 years post-natal.**

CC case ascertainment and classification

Ascertainment. For participating cohorts, identification of CC cases has been reliant on linkage to national (ALSPAC, DNBC, MoBa and JPS) or state (TIHS) cancer registries except for CPP. The latter relied on medical records [17] and indirect methods [18]. Each potential cancer diagnosis in the CPP was reviewed by two board-certified pediatricians.

Classification. To date, age at diagnosis for CC has been < 15 years, but going forward, will extend to < 20 years. Tumors were classified into six major groups based on the International Classification of Diseases for Oncology (ICD-O) Third Edition [19]. For cohorts with IRB approval to access more detailed information, the following was provided: -gender, date of birth, date of diagnosis, ICD-10 code, 3-digit ICD-O-3 topographic code and 4-digit ICD-O-3 morphology code. ICD-O-3 morphology codes for leukemia included 9800-9948, gliomas 9380-9480 and lymphomas 9590-9729. From this information, the IDCC used the following six groupings: any cancer, any leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), any lymphomas, any central nervous system (CNS)/brain tumor, or other cancers. Due to small numbers and confidentiality issues, ALSPAC provided only any cancer, any leukemia and acute lymphoblastic leukemia. For DNBC, MoBa and JPS, mandatory reporting of cancer cases to the respective registries has been in place since the 1940s to 1960s with completeness of coverage being $\geq 96\%$ [20]. In the UK, 2001 reports showed 94% of cancers ascertained during 1971–89 [21]. Since CPP cases were identified through indirect methods, some cancer cases may have been missed.

Exposure data

Identification of data domains and specific variables associated with CC. Thirty exposure domains were established for key exposures (e.g. birthweight, folic acid supplements, and others; see **Tables 3a-c**). The IDCC will submit requests to obtain additional data if needed for future proposals (See **Appendix C** for details of process). While the main domains center around the mother and child (see Tables 3a and 3c), some information on fathers is also available (see Table 3b).

Harmonization of exposure data. Our approach is similar other consortia [22] [23] [24]. Challenges include combining data from different racial and ethnic groups, collected over different time intervals or using heterogeneous data collection tools, and some variables so disparate that harmonization was not possible. The individual cohorts collected data in a standardized, structured approach from self-reported, telephone interview, or in-person administered questionnaires. Each cohort provided anonymized, individual-level. Data harmonization was carried out centrally by the IDCC project director (GT) with assistance from senior epidemiologists (TD, ALP). Each exposure variable was harmonized individually and the data evaluated for consistency within and across variables (see **Appendix D**)

Biological samples

Four of the participating cohorts (ALSPAC, DNBC, MoBa, TIHS) have biological specimens collected from mothers and/or offspring at various time points prior to the development of any cancer. Types of samples include: whole blood, serum, urine, and placentas from mothers; cord blood, blood (neonatal blood spots), hair, nails, and teeth from the offspring (**Appendix E**). All *additional emerging* cohorts are collecting a variety of biological samples.

Identification of additional emerging cohorts

Two groups of emerging cohorts are currently involved in I4C activities but not as yet contributing cancer cases, exposures or biospecimens to the pool. These are detailed in **Table 1b**. Group A includes five cohorts well established in recruitment and follow-up, collecting relevant data/ biospecimens, able to ascertain CC cases, and positioned to begin contributing data to the I4C pool within the next few years: the Born in Guangzhou Cohort Study (BGCS-China), the Etude Longitudinale Française depuis l'enfance (ELFE- France), the Nascita ed Infanzia: gli Effetti dell'Ambiente (NINFEA-Italy), the Japan Environment and Children's Study (JECS-Japan) and the Korean Children's Environmental Health Study (Ko-CHENS-China). Group B consists of four cohorts in various stages of development or early recruitment and follow-up from Australia, Brazil, China and Taiwan.

Housing of Data at the IDCC: Platform, Confidentiality, Privacy and Security Measures

The data transferred to the IDCC is securely housed on a web-based application located on the MCRI's secure e-Research portal (see **Appendix F**). Access is restricted to authorized personnel following approval by the I4C Steering Committee and a representative from each study contributing to the pooled dataset.

For added security, data files are encrypted before being sent to the IDCC. Most studies have excluded unique personal identifiers (e.g., name, residential address) and some have excluded month and day of birth. Individuals are identified by a study-specific identification number, and additional security is provided by assigning a unique I4C identification number used as the primary identifying key. The electronic data stored at the IDCC on a secure, password protected server. The network server, web server and SQL server undergo nightly

incremental backups plus a monthly full backup to tape for off-site storage. All users of the data must comply with the data sharing agreements.

Statistical consultation and support on study designs, data harmonization, and analyses

The I4C statistical team includes two senior biostatisticians (SL, GP) who provide input and advice on research proposals and undertake statistical analyses using the pooled dataset.

While complete harmonization of all questionnaire data is not feasible given cohort differences, decisions on pooling are based on the specific research question and what could be pooled with minimal compromise to the original recorded data.

Statistical methods and models used in I4C analysis

Time to event analyses use Cox proportional hazard regression models. Calculation of person-years of follow-up are based on the start time defined as the birth date (the date is set to zero years); the end time for those with cancer defined as the date of cancer diagnosis; the end time for those without cancer defined as the date the child is no longer under observation.

Statistical issues considered include: (1) accounting for different cohorts; (2) handling missing data for risk factors using multiple chained imputation techniques; (3) dealing with different lengths of follow-up of the contributing cohorts; (4) examining confounding and effect-modification of postulated risk factors; (5) finding the correct scale for continuous covariates and (6) testing the proportional hazard assumption for Cox regression models. Further details and strategies are in **Appendix G**.

RESULTS

Cohorts currently contributing data. Six cohorts (**Table 1a**) currently contribute data on

388,120 mother-child pairs as well as less extensive paternal data for certain domains

(**Tables 3a-c**). Recruitment periods span over six decades from the late 1950s (CPP), mid 1960s-mid70s (JPS), late 1980s (TIHS), early 1990s (ALSPAC), late 1990s (DNBC) and to early 2000s (MoBa). The cohorts range in size from 10,625 (TIHS) to 110,000 (MoBa) mother-child pairs. Time points for contacting mothers varied, with whole cohort follow-up ending for the TIHS cohort at 12 weeks, at 7 years for the CPP and ongoing for ALSPAC, DNBC and MoBa (**Table 1a**).

Additional emerging cohorts. Preliminary information about the targeted sample size, planned recruitment years, timing and source of recruitment, and data collection points for the new cohorts are in **Table 1b**. In summary, nine new cohorts within seven countries are collecting data on 627,500 mother-child pairs, with six recruiting mothers during pregnancy and the remaining cohorts at birth (ELFE from Group A and Gen V, TBCS from Group B).

Childhood cancer ascertainment by major category. The 675 CC cases ascertained in the six participating cohorts to date (see **Table 2**) include 198 leukemias (141 acute lymphoblastic leukemia), 65 lymphomas, 161 brain tumors and 251 cancers of other types. Based on the I4C target of 1 million mothers and children pooled from the participating and emerging cohorts, it is estimated that the I4C has the potential to accrue 2952 cases of CC (diagnosed <20 years) of which 791 will be CL [25].

Information at the IDCC according to data domain and specific exposures. Available data in the key exposure domains for mothers, fathers, and offspring is shown in **Tables 3a-c**.

Appendix A also lists information on known and suspected risk factors for CC, the likely /possible time window of effect and whether data are currently available at the IDCC or has been collected by the cohorts but have not to date been made available to the IDCC.

Data harmonization and descriptive results. To date, harmonized data includes over 20 ‘core’ variables. **Tables 4a-c** reveal variability in characteristics of subjects based on data collected within and across cohorts that may reflect secular changes in pregnancy and birth characteristics and societal changes over the six decades of recruitment. Substantial differences are apparent for mean age of mothers at birth of the index child (24.3, youngest age (CPP) to 30.5, oldest age (DNBC)); mean height (160.9 (CPP) to 168.1 cm (MoBa)); prevalence of smoking during pregnancy (11% (MoBa) to 51% (TIHS)). For offspring, the gender of the offspring enrolled in the cohort ranged from 50% (MoBa) to 69% male (TIHS- due to selection criteria favoring males given their higher risk of SIDS, the disease of focus when the cohort was established); caesarean section delivery (5% (CPP and JPS) to 21% (TIHS)); mean birthweight in grams (3108 (TIHS) to 3560 (DNBC)); history of any breast feeding to 6 months (63% (DNBC, TIHS) to 77% (MoBa)); and paid childcare during the first 6 months (0.1% (ALSPAC) to 6% (DNBC)).

As harmonization proceeded, emerging cohorts requested information about data collection strategies and forms to facilitate future pooling of data. In response, the IDCC has developed a “*New Cohort Protocol Support Package (NCPS)*” to provide researchers with a

standardized format for the collection of exposure data for etiologic studies (see **Appendix H**).

Publications. The first I4C publication using a pooled dataset examined the association between birthweight and risk of CC and maternal adiposity measures as potential effect modifiers. A linear relationship was demonstrated for increasing risk of total CC and childhood leukemia with each kilogram increase in birthweight adjusted for gender and gestational age. No significant interactions were seen with maternal pre-pregnancy overweight or pregnancy weight gain. Birthweight >4.0 kg was linked with non-leukemia cancers but, only among children diagnosed at age three or older [4].

I4C members have described a new optimized method for extracting DNA from neonatal dried blood spots for application in methylome profiling [26] [27] using samples from several of the contributing cohorts. A review paper describes the characteristics of the epigenome as a key component of fetal exposure in evaluating in utero exposures and childhood cancer risk [28]. More recently, I4C members have begun cataloguing –omics signatures of early-life factors that could be associated with CC [29,30]. These signatures will be analyzed across the different I4C cohorts with available biological samples. This work will complement the I4C questionnaire-based epidemiological investigations and may provide mechanistic insights into CC etiology.

Ongoing data analyses. Current efforts are focused on: examining prospectively, the association of birth order and CL and the potential modifying roles of paternal age and birthweight; parental occupational exposure to pesticides, animals, and organic dust and risk of CC utilizing geocoded residential addresses (using DNBC for first analysis) to evaluate

pesticide use near the residences during the pregnancy as well as parental occupational exposure; prenatal maternal folic acid supplementation and risk of CC; maternal infections during pregnancy and CC; epigenetic precursors of CL.

Process for requesting data for new research proposals

The I4C Steering Committee facilitates data sharing provided that all approvals are in place. The process for requesting data from any of the I4C contributing cohorts and the parallel steps undertaken at the IDCC to provide the data are in **Appendix B**.

COMMENTS

The I4C is a valuable resource comprising both questionnaire-based epidemiological data and biological samples offering unique opportunities to advance our understanding of the etiology and mechanisms of carcinogenesis in children. It is the first established pregnancy/birth cohort consortium to have published findings on CC using harmonized variables across six cohorts.

The six participating cohorts provide an extensive set of covariates that can be leveraged with different follow-up periods ranging from pregnancy to adolescence. Ongoing collaborative work involves molecular cancer epidemiology studies and the potential for evaluation of other biomarkers.

One of the aims of the I4C has been to verify the associations reported by case-control studies for the more commonly examined exposures such as birthweight. Our analysis of birthweight included 377 cases of any cancer (115 CL and 98 ALL) and showed a linear relationship for each kilogram increment for any leukemia (Hazard ratio [HR]=1.35; 95%CI

0.90, 2.02) with similar trends observed for ALL [4]. Risk estimates from our study of birthweight were similar to those reported in the pooled analyses from the Childhood Leukemia International Consortium (CLIC) (7348 cases of CL and 12,489 controls) with an odds ratio (OR) of 1.24 for large-for-gestational age children and from a second pooled analysis from the USA, UK and Germany (4,075 cases and 12,065 controls) with an OR of 1.2 per kg increase in birthweight [31,32], although a UK and US registry-based case-control study (40,000 cases and 87,000 controls) reported lower increases of CL per 0.5 kg increases of OR= 1.10 for US and 1.07 for UK data. [33].

There is a critical role for prospective assessment of exposure using pre-diagnostic questionnaire data and biological samples, but the rarity of CC and identification of an expanding number of molecularly different CC subtypes underscores the strengths and limitations of the I4C. Pooling of multiple pregnancy and birth cohorts offers prospectively collected risk factor and mechanistic data to that obtained from case-control studies. For example, information about maternal diet, viral infections, and use of folic acid and other vitamin supplements periconceptionally or during pregnancy may not be accurately recalled or available in medical records and thus not captured well in case-control studies. Relatively minor infections during infancy, details of breast-feeding, and daycare may similarly not be accurately recalled years later. Despite these potential strengths, cohort studies may also suffer from methodologic shortcomings including selection bias (cohort members are generally volunteers), under-ascertainment or misclassification of cancer outcomes, loss to follow-up over time, limited time points of data collection and measurement error (depending on the exposure assessment methods and follow-up time periods). By jointly undertaking projects with investigators leading case-control studies, the strengths of each

study design can be maximized and the limitations and potential biases can be identified and quantified.

Future Directions

The I4C includes a growing number of participating cohorts and is poised to significantly increase its sample size within the next five years. I4C studies are incorporating a growing range of exposure assessment methods and tools, including Geographic Information Systems (GIS) to assess agricultural and pesticide exposures near residences, satellite measurements to measure ambient ultraviolet radiation and assignment of occupational exposures using job exposure matrices. Statistical approaches include sophisticated methods for quantifying temporal and age effects in the assessment of associations between exposure and outcome. Collaborative efforts have recently been undertaken to develop joint projects with the Childhood Leukemia International Consortium during future planned joint meetings. The prospects for combining multiple sources of pre-diagnostic exposure data and biological samples in conjunction with collaboration with other birth cohort and pediatric cancer case-control consortia offer the potential for future breakthroughs in pediatric cancer etiologic research.

ACKNOWLEDGEMENTS

This work was supported by: the NIH intramural research program (NCI, NICHD) –USA; National Children’s Study – USA; Tour de Cure – Australia; the Children’s Cancer Centre Foundation – Australia; Bluey Day Foundation – Australia; Baxter Family Foundation – Australia; The Rotary Club of North Brighton –Australia; Private philanthropic donations – Australia; and Murdoch Children’s Research Institution (M1300049), Australia. The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. The Maria Ascoli Foundation, Jerusalem, Israel, provided support for data pooling of the JPS. This work was partly supported by the Research Council of Norway through its Centres of Excellence funding scheme, project number 262700, and Innovation Fund Denmark (grant no. 09-067124). The work within the I4C carried out by the Epigenetics Group at IARC is supported by a grant from the Institut National du Cancer (INCa, Plan Cancer-EVA-INSERM, France) to Z.H. and A.G.

REFERENCES

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 2014;64:83-103.
2. Roman E, Lightfoot T, Picton S, Kinsey S. Childhood cancers. In: Thun M, Linet M., Cerhan J., Haiman, C. & Schottenfeld, D. , ed. Schottenfeld and Fraumeni Cancer Epidemiology and Prevention, Fourth Edition. New York: Oxford University Press; 2018:1119-1154.
3. Postema FAM, Hopman SMJ, Aalfs CM, Berger LPV, Bleeker FE, Dommering CJ, *et al.* Childhood tumours with a high probability of being part of a tumour predisposition syndrome; reason for referral for genetic consultation. *Eur J Cancer* 2017;80:48-54.
4. Paltiel O, Tikellis G, Linet M, Golding J, Lemeshow S, Phillips G, *et al.* Birthweight and Childhood Cancer: Preliminary Findings from the International Childhood Cancer Cohort Consortium (I4C). *Paediatr Perinat Epidemiol* 2015;29:335-345.
5. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, *et al.* Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;343:78-85.
6. Bailey HD, Fritschi L, Metayer C, Infante-Rivard C, Magnani C, Petridou E, *et al.* Parental occupational paint exposure and risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. *Cancer Causes Control* 2014;25:1351-1367.
7. Bailey HD, Metayer C, Milne E, Petridou ET, Infante-Rivard C, Spector LG, *et al.* Home paint exposures and risk of childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium. *Cancer Causes Control* 2015;26:1257-1270.
8. Marcotte EL, Thomopoulos TP, Infante-Rivard C, Clavel J, Petridou ET, Schuz J, *et al.* Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). *Lancet Haematol* 2016;3:e176-185.

9. Rudant J, Lightfoot T, Urayama KY, Petridou E, Dockerty JD, Magnani C, *et al.* Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium study. *Am J Epidemiol* 2015;181:549-562.
10. Metayer C, Milne E, Dockerty JD, Clavel J, Pombo-de-Oliveira MS, Wesseling C, *et al.* Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a Childhood Leukemia International Consortium study. *Epidemiology* 2014;25:811-822.
11. Olshan AF, Anderson L, Roman E, Fear N, Wolff M, Whyatt R, *et al.* Workshop to identify critical windows of exposure for children's health: cancer work group summary. *Environ Health Perspect* 2000;108 Suppl 3:595-597.
12. Hatch EE, Kleinerman RA, Linet MS, Tarone RE, Kaune WT, Auvinen A, *et al.* Do Confounding or Selection Factors of Residential Wiring Codes and Magnetic Fields Distort Findings of Electromagnetic Fields Studies? *Epidemiology* 2000;11:189-198.
13. Infante-Rivard C, Jacques L. Empirical study of parental recall bias. *Am J Epidemiol* 2000;152:480-486.
14. Searles Nielsen S, Mueller BA, De Roos AJ, Viernes HM, Farin FM, Checkoway H. Risk of brain tumors in children and susceptibility to organophosphorus insecticides: the potential role of paraoxonase (PON1). *Environ Health Perspect* 2005;113:909-913.
15. Zuna J, Ford AM, Peham M, Patel N, Saha V, Eckert C, *et al.* TEL deletion analysis supports a novel view of relapse in childhood acute lymphoblastic leukemia. *Clin Cancer Res* 2004;10:5355-5360.
16. Brown RC, Dwyer T, Kasten C, Krotoski D, Li Z, Linet MS, *et al.* The international childhood cancer cohort consortium (I4C). *Int J Epidemiol* 2007;36:724-730.
17. Klebanoff MA, Read JS, Mills JL, Shiono PH. The risk of childhood cancer after neonatal exposure to vitamin K. *N Engl J Med* 1993;329:905-908.
18. Shiono PH, Chung CS, Myrianthopoulos NC. Preconception radiation, intrauterine diagnostic radiation, and childhood neoplasia. *J Natl Cancer Inst* 1980;65:681-686.

19. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin M, *et al.* International Classification of Diseases for Oncology. Third Edition ed: World Health Organization; 2000. 2000.
20. International Agency for Cancer Registries. <http://www.iacr.com.fr/> (Accessed 01 July 2018).
21. Dickinson HO, Salotti JA, Birch PJ, Reid MM, Malcolm A, Parker L. How complete and accurate are cancer registrations notified by the National Health Service Central Register for England and Wales? *J Epidemiol Community Health* 2001;55:414-422.
22. Fortier I, Burton PR, Robson PJ, Ferretti V, Little J, L'Heureux F, *et al.* Quality, quantity and harmony: the DataSHaPER approach to integrating data across bioclinical studies. *Int J Epidemiol* 2010;39:1383-1393.
23. Esteve A, Sobek M. Challenges and methods of international census harmonization. *Historical Methods: A Journal of Quantitative and Interdisciplinary History* 2003;36:66-79.
24. Schaap LA, Peeters GM, Dennison EM, Zambon S, Nikolaus T, Sanchez-Martinez M, *et al.* European Project on Osteoarthritis (EPOSA): methodological challenges in harmonization of existing data from five European population-based cohorts on aging. *BMC Musculoskeletal Disorders* 2011;12:272.
25. Cancer incidence in five countries Volume XI. at http://ci5.iarc.fr/CI5-XI/Pages/summary_table_pop_sel.aspx (Accessed 20 July 2018)
26. Ghantous A, Saffery R, Cros MP, Ponsonby AL, Hirschfeld S, Kasten C, *et al.* Optimized DNA extraction from neonatal dried blood spots: application in methylome profiling. *BMC Biotechnol* 2014;14:60.
27. Ghantous A, Hernandez-Vargas H, Herceg Z. DNA Methylation Analysis from Blood Spots: Increasing Yield and Quality for Genome-Wide and Locus-Specific Methylation Analysis. *Methods Mol Biol* 2018;1708:605-619.
28. Ghantous A, Hernandez-Vargas H, Byrnes G, Dwyer T, Herceg Z. Characterising the epigenome as a key component of the fetal exposome in evaluating in utero exposures and childhood cancer risk. *Mutagenesis* 2015.

29. Joubert BR, den Dekker HT, Felix JF, Bohlin J, Ligthart S, Beckett E, *et al.* Maternal plasma folate impacts differential DNA methylation in an epigenome-wide meta-analysis of newborns. *Nat Commun* 2016;7:10577.
30. Sharp GC, Salas LA, Monnereau C, Allard C, Yousefi P, Everson TM, *et al.* Maternal BMI at the start of pregnancy and offspring epigenome-wide DNA methylation: findings from the pregnancy and childhood epigenetics (PACE) consortium. *Hum Mol Genet* 2017;26:4067-4085.
31. Milne E, Greenop KR, Metayer C, Schuz J, Petridou E, Pombo-de-Oliveira MS, *et al.* Fetal growth and childhood acute lymphoblastic leukemia: findings from the childhood leukemia international consortium. *Int J Cancer* 2013;133:2968-2979.
32. Roman E, Lightfoot T, Smith AG, Forman MR, Linet MS, Robison L, *et al.* Childhood acute lymphoblastic leukaemia and birthweight: insights from a pooled analysis of case-control data from Germany, the United Kingdom and the United States. *Eur J Cancer* 2013;49:1437-1447.
33. O'Neill KA, Murphy MF, Bunch KJ, Puumala SE, Carozza SE, Chow EJ, *et al.* Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. *Int J Epidemiol* 2015;44:153-168.