International and Multidisciplinary Collaborations to Advance Etiologic Research on Leukaemia and Other Cancers in Children

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Epidemiologic studies of childhood leukaemia and other cancers are challenging due to the rarity of the disease and tumor heterogeneity. Moreover, most childhood cancers are likely to be multifactorial implicating an array of genetic and non-genetic factors. These characteristics have forged how researchers from several countries and disciplines have worked in the past years to uncover factors that are associated with the development of childhood cancers.

Drawing from research on childhood leukaemia, the most common cancer in children and probably the most studied to date, this session will describe how researchers around the world gathered 12 years ago to establish the Childhood Leukemia International Consortium (CLIC). This collective of senior and junior investigators from 18 countries have shared their expertise, time, and data for up to 40,000 leukaemia cases and 350,000 controls from 35 case-control studies. This unprecedented large sample size has allowed us to conduct pooled and meta-analyses for major leukaemia subtypes and socio-demographics subgroups, providing the most robust findings to date on pre- and/or postnatal factors related to pregnancy and birth characteristics, medical conditions, diet and vitamin supplementation, chemical exposures at home and at work, and measures of immune function and infections. CLIC analyses incorporate methodological evaluations of possible biases inherent to case-control design by comparing hospital-based vs. registry-based studies, and by conducting sensitivity bias analyses. As more CLIC studies have generated genome-wide data, CLIC is now entering a new phase to incorporate genetic only and gene-environment analyses. The success of CLIC to date is measured not only by a total of 13 publications and over 10 ongoing pooled analyses, but also by the training of young investigators in the field of molecular epidemiology of childhood cancers. Following the success of CLIC, the consortium recently expanded to other pediatric cancers to form the CLIC-*plus* consortium, with a current focus on childhood brain tumors (~14,000 cases) and embryonal tumors (~11,000 cases).

While the strength of international consortia resides in numbers and geographical variation that enables examination of the disease and exposure heterogeneity, other approaches are needed to provide mechanistic understanding of the observed associations, and to uncover factors that cannot be identified from “traditional” epidemiologic studies that use primarily self-reports or registry-based data. To that effect, the Center for Integrative Research on Childhood Leukemia and the Environment (CIRCLE) was established in 2004 by researchers at the University of California Berkeley to foster multidisciplinary research in the fields of epidemiology, molecular biology, genetics, epigenetics, toxicology, exposure assessment, animal models, biostatistics, preventative medicine, and research translation. CIRCLE has developed innovative targeted and untargeted biomarker studies to better characterize the disease, as well as exposures before and after birth. Selected findings will be presented on how home dust samples can provide a useful snapshot of persistent chemicals in the child’s environment, increasing the chemical body burden and subsequent risk of childhood leukaemia. Results from the CLIC consortium and the children center CIRCLE provide strong foundations to recommend preventative measures to reduce the risk of childhood leukaemia (examples will be presented during the conference, Dr. Miller, Day 3).

The incidence rate of childhood leukaemia and other cancers has been increasing at a fast pace in the last 40 years in certain populations. Despite alarming statistics, federal funding for research that aims to identify causes of childhood cancers and promote prevention has been consistently dismal, putting more children at risk to be diagnosed with cancer and to suffer short- and long-term complications throughout their lives. It is therefore critical to invest in childhood cancer etiologic research and research translation that requires international and multidisciplinary collaborations.

Publications from the CLIC Consortium

1. Milne E et al. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: a pooled analysis from the childhood Leukemia International Consortium. Cancer Causes Control. 2018 Jun;29(6):539-550.

2. Orsi L. and *al*. Living on a farm, contact with farm animals and pets, and childhood acute lymphoblastic leukemia: pooled and meta-analyses from the Childhood Leukemia International Consortium. Cancer Med. 2018 Jun;7(6):2665-2681.

3. Petridou ET et *al*. Advanced parental age as risk factor for childhood acute lymphoblastic leukemia: results from studies of the Childhood Leukemia International Consortium. Eur J Epidemiol. 2018 May 14. [Epub ahead of print]

4. Metayer C et *al*. Parental tobacco smoking and acute myeloid leukemia: The Childhood Leukemia International Consortium. Am J Epidemiol. 2016 Aug 15;184(4):261-73.

6. Marcotte EL et *al*. Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). Lancet Haematol. 2016 Apr;3(4):e176-85.

7. Bailey HD et *al*. Home pesticide exposures and risk of childhood leukemia: Findings from the childhood leukemia international consortium. Int J Cancer. 2015 Dec 1;137(11):2644-63.

8. Bailey HD et *al*. Home paint exposures and risk of childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium. Cancer Causes Control. 2015 Sep;26(9):1257-70.

9. Rudant J et *al*. Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium study. Am J Epidemiol. 2015 Apr 15;181(8):549-62.

10. Metayer 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 Nov;25(6):811-22.

11. Bailey HD et *al*. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium. Int J Cancer. 2014 Nov 1;135(9):2157-72.

12. Bailey HD 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 Oct;25(10):1351-67.

13. Milne E et *al*. Fetal growth and childhood acute lymphoblastic leukemia: findings from the childhood leukemia international consortium. Int J Cancer. 2013 Dec 15;133(12):2968-79.

14. Metayer C et *al*. The Childhood Leukemia International Consortium. Cancer Epidemiol. 2013 Jun;37(3):336-47.

Additional information on CIRCLE and CLIC is available at
www.circle.berkeley.edu
http://circle.berkeley.edu/research/childhood-leukemia-international-consortium/