HEALTH EFFECTS
REVIEW

Environmental Causes of Brain Cancer in Children

Introduction

Brain cancer is one of the most prevalent childhood cancers in the United States and Canada, second only to leukemia [1, 2]. The overall incidence of childhood brain tumors, the most common solid tumor in children, rose from 2.3 cases per 100,000 in 1975 to 3.0 cases per 100,000 in 1998 in the United States [1]. Similar rates were also seen in Canada [2]. One concern is that the elevated risk over the past two decades is a result of increased exposure to environmental risk factors. Another explanation is that changes in classifying brain tumors and improvements in detecting tumors (magnetic resonance imaging, MRI) have lead to increases in the rate, though this in itself is controversial [3].

The etiology of childhood brain cancer remains largely unknown. Several genetic and chromosomal conditions, such as tuberous sclerosis, Li-Fraumeni syndrome, and Down syndrome, explain a small percentage of cases [4]. Exposure to therapeutic irradiation has also been linked to childhood brain cancer [5].

Although the incidence in brain tumors has risen, childhood brain cancer remains a rare disease with few cases available to study. In addition, exposures during pregnancy and other critical time periods are difficult to assess and are subject to recall bias. A further complication is that many studies investigate all childhood brain tumors as one disease, although unique etiologies may exist for different tumor types.

While scientists suspect environmental causes are associated with childhood brain cancer, the evidence is not conclusive. This paper summarizes possible environmental risk factors and the strength of their association with childhood brain cancer. Potential environmental risk factors include pesticides, electromagnetic fields, and N-nitroso compounds.

Childhood Brain Tumors

Brain tumors account for 19% of all incident childhood cancer cases, and 27% of all cancer deaths [4]. The most common brain tumors, accounting for approximately half the childhood brain cancer cases, are astrocytomas (52%). The remainder of the tumors consists of primitive neuroectodermal tumors/ medullo-blastomas (21%), gliomas (19%), and ependymomas (9%)[3]. Proportions are similar for childhood brain cancers in Canada [2].

The reported incidence of childhood primary malignant brain tumors increased from 1977 to 1994 by over 20%. In a study using data from the national Surveillance, Epidemiology, and End Results (SEER) program, Smith and colleagues determined that the increase in rate was largely due to a sharp rise in rates from 1984-1985 [6]. Results from a step function model suggested that incidence rates from childhood brain cancer were stable before

1984, jumped in 1984-1985, and established a new baseline rate after 1985. There are many possible reasons for this change.

The sharp rise in brain cancer rates coincided with the introduction and application of MRI technology during the mid-1980s. The types of tumors with the highest reported increases in incidence during that time period, low-grade gliomas in the brain stem and cerebrum, are the types MRIs can most successfully detect [6]. Also during the mid-1980s, the classification of brain tumors changed. Tumors that were earlier designated benign were now considered malignant [2]. Specific diagnoses were also influenced by improvements in neurosurgical techniques for biopsying brain tumors. Last, the increase in incidence may be due to increased environmental exposures. While improvements in detecting tumors and changes in classification may contribute to the increase in glioma subgroups, these changes do not explain the increases observed for other tumors [7].

Environmental Causes

While there may be a sense of relief that the elevated incidence did not represent increases in environmental exposures, the fact still remains that we know little about these exposure and their mechanisms for causing brain cancer. The little evidence that is available suggests that biological timing of environmental exposures may be critical to the development of childhood brain tumors.

Four possible mechanisms for childhood brain cancer have been suggested: (1) exposure at preconception resulting in genetic alterations; (2) in utero exposure causing genetic or teratogenic effects; (3) postnatal exposure via the mother's breast milk; and (4) direct exposure to the child.

While many different factors have been suggested, few associations have been extensively studied or replicated. Studies investigating the use of drugs and medications during pregnancy have provided inconsistent results. Antinausea medications, anesthetic drugs, and neurally active barbiturates have been positively linked to childhood brain tumors in some studies, while other studies have found no associations. Similar inconsistencies exist with exposures to parental smoking and drinking. Three exposures that have received the most attention are pesticides, electromagnetic fields, and N-nitroso compounds.

Pesticides

Although the exact mechanism of how pesticides may lead to cancer is poorly understood, associations have been found between pesticides and childhood brain cancers in a number of epidemiologic studies. A review was conducted to compare the methods and results of 16 case-control studies and one cohort study published from 1974-1997 [8]. Fourteen of the seventeen studies observed elevated risks in childhood brain cancer, nine of which were statistically

significant results. In a study by Pagoda and Preston-Martin [9], prenatal exposure to flea/tick sprays and foggers significantly increased brain cancer with an odds ratio of 10.8. However, no association was observed when direct exposure to flea/tick products occurred during childhood, suggesting that the timing of exposure is critical for developing brain cancer.

In a cohort study by Kristensen et al. [10], census data was used to identify exposure indicators for farms in Norway. The association between possible risk factors and childhood cancers in the offspring of farm workers was investigated. A significant relative risk of 1.59 was observed for brain tumors in association with pig farming. Elevated risks were also observed for chicken and grain farming and pesticide use, but results were more modest and non-significant. A dose-response relationship was observed between brain tumors and the level of pesticide use with a significant relative risk of 3.28 observed at the highest level. The most elevated significant risk of 8.01 was seen for the association between gliomas and pesticide use on grain farms. There were, however, only six cases in this exposure classification.

Some of the common limitations of pesticide studies are small case numbers, exposure misclassification, and recall bias. The strongest associations were observed in studies where exposure was reported by parents rather than using occupational classifications. This suggests that defining exposure based on occupations thought to involve pesticide exposure results in exposure misclassification. Parent-reported exposures, however, are subject to possible recall bias and differential misclassification.

Unfortunately, the information collected on pesticide use is usually not detailed enough to properly identify which chemical is causing cancer. Frequency and exposure are rarely considered, but even if questions are included, it is often difficult for parents to remember. While studies have suggested an association between pesticides and childhood brain cancer, these findings should be interpreted with caution due to the limitations of the studies.

Electromagnetic Fields

Despite the numerous studies investigating electromagnetic fields and childhood cancers, the strength of an 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. Although initial studies found associations with leukemia and childhood brain tumors, results from recent studies are generally inconsistent [11].

These inconsistencies in epidemiological findings may be due to the use of 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 by Preston-Martin and colleagues to examine childhood brain cancer risk and magnetic-fields using both wire codes and measured magnetic fields to quantify exposure [12]. Exposure was calculated for all residences from conception to diagnosis. The study enrolled 298 children under age 20 years with a primary brain tumor diagnosed from 1984 to 1991 and 298 control children identified by random digit dialing. Results showed no association between childhood brain cancer and exposure to magnetic-field levels for either assessment method. Savitz et al. conducted a similar study examining the two methods of exposure assessment [13]. A positive association was found using the Wertheimer-Leeper wire coding, but not measured fields.

A meta-analysis of magnetic fields and childhood leukemia, lymphomas, and nervous-system tumors examined data from 13 studies published during 1979-1993 [14]. The only significant association was with childhood brain tumors, yet the authors caution that the exposure assessment was found to be imperfect and imprecise. The consensus among studies is that additional high quality epidemiological research is needed to determine the true association between electromagnetic fields and childhood brain cancer.

N-nitroso Compounds

Human exposure to N-nitroso compounds is done primarily via consumption of cured meats, although beer, incense, make-up, antihistamine, diuretics, and rubber baby bottle and pacifier nipples also contain various amounts [15]. Results of numerous studies suggest that maternal consumption of N-nitroso compounds is associated with childhood brain cancer. These studies were prompted by laboratory experiments that showed trans-placental exposure can cause brain tumors in several animal species.

A review of the epidemiological evidence was conducted by Blot et al. [16]. Many of the 13 case-control studies reviewed did not show significant results. However, unlike electromagnetic fields, the association is supported by the fact that a biologically plausible mechanism exists for N-nitroso compounds and childhood brain cancer.

One of the largest and most well-designed studies to investigate this association showed a significant trend in childhood brain cancer as cured meat intake increased [17]. Preston-Martin et al. enrolled 540 cases and 801 controls from California and Washington diagnosed during 1984-1991. The odds ratio was 2.1 with a confidence interval of 1.3-3.2 for eating cured meats at least twice a day compared to not eating any. An increased risk in all three major brain tumors was observed. Although the evidence for maternal consumption of cured meats is suggestive of an association with childhood brain cancer, results are not conclusive since most aspects of diet have not been studied yet. Nevertheless, future research is certainly warranted.

Conclusion

The environmental etiology of brain 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 pesticides, magnetic fields, and N-nitroso compounds, the occurrence of childhood brain tumors cannot be completely explained by any of these exposures. Additional studies are necessary to continue searching for possible environmental causes.

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