Environmental Exposures and Childhood Cancer: Our Best May Not Be Good Enough

Childhood cancer ranks high among public concerns, evoking the public's fear of cancer as well as the special emotional attention that is focused on children. Although it is rare, its priority is elevated on the basis of years of life lost and its prominence among life-threatening diseases of children. Despite great success in the treatment of childhood cancers such as Wilms' tumor and leukemia, cancer continues to be life threatening in children.

For several decades, clusters of childhood leukemia have been investigated, in a search first for an infectious etiology and then for an environmental etiology,[1] both without success. Childhood cancer clusters continue to generate public concern and consume health department resources, but there has been little progress in understanding the etiology or identifying preventive measures. The focus often turns to the role of environmental pollutants such as pesticides, electromagnetic fields, and chemicals found in hazardous wastes. The rationale for seeking exogenous, modifiable causes of childhood cancer that can be avoided, leading to a reduction in the risk of disease, is compelling. The negative consequence of such public demand and support for epidemiologic research is the temptation to overinterpret every shred of fallible evidence that emerges. The public and media tend to place much more faith than is warranted in isolated findings, to the detriment of sound policy and the credibility of researchers.

Epidemiologic research into potential environmental contributors to the etiology of childhood leukemia, brain cancer, and other pediatric malignancies has been pursued intensively for over 20 years. Motivated by scientific interest and public concern, a number of studies have evaluated the role of pesticides,[2] ionizing radiation,[3] nonionizing radiation,[4,5] and a wide range of occupational and environmental exposures.[5–7] Dozens of epidemiologic studies have been conducted on these topics, some with sophisticated designs, large populations, and attention to exposure assessment, such as the report in this issue by Freedman et al.[8] on solvent exposure and childhood acute lymphoblastic leukemia.

Scientific Challenges to Identifying Causes of Childhood Cancer

The scientific challenges to identifying environmental contributors to the etiology of childhood cancer are daunting. We are uncertain about the relative importance of exposures of the mother, father, and child in disease etiology. Although the time frame is narrower than the half century of potential relevance in the etiology of adult cancer, the origins of childhood cancer may lie anywhere between conception and diagnosis. The appropriate disease entities for study cannot be defined with confidence, so histology, age at onset, and tumor biology are all potential markers of etiologic heterogeneity. The goal of creating ever-finer case subgroups must be reconciled with the overall rarity of cancers in children. The trade-off is between potential gains in validity achieved by creating more homogeneous case groups and a definite loss of precision as the group size is reduced.

Because childhood cancers are so rare, true prospective studies are virtually impossible, necessitating continued reliance on case–control studies. As noted by Freedman et al.,[8] the 2 key challenges associated with that design are control selection and exposure assessment. Except in locations with complete birth registries or population rosters (mostly in northern Europe), identifying and recruiting a sample of the case-generating study base pose great challenges.

Hospital-based studies make it impossible to define the source of cases, particularly for diseases that result in referrals from a wide geographic area**.** Because few children are hospitalized for any reason, finding "exposure-neutral" diagnostic groups of children as a source of controls is even more challenging than it is for adults. In population-based studies, nonresponse is inevitable, often reaching levels of 20% to 40% of the eligible population. As a reminder that this nonresponse is capable of distorting measures of association, virtually all case–control studies of childhood leukemia in the United States, including the study by Freedman et al., have found higher risk in the lower social classes, despite there being an established, though modest, positive correlation between higher social class and risk for child cancer[5] on the basis of registry information. The overrepresentation of upper-social-class controls relative to lower-social-class controls, stronger than the corresponding trend among cases, appears to be the source of this effect, replicated across studies. Adjustment for social class can be made, but this consistent observation suggests that other aspects of nonresponse (particularly among controls) may well have more insidious effects.

The second consequence of conducting case–control studies is the loss of information associated with retrospective exposure assessment. Until the cancer is identified (or the control child reaches the equivalent age), we cannot ascertain exposure and are thus faced with reconstructing exposure throughout the potential etiologic period. Studies that identify the cases as they are diagnosed, as was done by Freedman et al.,[8] avoid the additional time delay associated with recruiting cases diagnosed before the initiation of data collection, but there is still a limit to the accuracy of exposure assessment for periods extending back as far as 15 years. Biological markers of exposure are clearly not applicable, and direct measurement of environmental agents in the physical locations of interest is of uncertain relevance owing to the passage of time. We are forced to rely on memory, which itself is limited in accuracy and objectivity with regard to the important details about workplaces and the home environment that can affect exposure.

Solvents and Childhood Leukemia

Recognizing all these limitations, the report by Freedman et al. reflects the "state of the art" in childhood cancer epidemiology with regard to study size (640 cases included in the analysis), homogeneity of disease classification (all acute lymphoblastic leukemia), method of control selection (random-digit dialing), and approach to exposure assessment (structured questionnaire addressing frequency and duration of exposure). As would be predicted, the greatest concerns with bias arise from nonresponse and exposure misclassification. Only 64% of eligible controls were enrolled, and despite some evidence against the available measures of social class being associated with solvent exposure, that level of nonparticipation leaves open the possibility of distorted results. Relative to an ideal measure of actual solvent exposure, as might be obtained through personal monitoring, the effectiveness of the exposure assessment questions is uncertain. The investigators focus on differential error, which could contribute to elevated measures of association, but nondifferential misclassification is more certain to be present and can be invoked as an argument that observed associations are more likely to be underestimates of any underlying causal association.

This study advances the hypothesis that solvent exposure may contribute to the etiology of childhood leukemia, moving it from a plausible hypothesis with no direct epidemiologic support to one with very limited epidemiologic support. The total evidence supporting the hypothesis that household solvent exposures cause childhood leukemia nevertheless remains weak but deserving of further study. Perhaps the most disconcerting challenge posed by the study is *how* to make progress in evaluating the hypothesis further. The very strengths of the study by Freedman et al. make it difficult to suggest improvements. Certainly, pure replication, assessing whether the same study design generates the same results in other settings, would be welcome. There is clearly some room for refinements in the approach to exposure assessment, with more detailed query pertaining to exposure determinants. Those who are already engaged in such studies would do well to include pertinent questions regarding household solvent exposure. However, given the rarity of the disease and the expense associated with studies of this size, it is difficult to advocate initiating new studies with household solvent exposure as a primary justification.

Even though the epidemiologic studies directly tackle the exposure and disease of interest, more insight may be generated by strong findings of indirect relevance than by more weak findings of direct relevance. Research that addresses the impact of self-reported activities on measured solvent exposure would be highly beneficial to interpreting this study and could lead to improved methods of retrospective exposure assessment. Toxicologic studies of implicated agents, such as methylene chloride and benzene, focusing on animal models of childhood leukemia may help in the interpretation of these results. For a possible paternally mediated pathway linking solvent exposure to childhood leukemia, further work on sperm-mediated genetic alterations associated with solvent exposures could be contributory. With regard to childhood exposure, focus might shift to endpoints that can be measured prospectively in modest populations, ideally, biomarkers of early effect such as cytogenetic damage. If we are to attain the conclusive results pertaining to solvent exposure (or pesticides, nonionizing radiation, etc.) and leukemia (or other childhood cancers)—an elusive goal so far—it is very unlikely to come through sheer weight of replicated findings from conventional epidemiologic studies. □

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