

Commentaries

Unrecognized or Potential Risk Factors for Childhood Cancer

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Epidemiologic methods only seldom identify causes of childhood cancer associated with relative risks below a factor of $1\frac{1}{2}$ –2. Children are at risk of exposure to over 15,000 high-production-volume chemicals and are certainly exposed to many carcinogens. The individual impacts of most of these agents are too small to be detected, but collectively these unrecognized factors are potentially important. Infants and children are exposed to higher levels of some environmental toxicants and may also be more sensitive. During intrauterine development and childhood, cells divide frequently, and the mutant frequency rises rapidly. Endocrine-related cancers or susceptibility to cancer may result from developmental exposures rather than from exposures existing at or near the time of diagnosis. That environmental exposures may be important

causes of childhood cancers is indicated by associations of enzyme polymorphisms with risk. *Key words:* childhood cancer; epidemiology; low-dose effects; exposure; sensitivity; environmental factors; polymorphisms.

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Limitations of Traditional Epidemiology

In the Baseline Report on Childhood Cancer in the Framework of the European Environment and Health Strategy, by the Technical Working Group on Priority Diseases, Subgroup Childhood Cancer,¹ the epidemiologic evidence of the role of environmental chemical exposures in childhood cancer was reviewed. This report stated that the likely contribution of environmental agents identified as possible etiologic factors in the overall burden of childhood cancer may be minor. However, epidemiologic methods can only seldom identify causal factors associated with relative risks (RRs) of less than a factor of $1\frac{1}{2}$ –2.²

Approximately 10% of non-polymer, synthetic chemical substances have some carcinogenic potency in animals.^{3,4} In view of the many similarities between animal and human carcinogenesis, it is likely that most animal carcinogens are also to some extent carcinogenic in humans. According to the International Agency for Research on Cancer, in the absence of adequate data relative to humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans.⁵ Both mechanistic insights (see appendix on mechanisms of carcinogenesis in the Baseline Report¹) and experiments on animals point to the importance of mutagenic and of hormone-disturbing agents in the causation of cancer.

Children are at risk of exposure to over 15,000 high-production-volume synthetic chemicals, nearly all of them developed over the past 50 years. These chemi-

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cals are used widely in consumer products and are dispersed in the environment.⁶ More than 2,800 chemicals have been identified in ambient air.⁷ It is thus certain that children are exposed to hundreds of substances that can contribute to carcinogenesis. The individual impacts of most of these agents are too small to be detected. Collectively, however, these unrecognized factors make a potentially important contribution to the incidence of childhood cancer.

Low-dose Effects

Environmental exposures typically involve low doses. Risk assessments for genotoxic carcinogens have generally used a linear, no-threshold model to predict carcinogenic effects at low doses. For example, studies of alpha particles using a microbeam source showed that a single-particle traversal was highly mutagenic.⁸ In addition, there are frequently, although not always, linear relationships between the dose of genotoxic agents and the amounts of DNA adducts,^{9,10} and also between the doses of mutagenic agents and the numbers of induced mutations.^{10,11} In contrast, epigenetic carcinogens may be effective only above certain thresholds. For receptor-binding chemicals such as dioxins and some dioxin-like PCBs, even very low, incremental doses might increase risk.¹²

Exposure and Sensitivity of Children

Infants and children differ from adults in their exposures both qualitatively and quantitatively, in part because they eat more food, drink more water, and breathe more air per unit of body weight than adults.¹³ For example, the air intake of a resting infant is twice that of an adult under the same conditions,¹⁴ and the activity patterns of children further increase their exposures to pollutants. Because children are typically engaged in more physical activity, play close to the ground, and engage in characteristic hand-to-mouth behavior, they are exposed to higher levels of toxicants such as pesticides, radon, and particulate matter than are adults.¹⁵

Infants and very young children, including the fetus, may be more sensitive to some carcinogenic agents. The earlier exposure takes place, the earlier cancer may develop, and the greater the probability that a given exposure can result in cancer. During intrauterine development and childhood, the number of cell divisions per unit of time is much greater than in adulthood, and the mutant frequency rises rapidly. In mice, about one third of spontaneous mutations arise before birth, about one third during growth to adulthood, and the remaining third during the rest of the animal's life.¹⁶ Also, cancer cells have been shown to grow and metastasize more easily in very young animals.¹⁷ Recent findings suggest that causes of endocrine-related can-

cers or susceptibility to cancer may be a result of developmental exposures rather than exposures existing at or near the time of tumor detection.¹⁸

Polymorphisms Point to Exogenous Chemicals

That environmental exposure may be important in the causation of childhood cancers is indicated by observations on associations of enzyme polymorphisms with risks of childhood cancers.¹⁹⁻²⁴ Exogenous as well as endogenous chemicals are excreted from the body after metabolic conversion by enzymes mediating activation (Phase I) and detoxification (Phase II). For several childhood cancers risks are modified by genetic characteristics affecting these enzymes and the activation or inactivation of exogenous chemicals. This holds also for acute lymphoblastic leukemia (ALL), the most common pediatric cancer. The risk for ALL increased to an odds ratio of 3.3 for children who presented three such genetic traits: NAT2 slow-acetylation, GSTM1 null, and CYP1A1*2A alleles.²² This supports the hypothesis that environmental exposure is important in the causation of childhood cancers.¹⁹⁻²⁴ A comparative inability of a segment of the population to process the chemicals to which they are environmentally exposed due to polymorphisms in Phase I and II systems might be involved in a sizeable fraction of childhood cancers.

Agents That Could Be Involved

The agents that are likely to contribute to childhood cancers include, among others, infectious agents; some forms of radiation; many reactive or hormone-like chemicals, such as some polycyclic aromatic hydrocarbons and their atmospheric reaction products; some alkenes and chlorinated alkenes; trihalomethanes; some nitrosamines; dietary mutagens such as heterocyclic amines; benzene and other solvents; cadmium; lead; arsenic; chromium and possibly other heavy metals; PCBs; dioxins; some bromine-containing flame retardants; some natural or synthetic estrogenic chemicals; and some pesticides. Findings indicate that instances of pesticide exposures are frequent and that pesticides are readily transferred to the developing fetus during pregnancy.²⁵

Transplacental chemical exposure to Baygon and other carbamate-based insecticides is reported to be associated with increased risk of a subtype of infant leukemia.²⁶ A case-control study regarding the effect of traffic exhaust on cancer in children showed that a mean NO₂ concentration equal to or greater than 50 µg/m³ in the outdoor air was associated with a relative risk of 2.7 (95% CI 0.9-8.5) compared with a situation in which this concentration in outdoor air was equal to or less than 39 µg/m³. At concentrations equal to or greater than 80 µg/m³, the relative risk amounted to 3.8 (CI 1.2-12.1).²⁷ Exposure in utero or during child-

hood to the aforementioned agents and to asbestos and some ceramic fibres will probably contribute more to life-time cancer incidence than exposure of the same intensity later in life.

Need for Molecular Epidemiology

The observations reviewed here point to the likelihood that children are potentially more at risk for cancer from environmental exposures encountered during development and childhood than are adults, who receive such exposures later in life. Nonetheless, traditional epidemiologic studies have indicated that environmental agents play only a minor role in the risk for childhood cancer. Few of these studies have employed molecular epidemiologic methods. Thus, future studies using molecular methods are needed to confirm or deny the conclusion drawn from traditional epidemiologic studies regarding risks for childhood cancer from environmental agents.

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