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The Childhood Leukemia International Consortium

Catherine Metayer^{a,*}, Elizabeth Milne^b, Jacqueline Clavel^{c,1}, Claire Infante-Rivard^{d,1}, Eleni Petridou^e, Malcolm Taylor^f, Joachim Schüz^g, Logan G. Spector^h, John D. Dockertyⁱ, Corrado Magnani^j, Maria S. Pombo-de-Oliveira^k, Daniel Sinnett^l, Michael Murphy^m, Eve Romanⁿ, Patricia Monge^o, Sameera Ezzat^{p,q}, Beth A. Mueller^{r,s}, Michael E. Scheurer^{t,u}, Bruce K. Armstrong^v, Jill Birch^w, Peter Kaatsch^x, Sergio Koifman^y, Tracy Lightfootⁿ, Parveen Bhatti^{f,s}, Melissa L. Bondy^{t,u}, Jérémie Rudant^c, Kate O'Neill^m, Lucia Miligi^z, Nick Dessypris^e, Alice Y. Kang^a, and Patricia A. Buffler^a

Catherine Metayer: cmetayer@berkeley.edu; Elizabeth Milne: lizm@ichr.uwa.edu.au; Jacqueline Clavel: jacqueline.clavel@inserm.fr; Claire Infante-Rivard: claire.infante-rivard@mcgill.ca; Eleni Petridou: epetrid@med.uoa.gr; Malcolm Taylor: gmtaylor@manchester.ac.uk; Joachim Schüz: schuzj@iarc.fr; Logan G. Spector: spector@umn.edu; John D. Dockerty: john.dockerty@otago.ac.nz; Corrado Magnani: magnani@med.unipmn.it; Maria S. Pombo-de-Oliveira: mpombo@inca.gov.br; Daniel Sinnett: daniel.sinnett@umontreal.ca; Michael Murphy: michael.murphy@crg.ox.ac.uk; Eve Roman: Eve.Roman@egu.york.ac.uk; Patricia Monge: patmonge@gmail.com; Sameera Ezzat: Sameera.ezzat@57357.com; Beth A. Mueller: bmueller@fhcr.org; Michael E. Scheurer: scheurer@bcm.edu; Bruce K. Armstrong: bruce.armstrong@sydney.edu.au; Jill Birch: jillian.birch@manchester.ac.uk; Peter Kaatsch: peter.kaatsch@unimedizin-mainz.de; Sergio Koifman: koifman@ensp.fiocruz.br; Tracy Lightfoot: Tracy.Lightfoot@ecsg.york.ac.uk; Parveen Bhatti: pbhatti@fhcr.org; Melissa L. Bondy: mbondy@mdanderson.org; Jérémie Rudant: jeremie.rudant@inserm.fr; Kate O'Neill: kate.oneill@crg.ox.ac.uk; Lucia Miligi: l.miligi@ispo.toscana.it; Nick Dessypris: ndessyp@med.uoa.gr; Alice Y. Kang: aykang@berkeley.edu; Patricia A. Buffler: pab@berkeley.edu

^aUniversity of California, Berkeley, School of Public Health, 1995 University Avenue, Suite 460, Berkeley, CA 94704-1070, United States ^bTelethon Institute for Child Health Research, Centre for Child Research, University of Western Australia, 100 Roberts Road, Subiaco, Western Australia 6008; PO Box 855, West Perth, Western Australia 6872, Australia ^cInserm, CESP Centre for Research in Epidemiology and Population Health, Environmental Epidemiology of Cancer Team, Université Paris-Sud, UMRs 1018, 16 Avenue Paul Vaillant-Couturier, F-94807 Villejuif Cedex, France ^dDepartment of Epidemiology, Biostatistics, and Occupational Health, Faculty of Medicine, McGill University, 1110 Pine Avenue West, Montréal, Province of Québec H3A 1A3, Canada ^eDepartment of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Medical School, 75M. Asias Str. Goudi, Athens 115 27, Greece ^fCancer Immunogenetics Group, School of Cancer and Enabling Sciences, University of Manchester, Room L5.CT.387, St. Mary's Hospital, Manchester M13 9WL, United Kingdom ^gInternational Agency for Research on Cancer, Section of Environment and Radiation, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France ^hDivision of Epidemiology Clinical Research, Department of Pediatrics and Masonic Cancer Center, University of Minnesota, 420 Delaware Street, SE, MMC 715, Minneapolis, MN 55455, United States ⁱDean's Department and Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, PO Box 913, Dunedin, New Zealand ^jDipartimento di Medicina Traslazionale – Università del Piemonte Orientale, SCDU Epidemiologia dei Tumori, ASO Maggiore della Carità e CPO – Piemonte, V. Solaroli 17 28100 Novara, Italy ^kPediatric Hematology-Oncology Program, Research Program, Instituto Nacional de Cancer, Rua André Cavalcanti, 37, 6° andar, CEP 20231050, Rio de Janeiro, Brazil ^lDepartment of Pediatrics, University of Montréal, Division of Hematology-Oncology, Research Center, Sainte-Justine University Hospital Center, 3175,

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*Corresponding author. Tel.: +1 510 643 1156; fax: +1 510 643 1735.

¹Authors equally contributed.

Conflict of interest

None declared.

chemin de la Côte Ste-Catherine, Québec, Montréal H3T 1C5, Canada ^mChildhood Cancer Research Group, Richards Building, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LG, United Kingdom ⁿDepartment of Health Sciences, University of York, Seeborn Rowntree Building, Heslington, York YO10 5DD, United Kingdom ^oCentral American Institute for Studies on Toxic Substances, Universidad Nacional (IRET-UNA), PO Box 86, Heredia 3000, Costa Rica ^pResearch Department, Children's Cancer Hospital, 57357, Egypt ^qMenoufiya University, 1 Seket Al-Emam St., el Sayeda Zeinab, Cairo 11441, Egypt ^rPublic Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, United States ^sEpidemiology Department, University of Washington School of Public Health, PO 19024, Seattle, WA 98109-1024, United States ^tBaylor College of Medicine, Department of Pediatrics, Section of Hematology-Oncology, Houston, TX, United States ^uTexas Children's Cancer Center, Houston, One Baylor Plaza, MS-BCM305, Houston, TX 77030, United States ^vSydney School of Public Health, University of Sydney, Room 207, Queen Elizabeth II Research Institute D02, NSW 2006, Australia ^wCancer Research UK Paediatric and Familial Cancer Research Group, University of Manchester, The Medical School, Stopford Building, Room 1.900, Oxford Road, Manchester M13 9PL, United Kingdom ^xGerman Childhood Cancer Registry (GCCR) at the Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Centre, Johannes Gutenberg University Mainz, 55101 Mainz, Germany ^yNational School of Public Health, Oswaldo Cruz Foundation (FIOCRUZ), Ministry of Health, Rio de Janeiro, Brazil ^zISPO-Cancer Prevention and Research Institute, Occupational and Environmental Epidemiology Unit, Ponte Nuovo – Padiglione Mario Fiori, Via delle Oblate 2, 50141 Florence, Italy

Abstract

Background—Acute leukemia is the most common cancer in children under 15 years of age; 80% are acute lymphoblastic leukemia (ALL) and 17% are acute myeloid leukemia (AML). Childhood leukemia shows further diversity based on cytogenetic and molecular characteristics, which may relate to distinct etiologies. Case-control studies conducted worldwide, particularly of ALL, have collected a wealth of data on potential risk factors and in some studies, biospecimens. There is growing evidence for the role of infectious/immunologic factors, fetal growth, and several environmental factors in the etiology of childhood ALL. The risk of childhood leukemia, like other complex diseases, is likely to be influenced both by independent and interactive effects of genes and environmental exposures. While some studies have analyzed the role of genetic variants, few have been sufficiently powered to investigate gene-environment interactions.

Objectives—The Childhood Leukemia International Consortium (CLIC) was established in 2007 to promote investigations of rarer exposures, gene-environment interactions and subtype-specific associations through the pooling of data from independent studies.

Methods—By September 2012, CLIC included 22 studies (recruitment period: 1962–present) from 12 countries, totaling approximately 31 000 cases and 50 000 controls. Of these, 19 case-control studies have collected detailed epidemiologic data, and DNA samples have been collected from children and child-parent trios in 15 and 13 of these studies, respectively. Two registry-based studies and one study comprising hospital records routinely obtained at birth and/or diagnosis have limited interview data or biospecimens.

Conclusions—CLIC provides a unique opportunity to fill gaps in knowledge about the role of environmental and genetic risk factors, critical windows of exposure, the effects of gene-environment interactions and associations among specific leukemia subtypes in different ethnic groups.

Keywords

Leukemia; Children; Consortium; Epidemiology; Genetics

1. Introduction

Leukemia is the most common cancer among children, representing about a third of all cancers occurring before the age of 15 years; approximately 80% are acute lymphoblastic leukemia (ALL) primarily in children 1–4 years old, 17% acute myeloid leukemia (AML), and 3% chronic myeloid leukemias, with some variation in ALL and AML incidence rates worldwide [1,2]. Further classification of childhood leukemia is made on the basis of cell types for ALL, and cytogenetic/molecular characteristics (e.g., chromosome translocations such as $t(12;21)$, the *MLL* gene fusion, and aberrant chromosome number such as hyperdiploidy) [3]. These leukemia subtypes exhibit heterogeneity with regard to pathophysiology, clinical manifestations, response to treatment, and prognosis, which suggests distinct etiologies [4]. Biological studies have shown that both prenatal initiating events and postnatal promoting events could be involved in the development of childhood leukemia, consistent with the “two-hit” model confirmed in the natural history of several tumor sites and hypothesized for leukemogenesis [5].

Apart from established associations with rare and specific inherited and congenital genetic instability disorders (e.g., Down syndrome, Fanconi anemia, ataxia telangiectasia and others), prenatal exposure to X-rays and chemotherapeutic agents, epidemiologic studies of childhood leukemia conducted during the last two decades have investigated the role of the child’s immune function, fetal growth and other perinatal characteristics, as well as associations with in utero and early life exposures, including a range of environmental agents. In brief, a decreased risk of childhood B-cell ALL has been associated with surrogate measures of early common infection, such as high levels of social contact in daycare settings [6-9]. Elevated risks of childhood ALL have been reported with high birth weight [10], home use of pesticides [11], tobacco smoking [12,13], diet [14-17], parental occupational chemical exposures such as solvents and hydrocarbons, and some measures of outdoor air pollution [18-23]. Previous studies, mostly limited in scope, have evaluated the role of candidate genes involved in xenobiotic transport and metabolism [24-32], DNA repair [28,33,34], folate metabolic pathways [28,35-38], and immune regulation [28,39-42] including the histocompatibility complex (human leukocyte antigen (HLA) genes) [43-45]. Recent genome wide association studies (GWAS) of childhood B-cell ALL [46-49] and replication studies [50-53] reported associations with genes involved in the transcriptional regulation and differentiation of B-cell progenitors in Caucasian [46-48], Asian [49] and African-American populations [51]. However, it seems unlikely that childhood ALL, like other complex diseases, is determined solely by genetic or environmental factors, but may result from interactions between them. If this paradigm applies to childhood leukemia, the relative rarity of the disease may be explained by interactions between rare genotypes and multiple exposures. While some studies to date have attempted to investigate such gene–environment interactions in childhood ALL [24-27,29,31,36,39,54-62], most have lacked sufficient statistical power.

To overcome the limitations of single epidemiologic studies, the Childhood Leukemia International Consortium (CLIC) was established in 2007, building upon the wealth of data and biospecimens collected in over 20 case–control studies worldwide (<https://clic.berkeley.edu>). The unprecedented number of children whose data are available for pooling will enhance the statistical power to investigate the contribution of pre- and post-natal exposures to the etiology of childhood ALL, AML, and rarer subtypes, and will

facilitate investigation of gene–environment interactions. The aim of this paper describes the history and organization of CLIC, the participating studies, future directions and challenges.

2. CLIC history and organization

In 2005–2006, the investigator of the US-California childhood leukemia study (PAB) initiated contacts with investigators from Australia (EM), Canada (CIR), and France (JC) to discuss the establishment of an international consortium of epidemiologic studies of childhood leukemia. The primary goals were to share comparable epidemiologic and possibly genetic data in order to enhance statistical power of analyses and, most importantly, to exchange ideas among researchers from different disciplines including epidemiologists, tumor biologists, geneticists, immunologists, toxicologists, clinicians and statisticians about the possible causes of childhood leukemia. In collaboration with the International Agency for Research on Cancer (IARC), CLIC was established in 2007 with its first formal annual meeting. Several other leukemia investigators were invited to outline research priorities and the structure of the consortium, and consortium meetings have taken place each year since then. By September 2012, CLIC had expanded to include 22 existing individual childhood leukemia studies from 18 research groups in 12 countries within North, Central, and South America, Europe, Australia/Oceania, and Africa (<https://clic.berkeley.edu>). These studies have substantial similarities in research hypotheses and study designs (Table 1).

Two projects were initiated to demonstrate a proof of principle for pooling data within CLIC. One examined the associations between maternal vitamin and folate supplementation during pregnancy and the risk of childhood ALL and AML (supported by funding from the National Cancer Institute, NCI, USA), and the other investigated the association between two measures of fetal growth and childhood ALL (supported by funding from the Cancer Council Western Australia). These initiatives enabled CLIC to develop guidelines and procedures for requesting and pooling data, and guidelines for membership and authorship. The latter were modeled on successful consortia of adult cancers (i.e., the International Lymphoma Epidemiology Consortium, Interlymph, <http://epi.grants.cancer.gov/InterLymph/>); the International Lung Cancer Consortium, ILCCO, <http://ilcco.iarc.fr/>), and other references such as the International Committee of Medical Journal Editors (<http://www.icmje.org/>).

The consortium is governed by the Coordination Group, which comprises the principal investigators and designated co-investigators from CLIC studies. CLIC-wide activities such as those involving data pooling/management, disease classification/pathology, and other emerging needs are supported by the Core Logistics Groups. Research priorities for collaborative projects are set by the Interest Groups, including topics on (by alphabetical order) birth characteristics, environmental and occupational exposures, family history, genetic studies, infection and immunity, rare leukemia subtypes (such as infant leukemia, acute myeloid and promyelocytic leukemia, and T-cell ALL), and survival/outcome studies. The latter group was established as an extension of the etiologic research in leukemogenesis. This Interest Group aims to determine which case series of the case–control studies are (or can be) linked with information on vital status and course of disease. Subsequently, this Group will explore survival in relation to socio-demographic factors, clinical characteristics, and treatment modalities, whenever available. Pooling projects that are approved by the Coordination Group are then implemented by Working Groups. Lastly, the Management Group, which comprises an elected Chair, Vice Chair, and Members, facilitates all CLIC operations. Participation in all groups described above is voluntary (details on CLIC organization are available at <https://clic.berkeley.edu/organization>).

Members of the Coordination Group who contribute epidemiologic or genetic data are Active CLIC Members, while researchers with relevant expertise, but who do not contribute data, may apply for Associate Membership of CLIC. An individual study may solicit CLIC membership directly or upon invitation by a CLIC Member; inclusion and exclusion criteria include the robustness of the study design and the scope of epidemiologic data and biospecimen available for pooling projects. As a result, CLIC represents a large subset of childhood leukemia studies including most of the large case–control studies worldwide.

Currently, data are held locally by each study principal investigator, who following bilateral data transfer agreements, sends them to the pooling project leader for data harmonization and analyses. Protocols for harmonizing common variables such as parental education and ethnicity are shared between investigators. Now that CLIC has demonstrated its ability to share and analyze data, CLIC has opted to establish a central data coordination center hosted at the IARC, Lyon, France, in order to streamline the exchange of data and relevant study information between CLIC Members, under bilateral data transfer agreements. The short-term goal is to store common variables on socio-demographic characteristics and disease classification, other clinical characteristics and outcomes, as well as variables harmonized for pooled analyses addressing specific hypotheses. These data and their documentation will be checked for consistency and made available for future analyses after approval by principal investigators of each individual CLIC study. In addition, medium-term goals of the central data coordination center are to store original study data when requested by a principal investigator, and to develop an interactive inventory of data and biospecimens available in CLIC studies. Lastly, a long-term goal is to provide support for statistical programming, if requested by the pooling project leader.

3. CLIC studies

Table 1 describes the characteristics of 22 studies participating in CLIC as of September 2012. All individual studies had been approved by their respective ethics committee, and family members who provided data had given informed consent. Leukemia cases were identified from nation/region-wide population-based cancer registries, networks of hospitals or physicians – which in some countries are equivalent to national population-based coverage (14 studies), selected hospitals (6 studies), or clinical trials (2 studies). The source of controls was either population-registry based (14 studies), hospital-based (5 studies), or recruited using random-digit dialing (3 studies). In total, CLIC has accrued information for 31 239 leukemia cases and 50 166 controls (Table 2).

Approximately half of study participants in the CLIC data set (11 157 ALL, 1836 AML, and 21 375 controls) came from 19 case–control studies in which detailed epidemiologic data were obtained using standardized questionnaires to collect information on putative risk factors. The period of enrollment started from 1980, with recruitment ongoing in some studies. Therefore, any tables describing the size of the CLIC studies may be different from what has been published at the time of this manuscript. With few exceptions, children were less than 15 years of age at recruitment. The risk factors studied include medical conditions of the child and mother (e.g., reproductive and birth characteristics, drug use, diagnostic X-rays, infection and other conditions), lifestyle (diet, consumption of alcohol, coffee, and vitamin supplementation, tobacco smoking, markers of social contact), and pre- and postnatal exposures to chemicals (e.g., pesticides, paints, hair dyes, and solvents at home or work). Biospecimens were collected for DNA extraction in 15 of the 19 case–control studies, representing approximately 9400 cases and 7100 controls. Thirteen studies also obtained DNA from child–parent trios (Table 2), which offers a unique opportunity to enhance the validity of genetic association studies. Some CLIC studies have completed genotyping in a subset of cases and/or controls, mostly for selected single nucleotide

polymorphisms (SNPs) in candidate genes involved in xenobiotic and folate metabolism and DNA repair. Other investigators are currently conducting or analyzing data from large-scale genotyping and sequencing studies, or have specimens available for future genetic investigations.

The other half of the participants in CLIC studies (15 075 ALL, 2883 AML, 28 791 controls) were ascertained from two registry-based studies and one study comprising hospital records routinely obtained at birth and/or diagnosis. These studies, with enrollment starting as early as 1962, have limited epidemiologic data available.

Several pooled analyses that maximize the use of existing epidemiologic and genetic data, and possibly outcome data for some studies, are under way (Table 3). Following is an example illustrating the gain in statistical power to examine the association between maternal smoking during pregnancy and childhood AML within CLIC compared to individual studies: given a power of 0.80, an alpha of 0.05, a prevalence of exposure of 20%, and the use of unmatched analysis, the minimum detectable odd ratio is 1.26 for CLIC pooled analyses (930 cases and 7800 controls) vs. 1.69 and 2.96 for individual CLIC studies such as the UKCCS (248 AML cases/492 controls) or the NARECHEM study (105 AML cases/105 controls), respectively.

Classification on immunophenotypes of childhood ALL was available in 19 studies, comprising approximately 9000 B-cell and 1000 T-cell cases (Table 2). Information on molecular lesions, as identified by conventional karyotype at the time of the leukemia diagnosis, was available for most CLIC studies, at least on a subset of cases. Only a few studies have readily available information on gene translocations, duplications and deletions using fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) assays, which are mainly available for cases diagnosed after 2000. Quality and completeness of cytogenetic and molecular data in CLIC are currently being evaluated, as methods used for cytogenetic characterization of leukemia cases have evolved over time from conventional karyotyping to more sophisticated molecular biologic methods to detect chimeric gene products using FISH and PCR assays.

Currently, approximately 80% of study subjects in CLIC are classified as White/Caucasian/European, based on self-reports or population demographics when detailed information was not collected. The remaining 20% include children of various ethnic backgrounds, primarily enrolled in studies from the United States, Brazil, and Egypt. We estimate that about 780 cases and 1900 controls are Hispanics. Additionally, a study from Mexico [63] with 980 cases and 750 controls will soon join CLIC. In contrast, the numbers of children reporting Asian and African backgrounds remain low (~200 cases; 800 controls for each group). For a subset of CLIC studies, population admixture will be characterized using ancestry informative markers derived from GWAS.

4. Future directions and challenges

CLIC is a maturing consortium that brings together a large community of scientists and clinicians with expertise in childhood leukemia research, a wealth of epidemiologic data, and a substantial amount of genetic data from 12 countries in 5 continents. CLIC is reaching out to additional investigators in Central and South America, and to new studies in Asia and possibly Africa, to expand the participation of these underrepresented ethnic groups.

A number of meta-analyses of published data from childhood leukemia studies have been conducted (e.g., maternal folate [64], pesticides [11], and daycare attendance [6]). Beyond the advantage of pooling data to increase statistical power, CLIC provides access to original published and un-published data (therefore reducing potential for publication bias) and

detailed recruitment statistics. This allows the CLIC investigators to assess the suitability of individual studies in pooled analyses, and to address specific research questions with adequate statistical power, such as estimating risk of rare leukemia subtypes (e.g., understudied AML, T-cell ALL, and cytogenetic subtypes), effects of rare exposures (e.g., some paternal and maternal occupational exposures), multiple time periods of exposure (e.g., sole or combined contribution of exposures occurring during preconception, pregnancy as a whole or by trimester and after birth), dose–response relationships, and possible interactions between socio-demographic (S), environmental (E) and genetic (G) factors (e.g., ExE, ExS, GxG, and GxE interactions).

We acknowledge the challenges in harmonizing existing epidemiologic data collected across a wide range of studies using various designs, and that the limitations of the original studies remain. However, by having access to original data, CLIC investigators are able to conduct comprehensive sensitivity analyses to evaluate the nature and magnitude of various biases related, for example, to non-participation and missing data in individual studies.

To address some methodological limitations of case–control studies, the International Consortium of Childhood Cancer Cohorts (I4C) was established in 2006 to pool data for over 700 000 children from birth cohorts worldwide (<https://communities.nci.nih.gov/i4c/>) [65]. The I4C aims to enhance exposure classification through a prospective design; however, cohort studies are not exempt from selection bias and they face challenges in accruing sufficient numbers of leukemia cases in a reasonable time period. Indeed, while the major strength of CLIC is its access to data from several thousand children diagnosed with common and rare leukemia subtypes, the anticipated number of children with leukemia participating in I4C longitudinal studies is ~400 ALL and 100 AML (based on 700 000 children) [65]. Despite the respective strengths and limitations of CLIC and I4C, there are several possible areas for complementary work between the two consortia, such as cross-validation of findings using two methodological approaches, and joint projects to characterize biomarkers of prenatal exposures using pre-natal biospecimens that are available in I4C studies and in some CLIC case–control studies (such as archive newborn blood spots as listed in Table 2). The leaders and members of CLIC and I4C are working closely to maximize the benefits of the two methodological approaches, and to exchange expertise.

Other groups are collaborating to study genetic and/or environmental factors for childhood leukemia [65,66]. The strength of CLIC, however, lies in the availability of both environmental data and the child's genetic data and/or DNA, as well as parental DNA in a subset of studies. CLIC is currently examining gene–environment interactions with targeted environmental exposure data and functional SNPs (Table 3), and will aim to undertake relevant gene–environment analyses of SNPs with main effects that are replicated by GWAS. Lastly, because CLIC has a unique diversity of ancestries among subjects, it will be feasible to undertake GWAS among specific ethnic groups. This is particularly attractive given that leukemia incidence rates vary substantially between ethnic groups. Several practical concerns will guide the pooling of genetic data in CLIC, including the choice of genotyping platform, central vs. distributed genotyping, and the decision to pursue individual vs. consortium-wide funding.

The overarching objective of CLIC is to influence the focus and priorities for childhood leukemia research through large collaborative efforts. CLIC will continue to seek funding and partnerships to support its expanding research portfolio. CLIC is an open consortium willing to include additional collaborations. Furthermore, CLIC strives to be a dynamic consortium and has established mechanisms for the submission of new research proposals

and for the development of databases with common core variables and clear data dictionaries to facilitate current and future pooling projects.

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Appendix 1. Acknowledgments by study (listed by location and name in alphabetical order). Further information can be found in study references and websites, and <https://clic.berkeley.edu>

Australia, Aus-ALL [13,64,67]

Research and Clinical Investigators

Bruce Armstrong (Sydney School of Public Health); Elizabeth Milne, Carol Bower, Nicholas de Klerk, Ursula Kees, and Helen Bailey (Telethon Institute for Child Health Research); Frank van Bockxmeer (Royal Perth Hospital); Michelle Haber and Murray Norris (Children's Cancer Institute Australia); Rodney Scott and John Attia (University of Newcastle); Lin Fritschi (WA Institute for Medical Research); Margaret Miller (Edith Cowan University); Judith Thompson (WA Cancer Registry); Frank Alvaro (John Hunter Hospital, Newcastle); Catherine Cole (Princess Margaret Hospital for Children, Perth); Luciano Dalla Pozza (Children's Hospital at Westmead, Sydney); John Daubenton (Royal Hobart Hospital, Hobart); Peter Downie (Monash Medical Centre, Melbourne); Liane Lockwood (Royal Children's Hospital, Brisbane); Maria Kirby (Women's and Children's Hospital, Adelaide); Glenn Marshall (Sydney Children's Hospital, Sydney); Elizabeth Smibert (Royal Children's Hospital, Melbourne); Ram Suppiah (previously Mater Children's Hospital, Brisbane). **Funding:** Australian National Health and Medical Research Council.

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Research and Clinical Investigators

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Research Investigator

Claire Infante-Rivard (McGill University, Montréal). **Funding:** National Cancer Institute of Canada and CCERN, the Medical Research Council of Canada, the Canadian Institutes of Health Research, the Fonds de la recherche en santé du Québec, the Bureau of Chronic Disease Epidemiology, Health and Welfare Canada, the Leukemia Research Fund of Canada, and the National Health and Research Development Program, Ottawa.

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Costa Rica

Research Investigators

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Research Investigators

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France, Studies ADELE [26], ELECTRE [74], ESCALE [7,62], and ESTELLE (<http://cesp.inserm.fr/fr/>)

Research Investigators

Jacqueline Clavel and Jérémie Rudant (Inserm, CESP, Université Paris-Sud). **Funding:** **ADELE** Inserm, the French Ministère de l'Environnement, the Association pour la Recherche contre le Cancer (ARC), the Fondation de France, the Fondation Jeanne Liot, the Fondation Weisbrem-Berenson, the Ligue Contre le Cancer du Val de Marne, and the Ligue Nationale Contre le Cancer. **ELECTRE:** Inserm, the Ministère de l'Environnement et de l'Aménagement du Territoire, the Fondation pour la Recherche Médicale, ARC, the Fondation de France, and the Institut Electicité Santé. **ESCALE:** Inserm, the Fondation de France, ARC, the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), the Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET), the association Cent pour sang la vie, the Institut National du Cancer (INCa), the Agence Nationale de la Recherche (ANR), and the Cancéropôle Ile de France. **ESTELLE:** Association Enfants et Santé, the Ligue Nationale contre le Cancer, the Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES), the Institut National du Cancer (INCa), the Cancéropôle Ile de France.

Germany, German Childhood Cancer Registry (GCCR) [75-77]

Research Investigators

Peter Kaatsch and Jörg Michaelis (Johannes Gutenberg-University Mainz); Joachim Schüz (International Agency for Research on Cancer). **Funding** Federal Ministry of the Environment, Nuclear Safety and Nature Preservation.

Greece, Nationwide Registry for Childhood Haematological Malignancies (NARECHEM) [78-80]

Research and Clinical Investigators

Eleni Petridou, Paraskevi Panagopoulou, and Ioannis Matsoukis (University of Athens); Margarita Baka (Children's Hospital, Athens, Greece); Maria Moschovi (Athens University Medical School); Sophia Polychronopoulou ("Aghia Sophia" General Children's Hospital, Athens); Fani Athanassiadou (Aristotelion University of Thessaloniki, AHEPA General Hospital); Vassiliki Sidi (Hippokration Hospital, Thessaloniki), and Efthymia Stiakaki (University Hospital of Heraklion). **Funding** European Union and the University of Athens.

Italy, Studio sulla Eziologia dei Tumori Infantili Linfoemopoietici (SETIL) [81]

Research and Clinical Investigators

Corrado Magnani (Università del Piemonte Orientale); Lucia Miligi (ISPO, Firenze); Maurizio Aricò and Gabriella Bernini (AOU Meyer, Firenze); Antonio Acquaviva (AOU di Siena); Giorgio Assennato (ARPA, Bari); Giuseppe Basso, Stefania Varotto and Paola Zambon (Università di Padova); Pierfranco Biddau (Ospedale Microcitemico, Cagliari); Luigi Bisanti (ASL di Milano); Francesco Bochicchio, Susanna Lagorio, Cristina Nuccetelli, Alessandro Polichetti, Serena Risica, and Paolo Vecchia (ISS, Roma); Santina Cannizzaro and Lorenzo Gafà (LILT, Ragusa); Egidio Celentano (ARSan, Napoli); Pierluigi Cocco (Università di Cagliari); Marina Cuttini and Paolo Tamaro (IRCCS Burlo Garofolo, Trieste); Francesco Forastiere, Ursula Kirchmayer, and Paola Michelozzi (Dipartimento Epidemiologia Regione Lazio, Roma); Riccardo Haupt (Istituto Giannina Gaslini, Genova); Franco Locatelli (Università di Pavia); Lia Lidia Luzzatto (Ospedale Pediatrico Regina

Margherita, Torino); Giuseppe Masera and Carmelo Rizzar (Università Milano Bicocca, Monza); Pia Massaglia (Università di Torino); Stefano Mattioli, Guido Paolucci and Andrea Pession (Università di Bologna); Domenico Franco Merlo (INRC, Genova); Liliana Minelli (Università degli Studi di Perugia); Paola Mosciatti and Franco Pannelli (Università di Camerino); Vincenzo Poggi (AORN Santobono – Pausilipon, Napoli); Alessandro Pulsoni (Sapienza University, Roma); Roberto Rondelli (Policlinico S.Orsola, Bologna); Giovanna Russo and Gino Schilirò (Università di Catania); Alberto Salvan (IASI-CNR, Roma); Maria Valeria Torregrossa (Università degli Studi di Palermo). **Funding:** Italian Association on Research on Cancer, Ministry of Instruction, University and Research, PRIN Program, Ministry of Health (Ricerca Sanitaria Finalizzata Program), Ministry of Labour and Welfare, Associazione Neuroblastoma, Piemonte Region (Ricerca Sanitaria Finalizzata Program), Liguria Region, Comitato per la vita “Daniele Chianelli”- Associazione per la Ricerca e la Cura delle Leucemie, Linfomi e Tumori di Adulti e Bambini (Perugia).

New Zealand, New Zealand Childhood Cancer Study (NZCCS) [82-84]

Research Investigators

John D. Dockerty, Peter G. Herbison, David C.G. Skegg, and J. Mark Elwood (University of Otago). **Funding:** Health Research Council of New Zealand (NZ), the NZ Lottery Grants Board, the Otago Medical School (Faculty Bequest Funds), the Cancer Society of NZ, the Otago Medical Research Foundation, and the A.B. de Lautour Charitable Trust.

United Kingdom, Oxford, Childhood Cancer Research Group (CCRG) [85-87] (www.ccrq.ox.ac.uk)

Research Investigators

Michael Murphy, Kate O'Neill, and CCRG staff (University of Oxford). **Funding:** Department of Health, Scottish Government, National Cancer Intelligence Network, and CHILDREN with CANCER, UK.

United Kingdom, United Kingdom Childhood Cancer Study (UKCCS) [88-90] (www.ukccs.org)

Research Investigators

Eve Roman and Tracy Lightfoot (University of York), part of a team of ten clinical and epidemiological investigators, and two biological investigators (university departments, research institutes, and the National Health Service in Scotland). **Funding:** Leukaemia and Lymphoma Research.

United States, California State, California Childhood Leukemia Study (CCLS) [91]

Research and Clinical Investigators

Patricia A. Buffler and Catherine Metayer (University of California, Berkeley); Jonathan Ducore (University of California Davis Medical Center); Mignon Loh and Katherine Matthey (University of California, San Francisco); Vonda Crouse (Children's Hospital of Central California); Gary Dahl (Lucile Packard Children's Hospital); James Feusner (Children's Hospital Oakland); Vincent Kiley (Kaiser Permanente Sacramento); Carolyn Russo and Alan Wong (Kaiser Permanente Santa Clara); Kenneth Leung (Kaiser

Permanente San Francisco); Stacy Month (Kaiser Permanente Oakland). **Funding:** National Institute of Environmental Health Sciences, USA and the CHILDREN with CANCER, UK.

United States, Children's Oncology Group (COG) [92-94]

(<http://www.curesearch.org/Research/> and <http://www.childrensoncology-group.org/index.php/about>)

Research and Clinical Investigators

Logan Spector (University of Minnesota), and research and clinical investigators at the Children's Oncology Group (COG) and Children's Cancer Group (CCG) principal and affiliate member institutions. **Funding:** National Cancer Institute, USA, COG Foundation, and the National Childhood Cancer Foundation.

United States, Texas State

Research and Clinical Investigators

Melissa Bondy, M. Fatih Okcu, and Michael Scheurer (The Childhood Cancer Epidemiology and Prevention Center, Texas); David Poplack (Children's Cancer Center); Armando Correa and Jean Raphael (Texas Children's Hospital); Caryn Cohan and Anish Masharani (and the Texas Children's Pediatric Associates-Bellaire Clinic).

United States, Washington State [95]

Research Investigators

Beth Mueller, Parveen Bhatti, Eric Chow, Bill O'Brien, Michelle Williams, Danise Podvin, Carrie Kuehn (University of Washington). **Funding:** Washington State Department of Health, the Cancer Surveillance System of Western Washington part of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, and the Fred Hutchinson Cancer Center.

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Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
CLIC	Childhood Leukemia International Consortium
HLA	human leukocyte antigen
GWAS	genome wide association studies
IARC	International Agency for Research on Cancer
MTHFR	methylene tetrahydrofolatereductase
SNPs	single-nucleotide polymorphisms
FISH	fluorescence in situ hybridization
PCR	polymerase chain reaction
I4C	International Consortium of Childhood Cancer Cohorts

Description of Studies Participating in the Childhood Leukemia International Consortium (CLIC), April 2006–September 2012.

Table 1

Study location ^a , name	Institution (investigators)	Period of recruitment	Study design	Case source	Case eligibility criteria	Control source	Control eligibility criteria	Source of data collection	Primary objectives
Australia, Aus-ALL [13,64,67]	Telethon Institute for Child Health Research (Miline E.; Armstrong B.)	2003–2007	Case–control study; Frequency matching	Hospitals (nationwide)	Age 0–14 yrs; Incident ALL; No previous cancer; Biological mother available and at least one parent speaks English; Resident in Australia	RDD	Age 0–14 yrs; Biological mother available and at least one parent speaks English; Resident in Australia	Questionnaire	E, G, GxE
Brazil, Brazilian Collaborative Study Group (BCSG) [30,32,68]	Instituto Nacional de Cancer, Research Center, Rio de Janeiro (Pombo-de-Oliveira M.; Kofman S.)	1999–2007	Case–control study; Frequency matching (focus on infant acute leukemia, IAL)	Hospitals (in BCSG)	Age 0–2 yrs; Incident CL; Biospecimen available for IAL study; No genetic diseases or myelodysplastic syndrome	Hospitals	Age 0–4 yrs; No genetic disease or myelodysplastic syndrome	Questionnaire; Medical report	E, G, GxE
Canada, Quebec [55,69,70] ^b	McGill University (Infante-Rivard C.)	1980–2000	Case–control study; Individual matching; Case–and–control parental trios	Hospitals (province-wide)	Age 0–14 yrs; Incident ALL diagnosed from 1980–2000; No previous cancer	Health Insurance file population-based registry (province-wide)	Age 0–14 yrs	Questionnaire	E, G, GxE
Canada, Qc-ALL, Sainte Justine Hospital, Quebec [71–73] ^b	University of Montreal, Sainte-Justine Hospital (Simnett D.)	1989–present	Case–control study; Case–parental trios	Hospital (single)	Age 0–18 yrs; Incident ALL; Complete clinical history; Biological specimen available; No previous cancer	Varies by analysis (hospitals, biobank, or others)	Varies by analysis	Medical report	G
Costa Rica	Central American Institute for Studies on Toxic Substances, Universidad Nacional (Monge P.)	2001–2003	Case–control study; Frequency matching	Population-based cancer registry and hospitals (nationwide)	Age 0–14 yrs; CL diagnosed from 1995–2000	Birth Registry (nationwide)	Age 0–14 yrs	Questionnaire; Environmental measurement	E
Egypt, Children’s Cancer Hospital Egypt-57357 (CCHE)	CCHE (Ezzat S.)	2009–2011	Case–control study; Frequency matching	Hospital (single)	Age 0–14 yrs; B-cell ALL diagnosed within 6 months; Resident in Egypt; Biological mother available	Population (region-based)	Age 0–14 yrs; Resident in Egypt; Biological mother available	Questionnaire	E, G, GxE
France, ADELE [26]	InsERM U1018, Environmental Epidemiology of Cancer (Clavel J.)	1995–1999	Case–control study; Frequency matching; Case–parental trios	Hospitals	Age 0–14 yrs; Incident CL; No previous cancer; Biological mother available and speaks French; Child alive	Hospitals (same as cases)	Age 0–14 yrs; No previous cancer; Biological mother available and speaks French; Child alive	Questionnaire	E, G, GxE
France, ELECTRE [74]	InsERM U1018, Environmental Epidemiology of Cancer (Clavel J.)	1995–1999	Case–control study; Frequency matching	Population-based cancer registry (nationwide)	Age 0–14 yrs; Incident CL in 14 regions; Resident in 14 regions at diagnosis	Population quotas by age, sex, region (nationwide)	Age 0–14 yrs; Resident in 14 regions	Questionnaire	E
France, ESCALE [7,62]	InsERM U1018, Environmental Epidemiology of Cancer (Clavel J.)	2003–2004	Case–control study; Frequency matching; Case–parental trios	Population-based cancer registry (nationwide)	Age 0–14 yrs; All incident CL; No previous cancer; Biological mother available and speaks French; Child alive	Population quotas by age, sex, region (nationwide)	Age 0–14 yrs; No previous cancer; Biological mother available and speaks French; Child alive	Questionnaire	E, G, GxE
France, ESTELLE	InsERM U1018, Environmental Epidemiology of Cancer (Clavel J.)	2010–present	Case–control study; Frequency matching; Case–parental trios	Population-based cancer registry (nationwide)	Age 0–14 yrs; All incident CL; No previous cancer; Biological mother available and speaks French; Child alive	Population quotas by age, sex, region (nationwide)	Age 0–14 yrs; No previous cancer; Biological mother available and speaks French; Child alive	Questionnaire	E, G, GxE
Germany, German Childhood Cancer Registry (GCCR) [75–77]	GCCR, Institute for Medical Biostatistics, Epidemiology and Informatics (Kaatsch P.; Schütz J.)	1980–1996	Pooled case–control study (two time periods, see case eligibility criteria); Individual matched control recruitment; Frequency–matching in analyses	Population-based cancer registry (nationwide)	(1) CL diagnosed 1992–1994 (covering former Federal Republic of Germany before reunification; nationwide); (2) CL diagnosed 1988–1993 (state of Lower Saxony, regional)	Population-based registry (community-based but complete nationwide coverage)	Age 0–14 yrs; No previous cancer; Same residential criteria as cases	Questionnaire; Environmental measurement	E

Study location ^a , name	Institution (investigators)	Period of recruitment	Study design	Case source	Case eligibility criteria	Control source	Control eligibility criteria	Source of data collection	Primary objectives
Greece, Nationwide Registry for Childhood Haematological Malignancies (NARECHEM) [78-80]	Department of Hygiene, Epidemiology and Medical Statistics, Medical School, University of Athens (Petridou E.; Dessypris N.)	1996–present	Case-control study; Individual matching	Clinical cancer registry (NARECHEM)	Age 0–14 yrs; CL diagnosed since 1996; Resident in Greece for at least two years	Hospital	Age 0–14 yrs; No previous cancer; Resident in Greece for at least two years	Questionnaire; Medical report	E, G, GxE
Italy, Studio sulla Eziologia dei Tumori Infantili Linfemopoietici (SETIL) [81]	University of Eastern Piedmont (Magnani C.; Miligi L.)	1998–2001	Case-control study; Individual matching	Clinical cancer registry (nationwide)	Age 0–10 yrs; CL diagnosed from 1998–2001	Registry (nationwide)	Age 0–10 yrs	Questionnaire; Environmental measurement	E
New Zealand, New Zealand Childhood Cancer Study (NZCCS) [82-84]	Department of Preventive and Social Medicine, University of Otago (Dockerty J.)	1990–1993	Case-control study; Individual matching	National Cancer Registry; Children’s Cancer Registry; Hospital admission/discharge system (nationwide)	Age 0–14 yrs; Incident CL; Born and resident in New Zealand	Birth Registry (nationwide)	Age 0–14 yrs; Born and resident in New Zealand	Questionnaire; Medical report; Environmental measurement	E, G, GxE
UK, Manchester ^c	Pediatric and Familial Cancer Research Group, University of Manchester (Birch J.; Taylor M.)	1989–2001	Case-control study; Individual matching; Case-parental trios (1992–96) [3]; Case only (1989–1992; 1997–2001)	General practitioner (GP) registries (nationwide)	Age 0–10 yrs; CL born in Great Britain and diagnosed in North West England or North Wales	GP registry (nationwide)	Age 0–14 yrs; GP consent; Born and resident in England, Wales, Scotland; Not under local authority care; No previous cancer	Questionnaire; Registry; Medical report	E, G, GxE
UK, Oxford, Childhood Cancer Research Group (CCRG) [85-87] ^c	CCRG, Oxford University (Murphy M.; O’Neill K.)	1962–2006	Case-control study (birth registration record based); Individual matching	Population-based cancer registry (nationwide)	Age 0–14 yrs; Incident CL; Resident in England, Wales, or Scotland	Birth registry (nationwide)	Age 0–14 yrs; Resident in England, Wales, or Scotland	Registry	E
UK, United Kingdom Childhood Cancer Study (UKCCS) [88-90] ^c	Department of Health Science, Epidemiology and genetics Unit, University of York (Roman E.; Lightfoot I.)	1991–1998	Case-control study; Individual matching; Case-parental trios	GP registries (nationwide)	Age 0–14 yrs; Incident CL diagnosed from 1991–98; GP consent; Born and resident in England, Wales, Scotland; Not under local authority care; No previous cancer	GP registry (nationwide)	Age 0–14 yrs; GP consent; Born and resident in England, Wales, Scotland; Not under local authority care; No previous cancer	Questionnaire; Registry; Medical report; Environmental Measurement	E, GxE
US, California State, California Childhood Leukemia Study (CCLS) [91]	University of California, Berkeley (Bufler P.; Metayer C.)	1995–present	Case-control study; Individual matching	Hospitals	Age 0–14 yrs; Incident CL; No previous cancer; Biological parent(s) speak English or Spanish; Resident in study area	Birth registry (statewide)	Age 0–14 yrs; No previous cancer; Biological parent(s) speak English/Spanish; Resident in study area	Questionnaire; Registry; Medical report; Environmental measurement	E, G, GxE
US, Children’s Oncology Group (COG) (Children Cancer Group (CCG)-E14, CCG-E15) [92-94]	University of Minnesota, Minneapolis (Spector L.)	1989–1993	Case-control study; Individual matching	CCG clinical trials in the US and Canada)	Age 0–14 yrs; Incident cases enrolled in the CCG-14 (AML) and CCG-15 (ALL) trials from 1989 to 1993; No prior cancer; Biological mother with phone and speaks English	RDD	Age 0–14 yrs; Biological mother with phone and speaks English	Questionnaire	E
US, Texas State	Baylor College of Medicine, Department of Pediatrics, Section of Hematology-Oncology (Scheurer M.; Bondy M.)	2003–present	Case-control study; Individual matching; Case-parental trios (2007–present); Survival studies (2003–present)	Hospital (single)	Age 0–18 yrs; Incident CL for case-control study; Prevalent CL for survival study; No previous cancer	Hospital (single)	Age 0–18 yrs; No previous cancer	Questionnaire; Medical report	E, G, GxE
US, Washington State [95]	Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle (Mueller B.; Bhatti P.)	1974–2009	Case-control study; Frequency matching	Population-based cancer registry (regional 1974–1993; statewide 1994–2009)	Age 0–19 yrs; All incident leukemia cases identified in population registries; Exposure data from linked birth record 1974–1986 with additional birth hospitalization discharge record data 1987–2009	Birth registry (statewide)	Randomly selected from birth records, matched on birth year	Registry	E, G, GxE

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CL, childhood leukemia of all types; E, environmental studies; G, genetic studies; GxE, gene × environmental interaction studies; GP, General practitioner; RDD, random digit dialing.

^aBy alphabetical order.

^b Possible overlap of cases.

^c Possible overlap of cases and/or controls.

Table 2

Number of cases and controls in the Childhood Leukemia International Consortium (CLIC) Studies, April 2006–September 2012.

Study location ^a , name	Number of leukemia cases and controls					Biospecimens for DNA extraction					Sources of DNA				
	All cases combined					Controls					Case-child				
	ALL	B-cell ALL	T-cell ALL	AML							Case-child	Case-mother	Case-father	Control-mother	Control-father
Australia, Aus-ALL	393	393	349	37	0	1249		Blood; Buccal cells		✓	✓	✓	✓	✓	✓
Brazil, BCSG	486	359	326	33	118	539		Blood; Buccal cells		✓	✓				
Canada, Quebec ^b	790	790	683	75	0	790		Blood; Saliva; Buccal cells		✓	✓	✓	✓	✓	✓
Canada, Qc-ALL ^b	600	600	540	60	0	300		Blood; Saliva		✓	✓	✓	✓		
Costa Rica ^c	299	251			33	579		Buccal cells		✓	✓	✓	✓	✓	✓
Egypt, CCHE	299	299	299	0	0	351		Blood		✓	✓	✓	✓	✓	
France, ADELE	280	240	203	30	36	288		Blood		✓	✓	✓	✓	✓	
France, ELECTRE	473	407	344	55	65	567									
France, ESCALE	764	648	575	67	101	1681		Blood; Saliva		✓	✓	✓	✓		
France, ESTELLE	622	527	418	55	90	1421		Blood; Saliva		✓	✓	✓	✓		
Germany, GCCR	903	751	672	71	130	2458									
Greece, NARECHEM	1335	1164	1018	121	155	1084		Blood		✓					
Italy, SETIL	683	585	463	99	80	1044									
New Zealand, NZCCS	121	97	88	7	22	303		Blood		✓					
UK, Manchester ^d	468	367	314	44	88	998		Blood		✓	✓	✓	✓		
UK, Oxford, CCRG ^{d,e}	16 201	13 522			2679	16 201		ANBS (planned)		(planned)					
UK, UKCCCS ^d	1735	1403	1154	145	249	3450		Blood		✓	✓		✓		
US, California State, CCLS	997	839	756	76	145	1226		Blood; Saliva; Buccal cells; ANBS		✓	✓	✓	✓		
US, COG (CCG-EI4)	517	0	0	0	517	610									
US, COG (CCG-EI5)	1914	1914	1165	180	0	1987									
US, Texas State ^f	130	123			7	750		Blood; Saliva		✓	✓	✓	✓		
US, Washington State ^f	1229	953			204	12 290		ANBS (planned)		(planned)					
Sub-total, studies with comprehensive epidemiologic data ^g	13 209	11 157	8827	1095	1836	21 375				~8800	~4700	~2400	~2100	~1100	~1080
Sub-total, studies with limited epidemiologic data ^h	18 030	15 075	540	60	2883	28 791				~600	~300	~200	0	0	0
Total, all CLIC studies	31 239	26 232	9367	1155	4719	50 166				~9400	~5000	~2600	~2100	~1100	~1080

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANBS, archived newborn blood spots; ~ denotes estimated numbers of specimens based on surveys completed when studies entered the consortium (e.g., more samples could have been accrued or used since a study joined CLIC).

^aBy alphabetical order.

b Possible overlap of cases.

c Immunophenotype data not currently available.

d Possible overlap of cases and/or controls.

e Immunophenotype data is available for ~13,522 ALL cases. Precise count is not presently available.

f Number of leukemia subtypes available upon request.

g All studies except Canada, Qc-ALL; UK, Oxford, CCRG; US, Washington State.

h Only Canada, Qc-ALL; UK, Oxford, CCRG; US, Washington State.

Table 3

CLIC pooled analyses in progress (as of September 2012).

Risk factors	Outcome	CLIC studies ^a	ALL cases ^b	AML cases ^b	Controls ^b
Measures of fetal growth	Risk of ALL	12	7400	n/a	12 500
Maternal vitamin and folate intake before and during pregnancy (and MTHFR variants)	Risk of ALL, AML	11 (5)	6970	600	12 060
Parental smoking (and xenobiotic-metabolizing gene variants)	Risk of ALL	12 (4)	9100	n/a	14 860
Markers of early infections and allergies	Risk of ALL	10	7670	720	12 530
Indoor sources of benzene and hydrocarbons, xenobiotic transport and metabolic genes	Risk of AML	10 (4)	n/a	930	7800
Exposure to pesticides at home (and xenobiotic transport and metabolic genes)	Risk of ALL, AML	11 (4)	7650	1150	13 960
Parental exposure to pesticides at work (and xenobiotic transport and metabolic genes)	Risk of ALL, AML	10 (4)	8900	1400	16 440
Exposure to paints at home (and xenobiotic transport and metabolic genes)	Risk of ALL, AML	8 (4)	4900	380	6760
Parental exposure to paints at work (and xenobiotic transport and metabolic genes)	Risk of ALL, AML	11 (4)	7650	1150	13 960
Maternal consumption of coffee and tea	Risk of ALL				
Assisted reproductive technologies; time to pregnancy	Risk of ALL			Pending data	
Geographic distribution of AML, APL and cytogenetic subtypes	AML, APL				
Socio-demographic and clinical characteristics	Survival of ALL, AML				

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia.

^aNumber in parentheses represents the number of studies with genotyping data.

^bMaximum (rounded) numbers of cases and controls are provided, and numbers may vary by specific risk factor under study.