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**EDITORIAL**

# Etiology of Childhood Leukemia: Environment, Genes, Controversies, and Conundrums

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Despite several decades of epidemiological studies, the etiology of childhood leukemia is poorly understood. The only consistently observed risk factors are moderate-to-high single or fractionated doses of ionizing radiation, e.g., the acute exposure of the Japanese atomic bomb survivors and radiotherapy for malignant or benign conditions, respectively, diagnostic x-rays during pregnancy, and certain rare genetic disorders. In this issue, Buffler and colleagues evaluate the evidence linking these factors and other postulated etiologies including physical, chemical, lifestyle, immunological, and infectious agents.[1]

Controversies and unresolved issues abound. Numerous case-control studies have linked prenatal diagnostic x-ray exposures of mothers, particularly during the last trimester, to 40–50% elevated risks of childhood leukemia.[2] The absence of associations in the few cohort studies, including those children who were in utero at the time of the atomic bombings in Japan, has led some to question the relationship.[3] Earlier studies linking high socioeconomic status with childhood acute lymphoid leukemia[4] do not appear to be supported by more recent investigations.[5] Reasons are unclear for the small excess risk of childhood acute lymphoid leukemia among the tiny fraction of children exposed to residential, power-frequency residential magnetic field levels >0.3 or 0.4 microtesla.[6] Buffler and collaborators identify longstanding unanswered questions. For example, are known adult leukemogens, such as benzene, etiologically related to childhood leukemia? Extensive epidemiological data implicate an infectious origin for acute lymphoid leukemia, but what is the organism(s)? What are the critical time frame(s) for pediatric leukemogenesis?

Numerous epidemiological studies, particularly those focusing on chemical exposures, rely on ecological comparisons, proxy measures, or indirect exposure ascertainment, in part because of the rarity of childhood leukemia and the requirement for retrospective exposure assessment. Statistical power limitations are underscored further when assessing risks according to leukemia subtype, given the heterogeneity and small numbers of most forms of childhood leukemia defined by nonrandom cytogenetic abnormalities. Unlike adults, young children developing leukemia and age-similar controls do not have the ability to respond to complex questions, a critical component of virtually all childhood leukemia epidemiological studies. Human subjects' considerations limit further the ability to obtain biological specimens or conduct certain forms of exposure assessment in children.

Epidemiological studies have begun to investigate the postulated leukemogenic role of polymorphisms of genes encoding enzymes with key roles in activation or metabolism of xenobiotics, protection of cells against oxidative stress, DNA repair pathways, immunomodulation, and folic acid metabolism. Many of the initial molecular epidemiological studies are limited by small numbers of selected subjects due to low response in providing biological specimens. As Buffler and colleagues perceptively conclude, advances in our understanding of the causes of childhood leukemia will require rigorous attention to critical design and methodological issues in all components (including molecular) of epidemiological studies, as well as enrollment of appropriate controls. Improvements are needed in exposure assessment, statistical power, and participation levels. Adequate attention must also be given to potential confounders and effect modifiers, to minimizing recall and other forms of bias, and to incorporating sufficient quality control measures. Finally, combining data from multiple investigations using theta-analysis or pooled analysis will enable investigators to identify more accurately modest associations and consistency of findings.

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