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HEALTH EFFECTS REVIEW

Environmental Causes of Blood-related Cancers in Children

Introduction

Leukemia and lymphoma are caused by injury to the DNA of blood cells. Although the exact origin is unknown, environmental factors have been implicated as a possible cause of these childhood blood-related cancers. Despite the advances made in epidemiological methods over the past decade, no environmental association has been strong enough to entirely explain the occurrence of haemopoietic cancers in children.

Leukemias are the most common cancer in children and represent 30% of all incident cancer cases in children less than 15 years of age [1]. There are two types, lymphocytic and myelogenous, and each can be classified as acute or chronic. Acute lymphocytic leukemia (ALL) accounts for 80% of all childhood leukemia cases. Children less than 4 years of age are 7.5 times more likely to develop ALL than young adults 20-24 years of age. Over 2800 cases of childhood leukemia occurred in 2002 in the United States [1].

Lymphomas, both Hodgkin and non-Hodgkin, are the third most common cancer among children. Hodgkin lymphoma accounts for 4.4% of all childhood cancers and Non-Hodgkin lymphoma represents 4%. Non-Hodgkin is more prevalent in younger children and Hodgkin is more prevalent in adolescents. In children aged 0-19 years in the US, the age-adjusted incidence rates for leukemias, Hodgkin lymphoma, and non-Hodgkin lymphoma in 1995-99 were 40, 12, and 10 cases per 1,000,000 respectively [2]. Similar rates of 41, 15, and 10 cases per 1,000,000 were observed in Canada [3].

This report will summarize studies that investigate the associations between environmental exposures and lymphoma or leukemia. We focus on four commonly encountered potential causes: ionizing radiation, organic solvents, electromagnetic fields, and pesticides. The methods and results of these studies will be reviewed.

Leukemias & Lymphomas

Leukemias are marked by the uncontrolled multiplication of immature blood cells in the blood and bone marrow. The progression of acute leukemias is much more rapid than chronic leukemias. Blood cells are produced by haemopoietic stem cells in the marrow, where they undergo differentiation and develop into specific cell types. The lymphoblasts are the immature blood cells in acute lymphocytic leukemia. When fully developed, these cells are referred to as lymphocytes. Lymphocytes are a type of white blood cell that aids in our body's defense against infections. The rapid growth of the lymphoblasts overwhelms the functional blood cells. As a result, the production of normal marrow cells is inhibited, leading to deficiencies in red cells, platelets, and normal white cells in the blood. Weakened immune systems and anemia are often observed in children with leukemia [4].

Lymphomas are cancers that involve the mutation of lymphocytes in the lymphatic system. Similar to leukemia, uncontrollable growth gives malignant blood cells the advantage over normal cells. As the cells continue to multiply, lumps form causing lymph nodes to swell. Hodgkin lymphoma is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells, named after the pathologist who first described them [5].

Environmental Causes

One focus of childhood cancer research is determining the environment's role in the development of leukemias and lymphomas. While many different factors have been investigated, associations have been detected with the following exposures.

Ionizing Radiation

The causes of acute lymphocytic leukemia in most cases are unknown. Extensive work focused on Japanese survivors of the atomic bombs has shown increased risk of childhood leukemia. Conclusions are difficult to draw for the general public who are not exposed to such extreme doses of irradiation. Results from case-control studies looking at maternal obstetric X-ray examinations found a statistically significant 40% increase in the risk of childhood acute leukemia [6]. The authors also found a dose-response relationship where risk increased with the number of exposures. However, no excess of leukemia was observed in the cohort of Japanese children exposed in utero to the atomic bomb [7]. There is some evidence that suggests exposure to ionizing radiation from the Chernobyl accident in the northern Ukraine during early infancy or in utero is associated with childhood leukemia [8]. Results are difficult to interpret because increases were not statistically significant or were lower for areas of higher contamination.

Another study examined the association between childhood leukemia/non-Hodgkin's lymphoma and a father's preconceptional dose of ionizing radiation exposure from the Sellafield nuclear installation in northwest England [9]. The risk of leukemia/non-Hodgkin's lymphoma in children of radiation workers relative to children of non-Sellafield fathers was 1.9 with 95% confidence interval of 1.0-3.1. The authors also observed a significant dose response. While ionizing irradiation is widely accepted as a causal agent for childhood leukemia, detail of total exposure, rate of exposure, and timing are still being investigated.

Organic Solvents

Organic solvents have been implicated as an environmental risk factor for leukemia for many years. Occupational studies have long shown that benzene increases leukemia and lymphoma risk in adults, and environmental contamination by organic compounds has been associated with childhood leukemia [10]. Featured in the novel and film, A Civil Action, a leukemia cluster in Woburn, Massachusetts

prompted further investigation. After 15 years of use, two wells contaminated with chloroform, trichloroethylene (TCE), perchloro-ethylene (PCE), and other organic solvents were closed in 1979. By that time, 12 cases of childhood leukemia had been already diagnosed in Woburn. A total of 21 children developed leukemia between 1969 and 1986.

Among the numerous studies of Woburn is the 1996 Childhood Leukemia Study [11]. A water distribution model developed for an earlier investigation was used to determine exposure from contami-nated well water. Results showed an elevated leukemia risk for children whose mothers had access to contaminated well water while pregnant. Risk increased with the amount of contaminated water provided to the house. The authors warn that there are limitations in cluster analyses mainly due to the small numbers of cases.

Other associations with organic solvents have also been made. In a case-control study of childhood acute lymphocytic leukemia, researchers investigated the use of organic solvents in hobbies and home projects [12]. Children of mothers exposed to long durations of indoor home painting while pregnant were 1.7 times more likely to develop ALL than children of mothers who were not exposed. Results also showed an odds ratio of 4.1 for artwork using solvents. Both associations were statistically significant. The authors conclude with a recommendation for further investigation of household activities involving organic solvents.

Electromagnetic Fields

Public concern has primarily focused on the association between magnetic fields and childhood leukemia. The strength of the association, and even its existence, is uncertain. Early epidemiological studies have been criticized for their lack of proper exposure assessment and the absence of biological plausibility.

Results from epidemiological studies are inconsistent and difficult to compare due to their different methods for quantifying exposure. Visual assessment such as the Wertheimer-Leeper power-line classification has served as a proxy for actual measurements of magnetic fields. Estimates were calculated based on distance from the home and configuration type. Other studies took measurements of magnetic fields. Both approaches assess exposure for all residences.

Given the discrepancies in results from studies using different methods, a case-control study was undertaken to examine childhood leukemia risk and magnetic fields using the two approaches to quantify exposure [13]. Exposure was calculated for all residences during childhood and pregnancy. Results showed no association between acute lymphocytic leukemia and exposure to magnetic field levels greater than or equal to 0.2 micro-Tesla (μT) in utero or during childhood for either assessment method.

A recent pooled analysis of magnetic fields and childhood leukemia examined data from 15 studies, including the aforementioned study [14]. Odds ratios from studies using the surrogate for exposure varied widely, ranging from 0.7 to 3.0. Using Mantel-Haenszel summary statistics, the odds ratio comparing exposure levels >0.3 μT to the reference group was 1.7 (95% CI of 1.2 - 2.3). In the four studies included in the analysis that used both measures of exposure, an association observed with the visual assessment still remained after including measured exposures in the statistical analysis. The authors conclude that only weak evidence of an association between childhood leukemia and magnetic fields exists no matter which exposure assessment one uses.

Pesticides

Although the exact mechanism of how pesticides may lead to cancer is poorly understood, associations have been found between pesticides and childhood cancers in a number of epidemiologic studies. A review of these studies published from 1970-1996 was conducted to compare methods and results [15]. Most studies looked at the effects of pesticides on specific cancer types using a case-control study design. Some of the common limitations of these studies are small case numbers, exposure misclassification, and recall bias. A child's risk of leukemia was shown to be associated with parental occupational pesticide exposure during pregnancy and use of pesticides in the home, especially with higher frequency of applications [16]. A case-control study found that prenatal and postnatal exposure to garden insecticides and herbicides resulted in a significant increase in childhood acute lymphocytic leukemia [17].

For lymphomas, associations are harder to find because it is a rarer disease in children. Increased risk for non-Hodgkin lymphoma has been repeatedly observed for adults exposed to farming and pesticides, but a relationship with childhood lymphomas is not obvious [18]. A dose-response gradient was observed for frequency of maternal household insecticide use [19]. While a statistically significant association was observed with agricultural pesticide exposure during pregnancy, no association was observed for garden use or home extermination. Exposure to garden pesticides during childhood also showed no association. Home use of pesticides during childhood did significantly elevate risk of lymphomas [20]. A study of offspring of Norwegian farmers showed a dose response relationship for pesticide use and non-Hodgkin's lymphoma [17]. The highest pesticide exposure level had a significant relative risk of 2.5.

Unfortunately, the information collected on pesticide use is usually not detailed enough to properly classify exposure. Most measures are indirect and rely on the recall of parents or occupational title. Frequency and magnitude of exposure are rarely considered, but even if such questions are included, it is often difficult for parents to remember. Parents of cases may tend to recall more exposures, resulting in differential misclassification. Lumping all pesticides into one category is also problematic because different classes of chemicals will have different effects. Timing of exposure should always be considered. While studies have suggested an association between pesticides and leukemia or lymphomas, these findings should be interpreted with caution due to the limitations of these studies. Likewise, studies showing no apparent association are also subject to limitations.

Conclusion

The environmental etiology of haemopoietic cancers in children is an important public health concern. Our knowledge of this issue is limited by difficulties in exposure assessment. Despite the weaknesses of epidemiological studies, they serve as an important tool for detecting associations with environmental risk factors. Continued efforts should be made in improving the study design to reduce exposure misclassification. While associations have been observed with ionizing radiation, magnetic fields, organic solvents, and pesticides, the occurrence of childhood leukemias and lymphomas cannot be completely explained by any of these exposures. Additional studies are neces-

sary to continue searching for possible environmental causes. One such study is being conducted in Canada by the Population and Public Health Branch of Health Canada [17]. The Canadian Childhood Cancer Surveillance and Control Program is examining the etiology of childhood leukemia as part of a larger project, *Identifying Risk Factors for Developing Childhood Cancers*. The study is investigating the association between proximity to industrial plants and leukemia in subjects from the Western Canada Childhood Leukemia Case-Control Study. The results of this and other studies will contribute to our understanding of the environmental causes of childhood haemopoietic cancers.

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