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REVIEW ARTICLE

Environmental Exposure and Risk of Childhood Leukemia: An Overview

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Childhood leukemia is the most common cancer diagnosed in children worldwide. However, only a few causes have been established so far, mainly some genetic syndromes and high doses of ionizing radiation. Major efforts have been undertaken to study the relationship between environmental factors and the risk of childhood leukemia, inspired by geographical variation in incidence rates. Some evidence has emerged for parental occupational exposures to pesticides, whereas there is less evidence for an association with postnatal pesticide exposure. Diagnostic radiation and radon exposure have been suggested but there remains a lack of convincing studies. Extremely low-frequency magnetic fields consistently showed a small increase in risk in numerous studies, but bias and confounding cannot be ruled out as possible explanations. From among factors other than environmental and radiation-related, the most promising candidate is abnormal patterns to common infections, but which children are most at risk and the pathways are not fully understood. In conclusion, although childhood leukemia shows some distinct incidence patterns by sex, age, and geography suggesting a role of the environment in its etiology, no major environmental risk factors including radiation have been established as major contributors to the global childhood leukemia burden. Due to the young age at diagnosis and evidence of chromosomal damage before birth in many of the affected children, parental exposures remain of high interest. Although cure rates of childhood leukemia are high in economically developed countries, because of the adverse late effects of the disease and its treatment, identification of modifiable risk factors for implementing primary prevention remains the ultimate goal.

Key Words: Leukemia, Children, Risk factors, Environment, Radiation.

Introduction

Childhood leukemia is the most common cancer type diagnosed in children worldwide, accounting for about one third of all childhood cancers in economically developed countries to one fifth or less in developing countries (1–4). Acute lymphoblastic leukemia (ALL) is by far the most frequent type of childhood leukemia, accounting for >75% of cases in developed countries, followed by acute myeloblastic leukemia (AML). Chronic leukemias are very rare in children (1). Survival from childhood leukemia has improved considerably in developed countries over the last four decades, exceeding 90% in 5-year survival for ALL (3,5) but remains abysmal in developing countries (6). As a result of the improvement in survival, the number of childhood cancer survivors increases continuously. Survivors, however, may experience a wide spectrum of treatment-induced adverse late effects including increased risk of developing a second malignancy. Therefore, understanding the causes to implement primary prevention remains an essential goal.

Major efforts have been undertaken to study the relationship between environmental factors and the risk of childhood leukemia. These will be reviewed below. ''Environment'' is sometimes defined in a broad or less broad way, reaching from ''all other than genetics'' to focusing on pollutants. The main scope of this review is to focus on environmental pollutants including parental

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exposure and radiation, but evidence regarding lifestyle and intrinsic factors will be briefly summarized.

Descriptive Patterns

Incidence patterns are well documented and similar for economically developed countries. Recent age-standardized incidence rates of 56.5 and 53.1 per million children aged 0–14 years have been reported for Germany (3) and the U.S. (4), respectively. Incidence rates vary by subtype, race/ethnicity, sex, and age (1,2), which may give indications for its etiology. Boys have an ~20% higher risk of developing ALL than girls. There is a distinct ALL incidence peak at ages 2–4 years, compared to younger or older children. For AML, boys have a slightly higher risk than girls and the incidence peaks during infancy (1,2). Incidence differences by ethnicity/race are well recognized for the U.S., with the highest incidence being reported for white Hispanic children and the lowest for black children. The differences are particularly pronounced for ALL (2.5 fold) but smaller for AML (1.2 fold) (7). High-quality data from developing countries and, in particular, from Sub-Saharan Africa are limited (8). Childhood leukemia rates of 20.1, 8.5, and 7.9 per million were reported from Harare in Zimbabwe, Kyadono in Uganda, and South Africa (9). Reported rates in sub-Saharan Africa are particularly low in infants. Recent evidence from Brazil, India and South Africa suggests, however, that observed incidence differences across countries may also reflect under-diagnosis and under-reporting of cases in poor-resource countries (9–11). This may be due to limited access and utilization of health care services, high prevalence of other competing diseases (e.g., malaria, HIV/AIDS, tuberculosis) with sometimes cancer-like symptoms, high proportions of deaths from unknown causes and lack of systematic disease registration. Time trends in developing countries showed a modest increase in incidence rates for leukemia over the last three decades of the 20th century, followed by a levelling off in the early 2000s. The increasing rates appeared to be largely driven by the increase in ALL but not AML (1,2,5). However, the observed temporal trend might also reflect improvements in diagnosis, access to health care services and more complete reporting. Some reports from similar geographical regions have indicated stable rates (12,13).

These descriptive patterns are important for the interpretation of any findings from analytical studies on potential risk factors. This refers in particular to the early age of diagnosis and the distinct age peak for ALL. Differences across racial/ethnic groups may be due to their different environmental exposure profiles but could also indicate interactions between environmental exposures and genetic susceptibility. The observed geographical differences in incidence rates may indicate that unique genetic or environmental exposures may affect the risk of childhood leukemia or specific subtypes. However, geographical incidence differences should be interpreted cautiously as it has not yet been fully understood what portion of observed incidence differences are due to different underlying true leukemia risks compared to what portion may be explained by different diagnostic, referral, documentation and registration patterns across populations.

Moreover, some general considerations from both an exposure as well as biological perspective should be kept in mind. Exposure-wise (14), children could be directly exposed to carcinogenic agents at any time during their life. In utero exposures are of concern to the developing fetus. Because oocytes divide only during fetal life, it is even conceivable that a child's grandmother could have had a toxic in utero exposure that led to abnormalities in the dividing oocytes of the mother who, in turn, passed those on to her child. It is conceivable that the father could be exposed to carcinogens causing abnormalities in spermatogenesis, subsequently passed on to his child. Thus, putative environmental exposures of the child, the parents, and even the grandparents could potentially contribute to childhood leukemia risk (14). Children are potentially exposed to environmental contaminants at higher levels than adults. Young children spend more time on the floor or ground and are more likely to put various objects in their mouths. Children also have a higher intake of food, water, and air per unit body weight (14). From a biological perspective, there is solid evidence that the most common form of ALL results from two genetic "hits", with the first occurring before birth, as shown in many studies using neonatal blood spots (15). This adds plausibility to prenatal exposures playing an etiological role. Some inherited cancer predisposition syndromes are identified, for instance patients with Down's syndrome have a 10- to 20-fold increased risk of childhood leukemia (14). Inherited syndromes have been informative in understanding cancer biology but are rare and explain only a small minority of cases of childhood leukemia.

Environmental Factors

Pesticides are environmental factors extensively investigated over already some decades with respect to their potential link with childhood leukemia, including the child's postnatal exposure through domestic or garden use or living in the vicinity of agricultural activities and the parent's occupational or domestic exposure before the child's birth. The term "pesticide" covers a large, heterogeneous group of chemicals used to control insects, weeds, fungi and other pests, but active ingredients of each chemical may have different carcinogenic properties. More than 20 individual pesticides have been classified as at least probable or possible human carcinogens by the International Agency for Research on Cancer's Monograph program on the evaluation of carcinogenic risks to humans (16). A recent meta-analysis found indoor but not outdoor insecticide use to be