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Review

Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: A systematic review and meta-analysis

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ABSTRACT

Objective: To examine the potential association between parental occupational exposure to pesticides and the occurrence of brain tumors in children and young adults.
Methods: Studies identified from a MEDLINE search through 15 January 2013 and from the reference lists of identified publications were submitted to a systematic review and meta-analysis. Relative risk estimates were extracted from 20 studies published between 1974 and 2010. Most of the retrieved studies involved farm/agricultural jobs. Summary ratio estimates (SR) were calculated according to fixed and random-effect meta-analysis models. Separate analyses were conducted after stratification for study design, exposure parameters, disease definition, geographic location and age at diagnosis.
Results: Statistically significant associations were observed for parents potentially exposed to pesticides in occupational settings and the occurrence of brain tumor in their offspring after combining all case–control studies (summary odds ratio [SOR]: 1.30; 95%: 1.11, 1.53) or all cohort studies (summary rate ratio [SRR]: 1.53; 95% CI: 1.20, 1.95). Significantly increased risks were seen for prenatal exposure windows, for either exposed parent, for exposure defined as to pesticides as well as by occupational/industry title, for astroglial brain tumors and after combining case–control studies from North America or cohort studies from Europe.
Conclusions: This meta-analysis supports an association between parental occupational exposure to pesticides and brain tumors in children and young adults, and adds to the evidence leading to the recommendation of minimizing (parental) occupational exposure to pesticides. These results must, however, be interpreted with caution because the impact of work-related factors others than pesticide exposure is not known.

Contents

Abbreviations: ASTRO, astroglial brain tumors; 95% CI, 95% confidence interval; ICD, international classification of disease; SR, summary ratio estimate; SIR, standardized incidence ratio; SOR, summary odds ratio; SRR, summary risk ratio; OR, odds ratio; PNET, primitive neuroectodermal tumors; RR, relative risk; 95% UI, 95% uncertainty interval.

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1. Introduction

Brain tumors are the second leading cause of cancer-related mortality in children, although brain tumors are approximately half as frequent as leukemia (Pfister et al., 2009). Gliomas (astrocytomas, ependymomas and choroid plexus tumors, gangliogliomas, oligodendrogliomas) comprise approximately 60% of the pediatric brain tumors whereas the remaining 40% are nonglial tumors and consist of embryonal tumors (e.g., medulloblastoma, primitive neuroectodermal tumors [PNET]), cranyopharyngiomas, pineal tumors, meningiomas and others (Kaatsch, 2010; Pfister et al., 2009). The most frequent are astrocytomas (10.5%), embryonal tumors (5.0%, especially medulloblastomas and PNET, and ependymomas (2.2%), all of which are clinically, histologically and genetically heterogeneous. The age-standardized incidence rate of central nervous system tumors in children (0–14 years) in Europe is around 30 per million (Kaatsch, 2010). The incidence of childhood brain cancer has been rising steadily in the 1980s, but has subsequently remained relatively stable (Pollack and Jakacki, 2011). Overall, 5-year survival is 64–66% (Kaatsch, 2010; Peris-Bonet et al., 2006). The poorest diagnosis-related survival rate is observed for PNET (just above 60%) and the best for astrocytoma (75%). Overall, boys are more frequently afflicted by a brain tumor than girls, especially by PNET. Central nervous system tumors are clearly less frequent in adolescents (15–19 years) than in the younger age groups (Kaatsch, 2010; Kaatsch et al., 2001; Peris-Bonet et al., 2006).

The etiology of brain cancer in children is still unknown and a multifactorial process involving different variables such as genetic, immunological or environmental factors is the most likely explanation. Major cytogenetic and genomic aberrations associated with the above-mentioned four most common pediatric brain tumors were recently reviewed by Dubuc et al. (2010). A few genetic syndromes and ionizing radiation are established risk factors. Infectious agents and many environmental exposures (e.g., N-nitroso compounds, tobacco smoke, electromagnetic fields) have been suspected of playing a role in the development of brain tumors (reviewed by Baldwin and Preston-Martin, 2004 or Connelly and Malkin, 2007). The identification and a better understanding of risk factors for children brain tumors may facilitate disease prevention.

The role of environmental exposure to pesticides in the etiology of cancer, although strongly postulated, is still unknown. Many studies linking malignancies to pesticides reported a higher risk in children than in adults and it has been suggested that children may be particularly sensitive to the carcinogenic effects of pesticides (Zahm and Ward, 1998). Possible sources of children exposure are from a direct exposure to pesticides when used for residential pest control, as an example, and from indirect contamination from parental (occupational) exposure to pesticides. The present work analyses the potential association between pesticide exposure via parental occupational exposure and childhood brain tumors.

Epidemiologic studies assessing the role of parental occupational exposure in the occurrence of cancer have yielded mixed results. In spite of the preponderance of studies reporting a positive relationship, reviews of these studies revealed a lack of clear association and conflicting evidence with regard to parental occupational exposure to pesticides and childhood brain cancer (Baldwin and Preston-Martin, 2004; Bassil et al., 2007; Connelly and Malkin, 2007; Daniels et al., 1997; Infante-Rivard and Weichenthal, 2007; Jurewicz and Hanke, 2006; Nasterlack, 2006, 2007; Zahm and Ward, 1998). Methodological limitations including inadequate exposure assessment, small sample size and potential bias restrict conclusions.

The multifactorial causation of brain tumors, the inaccuracies in the recall of past exposures, and the study of all pediatric brain tumors as a single etiologic entity may contribute to hamper the identification of additional risk factors (Bunin, 2000). The present systematic review and meta-analysis were undertaken with the aim to enhance our understanding of the potential involvement of parental occupational exposure to pesticides in childhood brain cancers, by focusing on several issues including mainly exposure assessment and outcome definition.

2. Materials and methods

2.1. Study identification and selection

2.1.1. Study identification

A search on MEDLINE (National Library of Medicine, Bethesda, MD) was conducted for the period 1966 to 15th January 2013. An electronic search using "(pesticides OR herbicides OR fungicides OR insecticides) AND ((children OR childhood) AND brain cancer) AND (occupation OR occupational)" was initially undertaken. This was supplemented with various combinations of the following key words: pesticide(s), child, children, childhood, infant, newborn, preschool child, adolescent, youth, teenage, young adult, tumors, neoplasms, astroglial, astrocytomas, glial, primitive neuroectodermal, intracranial, occupation, occupational, farmers, agriculture, horticulture, pesticide applicators, manufacturing workers, industry, parental exposure with no restriction of publication type or publication date. The reference lists of the relevant publications identified were checked for additional studies. The search was limited to studies published in English in the open literature in peer-reviewed journals. All titles or abstracts were screened to determine the suitability of the publication.

2.1.2. Study selection

A study was considered eligible for further review if (1) it referred to all children and young adults (up to 24 years) exposed to pesticides from parental occupational exposure (farmers/agricultural workers, pesticide applicators, workers engaged in the manufacture of pesticides and others such as horticulturists, greenhouse workers, gardeners, etc.), (2) if the outcome included (subtypes of) brain tumors (astroglial tumors [ASTRO], PNET, other glial tumors,) and (3) if the study used a cohort or a case–control design. Excluded studies were those not reporting original results (reviews, meta-analysis, case-reports, comments, letters, editorials, abstracts), experimental studies and proportional mortality ratio (PMR) studies (mainly because of ambiguities in interpreting results) as well as ecological studies. Studies on veterans who served in Vietnam or Cambodia, studies on treatment outcome, with therapy-related brain tumors, or focusing on genetic data were not included. Studies not dealing with occupational exposure or dealing with combined occupational and domestic exposure with no separate reporting of occupational data were also excluded. Among the eligible studies, we excluded those providing no brain tumor cases or insufficient data to determine an estimator of relative risk (RR) for brain tumors and its confidence interval, redundant studies, and studies with