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MATERNAL OCCUPATIONAL EXPOSURE TO EXTREMELY LOW FREQUENCY MAGNETIC FIELDS AND RISK OF BRAIN TUMORS IN OFFSPRING

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Abstract

Background: The causes of childhood brain tumors (CBT) are essentially unknown. Exposure to extremely low frequency magnetic fields (ELF-MF) (3-3000Hz) is an ubiquitous part of modern life. However, very few studies have investigated the possible effect of maternal occupational ELF-MF exposure on CBT and the available findings are inconsistent across studies.

Methods: We examined the role of maternal occupational exposure to ELF-MF shortly before and during pregnancy on the incidence of childhood brain tumors. A total of 548 incident cases and 760 healthy controls recruited between 1980 and 2002 from two Canadian provinces (Québec and Ontario) were included and their mothers were interviewed. Tumors were classified as astroglial tumors, primitive neuroectodermal tumors (PNET), and other gliomas. Quantitative occupational ELF-MF exposure in microtesla units was estimated using individual exposure estimations or a job exposure matrix. We used three metrics to analyze exposure: cumulative, average, and maximum level attained.

Results: Using the average exposure metric measured before conception, an increased risk was observed for astroglial tumors (OR=1.5, and 95%CI=1.0-2.4). During the entire pregnancy period, a significantly increased risk was observed for astroglial tumors as well as for all childhood brain tumors with the average metric (OR=1.6, 95% CI=1.1-2.5 and OR=1.5; 95%CI=1.1-2.2, respectively). Based on job titles, a two-fold risk increase was observed for astroglial tumors (OR=2.3, 95% CI=0.8-6.3)

and for all childhood brain tumors (OR=2.3, 95% CI=1.0-5.4) among sewing machine operators.

Conclusion: Results are suggestive of a possible association between maternal occupational ELF-MF exposure and certain brain tumors in their offspring.

Keywords: brain tumors, occupational exposures, maternal exposures, magnetic fields, childhood cancer, job exposure matrix

Résumé

Contexte : Les causes des tumeurs au cerveau chez les enfants (CBT) sont pour la plupart inconnues. L'exposition à des champs magnétiques de fréquences extrêmement basses (3-3000Hz) (ELF-MF) fait partie intégrante de la vie moderne. Cependant, très peu d'études ont examiné l'effet possible de l'exposition maternelle aux ELF-MF en milieu de travail, et les résultats disponibles ne sont pas constants selon les études.

Méthodes : Nous avons examiné le rôle de l'exposition des mères à des ELF-MF en milieu professionnel peu de temps avant et pendant la grossesse sur l'incidence des tumeurs cérébrales chez leur enfant. Un total de 548 individus concernés et 760 individus contrôles sans problème de santé recrutés entre 1980 et 2002 dans deux provinces canadiennes (Québec et Ontario) ont été inclus et leurs mères ont été interviewées. Les tumeurs ont été classifiées de la façon suivante : astroglial tumeurs, tumeurs primitives neuroectodermiques (PNET), et d'autres gliomes. Les mesures quantitatives de l'exposition en milieu professionnel aux ELF-MF sont en unités microtesla, et ont été estimées par des approximations d'exposition individuelle ou par une matrice d'exposition au travail. Nous avons utilisé trois mesures pour analyser l'exposition : une mesure cumulative, la moyenne, et le niveau maximum atteint.

Résultats : Utilisation de l'exposition moyenne mesurée avant la conception métrique, un risque accru a été observé pour les tumeurs astroglial (OR = 1.5, 95% CI =1.0-2.4). Pendant toute la période de grossesse, une augmentation significative du risque a été

observée pour les tumeurs astroglial ainsi que pour tous les enfants de tumeurs au cerveau à la moyenne métriques (OR = 1.6, 95% CI = 1.1-2.5 et OR = 1.5, 95% IC = 1.1-2.2, respectivement). Sur la base de titres, d'une double augmentation du risque a été observée pour les tumeurs astroglial (OR = 2.3, 95%CI = 0.8-6.3) et pour tous les enfants des tumeurs cérébrales (OR = 2.3, 95% CI = 1.0-5.4) chez les couture Les opérateurs de machines.

Conclusion : Nos résultats suggèrent une possible association entre l'exposition des mères aux ELF-MF en milieu de travail et certaines tumeurs cérébrales chez leur enfant.

Mots-clés : tumeurs cérébrales, expositions en milieu de travail, expositions maternelles, champs magnétiques, cancers pédiatriques, matrice d'exposition en milieu de travail.

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List of acronyms

μT	microTesla
ALL	Acute lymphoblastic leukemia
CBT	Childhood brain tumor
CCDO	Canadian Classification and Dictionary of Occupations
CI	Confidence interval
CNS	Central nervous system
ELF-MF	Extremely low frequency magnetic fields
EMF	Electromagnetic frequencies
ICD-O-2	International classification of Disease-Oncology-Version 2
JEM	Job exposure matrix
JSQs	Job specific questionnaires
NOCs	N-nitroso compounds
ORs	Odds ratios
PNET	Primitive neuroectodermal tumors
SIC	Standard Industrial Classification
TWA	Time-weighted average

Appendix

Introduction

Each year approximately 2200 individuals under the age of 20 are diagnosed with a brain tumor in the United States (American Cancer Society). An increasing incidence of brain tumors in children has been reported in Italy, Sweden, Norway, Hungary and England (Dalmasso et al., 2005; Dreifaldt et al., 2004; Johannesen et al., 2004; Hauser et al., 2003 and McNally et al., 2001); this rising trend cannot be fully explained by diagnostic improvements or reporting changes, suggesting that this rise may be real. Despite the technological advances in diagnostic capability, the overall 5-year relative survival probability for children with brain tumors has not increased, and in the United States is only about 62% (Gurney et al., 1999).

On the other hand, the etiology of childhood brain tumor (CBT) is far from clear. Exposure to ionizing radiation, such as X-rays, is the only clearly established environmental cause, but this factor accounts for a minority of cases (Preston-Martin et al., 1996). Numerous other exposures, including N-nitroso compounds (NOCs), pesticides, parental occupations, infectious agents, and electric and magnetic fields (EMF), have been suspected of playing a role in the development of CBT. However, there is no consistent evidence to support a link between any of these factors and CBT, and the estimates of relative risks are all small.

These inconsistent results may stem in part from studying total CBT as a single entity when several different histological types occur, which may mask or attenuate a causal association. Furthermore, due to the rarity of CBT, small sample size in any individual

study limits the statistical power to detect an effect, if, in fact, one exists. In addition, common to childhood cancer studies, exposures happened several years ago, which contributes to the complexity of assessment occupational and environmental exposures.

Given that the incidence of CBT is possibly increasing and the etiology is not understood, two population-based case-control studies of this disease were carried out, one in Quebec and one in Ontario, respectively. These two studies collected information on a number of possible risk factors including occupations of the parents. Parental occupations may be a source of exposure to extremely low frequency magnetic fields (ELF-MF) (3-3000Hz), which is an ubiquitous part of modern life because of the many sources (e.g., computers, household appliances, electric power lines) that are powered by 60-Hz fields in North America. Although a potential biological mechanism through which ELF-MF may cause carcinogenic effects has not yet been identified, based on a meta-analysis of data from *in vivo* or *in vitro* studies (Juutilainen, 2006), one possible hypothesis has been proposed whereby ELF-MF may cause cancers by affecting the recombination probability of radical pairs and therefore influence the level of free radicals.

Associations between exposure to ELF-MF and certain adulthood cancers, particularly acute leukemia and brain tumors, have been suggested in some studies (Feychting et al., 1997 and Kheifets, 2001). In addition, several studies have been conducted on the association between residential ELF-MF exposure and childhood brain tumors; based on a recent meta-analysis of 13 epidemiologic studies, there was a consistent finding

of a moderate increased risk of CBT with residential exposure to magnetic fields above 0.3 or 0.4 microTesla (μT) (OR=1.68, 95%CI=0.83-3.43) (Mezei, 2008). However, the available findings for an association between CBT and parental occupational ELF-MF exposure are inconsistent across studies (Wilkins and Lynn, 1996; Sorahan et al., 1999; Feychting et al., 2000; and Ahlbom, 2001).

Compared with residential exposure, occupational environments present a greater opportunity for high-level ELF-MF exposure, such as in the electric utility industry (Deadman and Infante-Rivard, 2002). Most epidemiologic studies of the association between CBT and parental occupational exposures used a case-control study design where the retrospective exposure assessment poses a significant challenge. In the majority of previous studies, the ELF-MF levels were inferred from individual or group job titles (e.g., electrical occupations) or from job exposure matrices (JEMs) based on MF measurement data. However, reliance on job titles or job groups alone may not be the most accurate method for estimating ELF-MF exposure; the use of electrical equipments in the course of the work and the presence of such equipments in the work environment could be equally or more important (Kelsha et al., 2000). Maternal prenatal exposure is likely to be more important for fetal exposure than pre-conceptional paternal exposure, and thus should receive more attention than it has so far. Although a few studies have investigated maternal occupational ELF-MF exposure, the number of mothers in the studies with an occupation before and during pregnancy has generally been too small to allow meaningful analyses.

The goal of this study is to evaluate whether mothers' occupational exposure to ELF-MF, immediately before and during pregnancy, is associated with an increased risk of childhood brain tumors, using individual exposure estimations or a job exposure matrix based on ELF-MF sources, work environments and duration of exposure.

Literature review

Classification and development of CBT

Classification

The classification of CBT depends on the exact site of the tumor, the type of tissue involved, benign or malignant tendencies of the tumor, and some other factors. Brain tumors arise from different normal cells of the brain and spinal cord and the resulting neoplasms are designated accordingly. The brain is composed of two main types of cells: glia and neurons, which both arise in early development from the primitive neuroectoderm (Mischel and Vinters, 2001).

A large group of brain tumors in childhood (ages 0-14 years) arises from glia cells and is broadly categorized as gliomas, including astrocytomas, ependymomas, oligodendrogliomas, and ganglioglioma (Kleihues and Cavenee, 2000); these account for about 75% of all childhood primary brain tumors. Astrocytomas are further subdivided pilocytic astrocytoma and others. More than 80% of all childhood cerebellar gliomas are pilocytic astrocytomas, which are also considered to be Grade I astrocytomas by the WHO system. Other forms of astrocytomas, e.g. the "fibrillary" types, infiltrate surrounding tissues and fall along a spectrum of Grade II, III, and IV, including fibrillary astrocytoma, anaplastic astrocytomas, and glioblastomas multiform. Another class of brain tumors in children is the "embryonal" or "primitive neuroectodermal tumors" groups, including medulloblastoma, pineoblastoma, and cerebral neuroblastoma, and comprise about 25% of the brain tumors in children.

Development

The human brain's rapid growth begins early in gestation and peaks at approximately 4 months after birth, and continues for 2–3 years following birth, which is a much longer period than for the other major organs (Rice and Barone, 2000). These early stages of development are characterized by extensive amounts of intricately coordinated cell growth and differentiation, which is marked by extensive and highly controlled alterations in gene expression, and also conveys enhanced vulnerability to toxic exposures. Furthermore, the developing brain is also much more accessible to potential carcinogens early in life. The blood–brain barrier in fetuses does not fully develop until about 6 months of age (Andersen et al., 2000). So, molecules or compounds that are capable of crossing the placenta have the intrinsic potential to access to the fetal brain (Ring et al., 1999; Denning et al., 1990).

Different histological subtypes of brain tumors occur in children of different ages. Astrocytomas peak in incidence twice, at age 5 and again at age 13. PNET and ependymomas are most common in children under the age of 3, and then steadily decline as age increases (Gurney et al., 1999 and VandenBerg, 2001). Incidence rates with clear age-related histological patterns suggested that each type of histological cell may have a distinct period of time "window of vulnerability", during which it is most vulnerable to malignant transformation. Thus, the timing of a potentially toxic exposure may be as important as its nature in determining its influence on histological class of the brain tumor, if any.

Risk factors for CBT other than EMF exposures

Little is known about the causes of brain tumors in children. A few hereditary conditions play a clear and independent role in brain tumor etiology including neurofibromatosis, tuberous sclerosis, naevoid basal cell syndrome, turcot syndrome and Li-Fraumeni syndrome, which are responsible for less than 5% of all brain tumors (Bunin et al., 2000). Exposure to ionizing radiation, such as X-rays, is the only clearly established environmental causes, but this factor accounts for a minority of cases (Preston-Martin et al., 1996). Numerous other physical, chemical, and infectious agents that have been suspected to be risk factors have not yet been established as etiologically relevant (Baldwin and Preston-Martin, 2004). In this section, we summarize the epidemiological findings to date regarding the many environmental exposures other than EMF that have been hypothesized to contribute to the incidence of CBT.

N-Nitroso Compounds

N-Nitroso compounds are one of the most compelling risk factors for CBT. Humans are exposed not only to preformed N-nitroso compounds (NOCs), which comprise nitrosamines and nitrosoureas/ nitrosamides, but also to NOC precursors (e.g. nitrite and nitrogen oxides) that may form NOCs *in vivo* via the acidic environmental of the stomach. NOCs have been showed to be potent carcinogens in several experimental animal studies (Kleihue et al., 1976 and Rice and Ward, 1982). Nitrosoureas are direct alkylating agents which do not undergo metabolic activation, and therefore, are likely to influence tumor development at the exposure site. In rodent studies, nitrosoureas

have been unequivocally demonstrated to induce neurogenic tumors, particularly to increase brain mutations in offspring after transplacental exposure (Slikker et al., 2004). In contrast to nitrosoureas, nitrosamines require metabolic activation, usually by cytochrome P450 enzymes, to exert their carcinogenic effects. They are relatively weak carcinogens in rodent fetuses, but it has been suggested that the human fetus may be more susceptible (Preston-Martin et al., 1989), because nitrosamines might well be more effective (dose-for-dose) in humans than they are in rodents.

Cured meat may be the most important source of human NOC exposure because of the high level of reactivity produced by high concentration of nitrite that form around bits of cured meat in the stomach (Preston-Martin et al., 1996). In the late 1970s, based on the evidence of carcinogenicity from animal studies, and in particular the finding that the carcinogenic effects of NOCs may be age dependent with the fetus being particularly susceptible, Preston-Martin et al. (1982) began exploring the hypothesis that maternal cured meat consumption during pregnancy was associated with CBT. Their study provided suggestive evidence in support of the NOC hypothesis. In a large case-control study of childhood brain tumors (540 cases), Preston-Martin et al. (1996) found that an elevated brain cancer risk among children whose mothers frequently ate cured meats during pregnancy, compared with those who did not eat cured meats (OR=2.1, 95% CI=1.3-3.2). Many additional explorations have also been prompted by others (Sarasua and Savitz, 1994; McCredie et al., 1994b; Bunin, 1998; Pogoda and Preston-Martin, 2001; Huncharek and Kupelnick, 2004). Most of the studies showed no significant association between cured meat intake and CBT but more found

positive than negative relationships. Furthermore, several studies (Preston-Martin et al., 1996 and Pogoda and Preston-Martin, 2001) reported significant positive associations for maternal consumption of one or more cured meats, with odds ratios of twofold or greater reported among the highest consumers. The epidemiological results are not strong enough or consistent enough to confidently conclude that cured meats are a likely causal agent of CBT; nevertheless, given the compelling animal evidence, the hypothesis that eating nitrite-cured meats may influence CBT cannot be dismissed.

Tobacco smoke contains NOCs precursors, principally tobacco-specific nitrosamins. However, in contrast to the evidence that justifies further pursuit of the cured meat hypothesis, studies of maternal smoking hardly do. Maternal smoking during preconception or during pregnancy or maternal exposure to passive smoke has fairly consistently shown an absence of association with childhood brain tumors occurrence. In the seven studies (Gold et al., 1993; McCredie et al., 1994a; Norman et al., 1996; Boffetta et al., 2000; Filippini et al., 2000; Michael et al., 2002; Filippini et al., 2002) that have addressed the relationship between CBT and maternal exposure to tobacco smoke, one studies (Filippini et al., 2000) observed elevated risk for side stream tobacco smoke exposure of the mother during pregnancy, but the other five did not.

Drinking water, especially well water, may be also an important source of nitrate, which can be reduced to nitrite, a potential precursor of endogenously formed NOCs. However, no increased risk of CBT associated with self-reported use of well water was found (Bunin et al., 1994a and Beth et al., 2001). Other sources of NOCs, such as

certain brands of beer (Kuijten et al., 1990 and Cordier et al., 1994), face make-up (McCredie et al., 1994a and Bunin et al., 1994a), and hair dye (Bunin et al., 1994a and Elizabeth et al., 2002), have not been shown to be consistently associated with CBT.

Vitamins

During the past decade, maternal vitamins supplementation has been suggested as a factor reducing the risk of CBT. Vitamin C and E can act as nitrosation inhibitors by blocking the formation of N-nitroso compounds in the stomach and therefore are expected to exert a protective effect. An incidental finding in an early case-control study of pediatric brain tumors provided the first indication that prenatal vitamin supplementation might be related to reduced brain tumor risk (Preston-Martin et al., 1982). More than a decade later, several epidemiological studies reported similarly decreased risk related to maternal use of prenatal vitamins (Bunin et al., 1993; Sarasua and Savitz, 1994 and Bunin et al., 1994b). Recently, a large case-control study of childhood brain tumors (540 cases) (Preston-Martin et al., 1996) showed that the cured meat-brain cancer association was substantially weaker among children whose mothers took multivitamins during pregnancy (OR=0.54, 95%CI=0.39-0.75).

Folic acid is another vitamin of potential interest. Recent observational studies have reported that use of folic acid-containing vitamin supplements reduced neural tube defects by approximately 40% (Botto et al., 1999). It has been speculated that a common mechanism of altered development could lead to both NTDs and CBT, particularly the induction of medulloblastoma (Gurney et al., 2001). Foreman and

Pearson (Foreman and Pearson, 1993) reported a significant decrease in the incidence of medulloblastoma from 1976-1984 to 1985-1991, a time during which there may have been an increase in folate supplementation by women of reproductive age as the result of recommendations by Smithells et al. (Smithells et al., 1983). Folate is important in DNA replication and cell division through its involvement in the biosynthesis of purines and thymidylates (Magner, 1995). However, the specific mechanisms underlying the association of folate with CBT have not been elucidated fully. There is some suggestion that the metabolic pathway of folate may contain polymorphisms that alter the risk of NTDs and the same may be true for CBT as well (Gurney et al., 2001).

Pesticides

Pesticides have been suspected risk factors for childhood brain tumors. Because of their intentionally neurotoxic in activity, their potential for carcinogenicity in animal models (Gurney et al., 2001 and Zahm and Ward, 1998), and their extensive widespread use, a number of epidemiological studies have evaluated the development of childhood brain tumors associated with exposure to pesticides through parental occupation or by residential use (Wilkins and Sinks, 1990; Kuijten et al., 1992; Davis et al., 1993; Leiss and Savitz, 1995; Pogoda and Preston-Martin, 1997; Cordier et al., 1997; Daniels et al., 1997; Heacock et al., 2000; Feychting et al., 2001; Efird et al., 2003). However, these studies have not shown a conclusive relationship between pesticide exposure and childhood brain tumor risk, possibly because of the difficulty in accurately estimating individual pesticide exposure.

Parental occupational exposure to pesticides before and during pregnancy was associated with an increase in risk of CBT in several studies (Wilkins and Sinks, 1990; Kuijten et al., 1992; Cordier et al., 1997; Heacock et al., 2000; Feychting et al., 2001; Efird et al., 2003). In a cohort study in Sweden the authors found an increased risk of nervous system tumors related to paternal occupational exposure to pesticides (RR = 2.36; 95%CI, 1.27-4.39) (Feychting et al., 2001). Increased ORs for CBT have also been found among children whose mothers were occupationally exposed to pesticides in the 5 years before the index child's birth in an international brain tumor study (OR=2.0, 95%CI=1.2-3.2) (Efird et al., 2003). However, the results in most of these studies appeared to be imprecise, often dependent on a few exposed cases, and pesticide exposure often was indirectly inferred from job title or industry, which are generally poor proxies for identifying and quantifying specific exposures (McGuire et al., 1998).

Risk of CBT has frequently found to be elevated in association with residential use of pesticides, such as no-pest strips, flea/tick pesticides, and pesticide bombs (Davis et al., 1993; Leiss and Savitz, 1995; Pogoda and Preston-Martin, 1997; Daniels et al., 1997). Risk estimates appeared to be stronger during pregnancy or around time of delivery than during childhood. The studies reporting positive effects of residential pesticide exposure tended to be those that had an a priori interest in pesticides and ascertained exposure in more detail with respect to timing, intensity, or pesticide type (Davis et al., 1993 and Pogoda and Preston-Martin, 1997). However, most of the studies collected

and utilized less specific information, initially evaluating residential exposure as a confounder or covariate for other primary hypotheses.

Infectious agents

In animal experiments, brain tumors can be induced by polyomaviruses, including JC virus (JCV), BK viruses (BKV) and Simian Virus 40 (SV40); some laboratory evidence also supports the plausibility of an etiological role for polyomaviruses in human brain tumors (Gordon et al., 1998; Arrington and Butel, 2001). Krynska et al (1999) showed that 11 of 23 pediatric medulloblastoma tumor specimens tested by PCR were positive for JCV T-antigen DNA sequences. A recent meta-analysis of 11 original molecular controlled studies measuring viral DNA or gene products also found that SV40 was associated with brain tumors with an adjusted combined odds ratio of 3.9 (95%CI=6.0-8.0) (Vilchez and Butel, 2003). These findings could indicate that infection with polyomaviruses may be involved in the development of brain tumors. However, other studies (Huang et al., 1999 and Weggen et al., 2000) found either no evidence or a very low frequency of JC or BK viruses in human brain tumors.

Indirect support for an association of the risk of CBT and infections has come from some recent epidemiological studies. In a retrospective cohort study in England, the authors found an increased risk of brain tumors among children exposed around or soon after birth to higher levels of community infections, particularly measles (OR for trend=2.1, 95%CI: 1.3–3.6) and influenza (OR for exposure=3.3, 95%CI: 1.5 – 7.4) (Dickinson et al., 2002). The presence of space-time clustering and spatial clustering

as well as seasonal variation would also provide evidence of an infectious etiology. Space-time clustering may be described as the irregular grouping of cases of any disease simultaneously in space and time; spatial clustering is defined as the irregular grouping of cases of any disease in space. The researchers from two cohort studies (McNally et al., 2002 and McNally et al., 2004) using the same data-set found space–time clustering and seasonal variation, and absence of spatial clustering and ecological relationships for pilocytic astrocytoma and ependymoma in children aged 0–14 years, suggesting that pilocytic astrocytoma and ependymoma may be associated an infection occurred in mini-epidemics.

Some epidemiologic studies have also provided direct evidence of the involvement of maternal and childhood infections in CBT. Fear et al. reported (2001) an odds ratio of 10.60 in brain tumor cases compared with controls for documented viral infection during pregnancy. Another study has suggested that maternal influenza during pregnancy is a risk factor for brain tumors (Linos et al., 1998). Other authors (Linet et al., 1996) reported a statistically significant increased risk for total CBT (OR=2.40; 95% CI: 1.50-4.00) and for high-grade astrocytoma (OR=5.00; 95% CI: 1.00-24.80) associated with a wide variety of neonatal infections, whereas others found that childhood upper respiratory infections appeared as protective against brain tumors (OR=0.36; 95% CI: 0.13-1.03) (Pavlovic et al., 2005). This type of conflicting evidence for maternal and childhood infactions has also been reported on other papers (Bunin et al., 1994, McKinney et al., 1999).

The relationship between a diversity of maternal and childhood infections and CBT occurrence may reflect individual immunologic susceptibility to infection rather than a specific infection per se; an earlier clinical report supported the relationship between immunologic predisposition to infection and brain tumor risk among patients with ataxia telangiectasia, a rare primary immunodeficienct disorder (Hecht, 1990).

Occupational chemical exposures

Parental occupation as a source of exposure to chemicals has been investigated in over twenty studies. However, reliable information on specific exposure is seldom available. Many associations have been reported but few are consistent across studies. In many studies the results have been reported based on job or industry titles only. Since the early study by Fabia and Thuy (1974) that an elevated risk of CBT was associated with paternal occupational contact with hydrocarbon (Fabia and Thuy, 1974), several others have attempted to confirm these findings. Positive relationships have been reported for paternal employment as machinists, drivers, metal workers, painters, as well as in the paper and pulp, petroleum and chemical industries. The overall pattern is that exposure to paint and employment in the petroleum and chemical industries are the more consistent observations; both of these involve exposure to solvents and PAH.

In female working populations, occupational solvents are the most prevalent sources of chemical exposures (Teaf, 2000). In a multi-center population-based case-control study (Italy, France, Spain) (Cordier et al., 1997), using a job-exposure matrix developed earlier in the same countries, the authors found that maternal exposure to a

high level of industrial solvents during pregnancy or preconception was associated with an increased risk of both astroglial (OR=2.3, 95%CI: 0.9–5.8) and primitive neuroectodermal tumors (OR=3.2, 95%CI: 1.0–10.3). Another case-control study (Feingold et al., 1992) in the Denver using the JEM developed by Hoar et al (1980) found an elevated risk for all cancers (including 67 brain tumors patients) for maternal exposure to benzene (OR=1.9). Significant as well as non-significant increases in risk were also observed in several other studies (Kuijiten et al., 1992; McKean-Cowdin et al., 1998; Cordier et al., 2001; Ali et al., 2004), whereas no association was reported in some others (Mckinney et al., 2003; Zack et al., 1980). Kuijiten et al (1992) observed an increased risk of brain tumors in the offspring of women working as nurses, and Ali et al (2004) and Cordier et al (2001) showed an increased risk for children of women 'working in factories' or textile industry. However, all these studies used job tiles or type of industries to impute potential solvent exposure.

The role of exposure to chemicals in the workplace as etiologic agents for CBT is unclear, however, several hypotheses have been proposed, such as through preconceptional or transplacental exposure. Preconceptional exposure may cause mutation of parental germ cells or epigenetic effects (e.g., an effect on gene expression, genomic imprinting, or DNA methylation), whereas transplacental exposure may cause somatic or germinal mutations in the embryo/fetus that would affect cancer susceptibility in the child (Savitz and Chen, 1990a). Some evidence from experimental studies supports the hypothesis that exposure to exogenous agents before conception can alter the germ cells, which may increase the risk of cancer in the offspring

(Gaspari et al., 2003). Also, rodent female germ cells have been shown to have theoretical sensitivity to preconceptional carcinogenic effects (Anderson et al., 2000). In addition, many chemicals (solvents) have demonstrated cytogenetic, genotoxic, or mutagenic effects (Lynge et al., 1997).

Family history of cancers

Several studies have been conducted to assess whether the relatives of children with brain tumors had an increased risk of cancer compared with the general population. Siblings seem to be at 3-10 fold increased risk for brain tumors, and the risk for other childhood cancers, in particular tumors of bone, soft-tissue sarcoma, and haemolymphatic system, is also increased in some studies (Hemminki et al., 2000; Draper et al., 1977; Farwell and Flannery, 1984). In a nationwide study based on the Swedish Family-Cancer Database including 2060 childhood brain tumors diagnosed under age 15 in the period 1958–1996, Hemminki et al (2000) observed that risk for sibling nervous system cancer from childhood brain tumour probands was 3.55. This figure includes siblings who were diagnosed for nervous system cancer at ages 15–61 years. The occurrence of nervous system tumors in parents of affected children was increased 5-fold in the study of Farwell and Flannery (1984). Another study reported a near significant relative risk of 2 among offspring of survivors of childhood brain tumors (Sankila et al., 1998; Hemminki et al., 2000). In another study a risk of 10.26 for childhood astrocytoma was reported when a parent had meningioma (Hemminki et al., 2000). Significantly elevated risks were also found hemolymphatic malignancies

in the fathers of probands aged 0 - 14 years with brain tumors (SIR=13.3, p=0.0005) (Davide et al., 2003).

Clustering of cases of cancer in families may be due to chance association, inherited genetic mutations, common exposure to environmental agents or a combination of these factors. Grossman et al. (1999) sustained that environmental exposure explains an apparent familial brain tumor aggregation, but other authors rejected this hypothesis (de Andrade et al., 2001 and Jones et al., 1995). One study on spouse risks show that the degree of environmental sharing does not exceed an SIR of 1.24 and can only be noted for cancers with known strong environmental risk factors (Hemminki and Li, 2004). Thus, for most other sites, heritability is likely to be the main contributor. In a familial brain tumor study, no increased risks for any specific type of primary brain tumor was observed in the cohort of spouses, suggesting a genetic origin of the familial aggregation of brain tumours (Beatrice, 2003).

Other medical and birth-related factors

The possibility that the use of medications during pregnancy and early childhood could increase the risk for CBT has also been suggested in several studies. A large international population-based case-control study (including 1218 cases and 2223 controls) evaluated birth characteristics and maternal reproductive history and found an elevated risk for CBT among children aged 0-4 years linked to use of inhaled anesthetic gas during labour or delivery (OR=2.4, 95%=1.4-4.1) (McCredie et al., 1999). A Swedish record-linkage study based on data from medical records involving

570 cases reported that the use of inhaled penthrane (methoxyflurane) or narcotics during delivery was associated with an increased risk of all brain tumor types combined (OR = 1.5, 95%CI = 1.1-2.0 and OR = 1.3, 95%CI = 1.0-1.6, respectively) (Linet et al., 1996). There was no association of CBT with any other type of anesthetic (general anesthetic, injection-spine, injection-not spine). They also found increased risk associated with maternal exposure to oral contraceptives prior to conception (OR = 1.6, 95%CI = 1.0-2.8) (Linet et al., 1996). Other medications, such as metronidazole (Thapa et al., 1998), anticonvulsant (Gurney et al., 1997), and nitrosatable drugs (McKean-Cowdin et al., 2003) used during pregnancy have not been associated with an increased risk in offspring CBT.

Several birth and maternal characteristics have been studied as possible risk factors for CBT. Higher birth weight seems like the more likely factor to play a role in the development of brain tumors, particularly astrocytomas. In a cohort study on brain tumors in Swedish children, Mogren et al. (2003) reported that higher birth weight ($\geqslant$ 4000g) was associated with increased risk for astrocytomas grade I and II in young children (OR = 4.44, 95%CI = 1.19–11.38), but the OR was not significantly elevated for all tumors combined. Three studies done in the US have also found an increased risk of astrocytoma with higher birth weight (Kuijten et al., 1990; Emerson et al., 1991; Behren and Reynolds, 2003). However, other studies have not found such an association (McCredie et al., 1994a; Yeazel et al., 1997; McCredie et al., 1999). These studies did not differentiate by tumor subtype due to the insufficient number of cases. It is possible that higher birth weight is related to an increased risk of astrocytomas but

not other types of CNS tumors. Other children's cancers, including Wilms' tumor (Little, 1999), neuroblastoma (Daling et al., 1984), and leukemia (Ross et al., 1996), have also been associated with higher birth weight. Higher birth weight may be an indicator of increased cell division and fast growth. The rapid proliferation of cells may lead to increased vulnerability to carcinogens and increased mutations (Gold et al., 1979).

Other birth and maternal characteristics, including duration of breast feeding, maternal age at time of delivery, duration of gestation, previous fetal losses, birth order, and caesarean delivery have been investigated but the results have been conflicting and inconsistent (Daling et al., 1984; Emerson et al., 1991; Kuijten and Bunin, 1993; Bunin et al.,1994).

Summary of potential risk factors for CBT

Numerous potential occupational and environment risk factors have been suspected of playing a role in the development of CBT. However, there is inconsistent evidence to support a link with any of these factors and CBT, and relative risks are all small. It is likely that no single carcinogenic agent will be identified to explain the large proportion of CNS cancer occurrence in children. Nevertheless, several hypotheses are particularly compelling. The association found with cured meat consumption during pregnancy, the ability of polyomaviruses to initiate malignant transformation in the brain, occupational and residential exposure pesticides, the protective role of vitamin, and familiar history of cancers warrant further investigation. Most of the other

observed risk factors have been inconsistent and, in some cases, contradictory or come from exploratory analyses not yet based on prior hypotheses. Thus, the need for further research is obvious.

There are several limitations among the existing epidemiological studies. One difficulty may stem in part from studying total CBT as a single entity when several different histological types occur, which may mask or attenuate a causal association. Furthermore, due to the rarity of CBT, small sample size in any individual study limits the statistical power to detect an effect, if, in fact, one exists. In addition, common to childhood cancer studies, exposures happened several years ago, which contributes to the complexity of assessment occupational and environmental exposures. The immediate challenge for researchers involved in the association between CBT and occupational and environmental exposures is to develop valid and reliable exposure assessment methods, and to include in their studies an analysis of histological subtype of tumors. Future studies must include patients and collaborators from several geographic areas to obtain a large sample size due to the rarity of CBT.

Electromagnetic fields exposure and CBT

Although magnetic fields often occur together with electrical fields, there is no constant quantitative relationship between them. Magnetic fields are mostly created by the motion of current through a wire or equipment and measured in units of milligauss (mG) or microTesla (μT), whereas electrical fields are present whether or not the equipment is turned on, and the latter are measured in volts per metre (V/m).

Electrical fields are easily perturbed by material and other matter, whereas magnetic fields can easily pass through the body completely unperturbed. Although many studies do not attempt to distinguish the effects of magnetic fields from those of electrical fields, current thinking is that the magnetic fields are of the most biologically active.

The following literature review is based on experimental studies exploring the carcinogenic mechanism of EMF, as well as on epidemiologic studies of residential or parental occupational exposure to magnetic fields and /or electromagnetic fields studying the risk of brain tumors in children, with attention paid to the way in which exposures were assessed.

Experimental studies and potential mechanisms

Numerous experimental studies have been conducted to examine the carcinogenicity of MF, and the overall evidence for carcinogenicity is weak, based on many conflicting results of *in vivo* and *in vitro* studies. In the repetition of long-term animal experiments, Löscher and Mevissen's (1995) and Thun-Battersby et al.'s (1999) studies showed that compared with the control group, Sprague-Dawley (SD) rats exposed to 50 μT MF, after 7,12-dimethylbenz[a]-anthracene (DMBA) initiation, had an increased risk of breast cancers, however, a later study (Anderson et al., 1999) using different sub-strains of SD rats found no evidence for a cocarcinogenic or tumor-promoting effect of MF exposure. A NIEHS Working Group (Portier and Wolf,

1998) also reported that no significant effects of life long exposure to 50 or 60 Hz MF from 1000 to 1400 μT on cancer development were observed in rats or mice.

Although these studies suggest a lack of carcinogenicity in animals, these conflicting results may be due to the different genetic background which may play a pivotal role in effects of MF exposure. Recently, Fedrowitz et al. (2004) compared the two sub-strains of SD outbreed rats and found that MF exposure significantly increased mammary tumor development and growth in one of the strains of rats but not in the other. Furthermore, different specific exposure scenarios may have different potential to cause carcinogenic effects. One *in vivo* study (Nordenson et al., 1994) showed that intermittent exposure to MF caused chromosomal aberrations in human fetal cells, whereas continuous exposure did not, suggesting that average exposure may not be a relevant measure for carcinogenicity of MF. In addition, several studies suggested (review, McCann et al., 1993) that combined exposure to a known carcinogen may enhance the carcinogenic potential of MF.

Although potential biological mechanisms through which MF may cause carcinogenic effects has not yet been identified, based on a recent meta-analysis of data from *in vivo* or *in vitro* studies (Juutilainen et al., 2006), one possible hypothesis has been proposed whereby ELF-MF may cause cancers by affecting the recombination probability of radical pairs and therefore influence the level of free radicals.

Epidemiologic studies

Residential exposure

Concern about potential risk of EMF for brain tumors in children was initially brought to prominence by an epidemiological report two decades ago in Denver (Wertheimer and Leeper, 1979). The study, using electrical wire codes as a proxy measure of exposure to electric and magnetic fields, reported that children whose homes were close to high current power lines had an increased risk of leukemia and brain cancer. Since then, several studies have investigated the association between residential EMF and the risk of CBT. As described in four reviews (Kheifets, 2001; Ahlbom et al; 2001; NRPB, 2001; McKinney 2005), the results have not been homogeneous across studies.

The inconsistent results may be due to the use of indirect methods of exposure assessment in addition to differences in exposure assessment between the studies. The various approaches include, in the earlier studies, using wire codes to achieve a crude categorization of exposure, based on proximity of the residence to certain electrical installations such as power lines of different voltages. In the later studies, more sophisticated methods such as calculated and measured fields were used. With the development of new magnetic field meters, measurements of the magnetic fields in the homes were carried out over 24 h or even longer periods. One recent case-control study in Germany (Schuz et al., 2001) measuring the 50 Hz magnetic fields over a 24 hr period at the residence revealed a moderately increased CNS tumor risk with exposure to fields above 0.2 mT (OR=1.67; 95%CI: 0.32-8.84). Based on Waetenberg et al's (1998) meta-analysis of CBT and residential EMF exposure, an overall higher

risk estimate was present using calculated fields (OR=1.4, 95% CI: 0.8-2.3) and measured fields (OR=1.4, 95% CI: 0.8-2.4) than using wire codes (OR=1.2, 95% CI: 0.7-2.2) or proximity to electrical installations (OR=1.1, 95% CI: 0.7-1.7).

However, based on a recent met-analysis of 13 epidemiologic studies, there was a moderately increased risk of CBT with residential exposure to magnetic fields above 0.3 or 0.4 microTesla (μT) (OR=1.68, 95%CI=0.83-3.43), with no differences by method of exposure assessment (Mezei et al., 2008). The hypothesis that residential EMF exposure may influence CBT cannot be dismissed and further evidence is needed.

Electrical appliances

Electrical appliances such as electrical blankets, mattress pads, hair dryers, or water beds generate magnetic fields, and have been evaluated in several studies of CBT risk. Overall the evidence is inconclusive because the numbers of subjects associated with any increased risk are very small. Savitz et al. (1990b) reported a significant risk for brain tumor (OR=2.5) associated with prenatal electric blanket use; Dockerty et al. (1999) also found a significantly increased risk of brain tumors in children exposed to electric heating (OR=4.2) and a slightly increased risk in children using electric blankets (OR=1.6) or whose mothers used electric blankets during pregnancy (OR=1.6). However, the two reports cautioned against over-interpretation of these results in light of the small numbers and multiple comparisons.

Occupational exposure

Compared with residential exposure, occupational environments present a greater opportunity for a high-level ELF-MF exposure, such as in the electric utility industry (Deadman and Infante-Rivard, 2002). There are certain occupations that have higher levels of exposure to EMF, including power station operators, power line maintainers, sewing machine operators, welders, electric power electricians, and telephone cable splicers.

Parental occupational exposure to EMF or working in industries or at occupations involving potential EMF exposure has been investigated and reported in 12 studies published between 1985 and 2008. These are described in Table 1. All studies used a case-control design except one study. Maternal prenatal exposure is likely to be more important for fetal exposure than pre-conceptional paternal exposure, and thus should receive more attention than it has so far. However, only 9 of 12 studies investigated maternal exposure (Table 1). In addition, most studies that collected maternal occupational information did not present results due to the small number of exposed occupations. Although most studies did not find a significant positive association, reliable information on EMF exposure is seldom available. In many studies the results have been reported based on job or industry titles only (11 studies). Only one study used the JEM to estimate quantitative occupational MF exposure.

Five studies observed a higher CBT associated with paternal electrical occupations. Wilkins and Koutras (1988) carried out a mortality-based case-control study in Ohio

with the use of birth certificates to obtain paternal occupational information. Adjustments were made for potential confounding effects of several non-occupational factors, case fathers were more likely than control fathers to have been employed at birth in electrical work, such as electrical assembling and installing, and in repairing occupations in the machinery industries and structural work. Another case-control study (Johnson and Spitz, 1989) conducted in Texas also used birth certificate data to obtain paternal occupational information; an elevated relative risk of 3.6 was reported among fathers who were electricians and of 1.6 for paternal employment in industries linked with magnetic field exposure (at the time of birth). Although these two earlier studies both found an increased risks of CBT associated with paternal electrical occupations, the information of job titles obtained from birth certificate is usually limited to one job title and gives no information about the non-described job titles, which may not accurately represent the parental occupational exposures relevant to the development of brain tumors in their child. Two recent studies (Mckinney et al., 2003; Cordier et al., 2001) using interview information examining EMF exposures did not show that CBT are etiologically linked with exposure to occupational sources of EMF. However, the other three CBT studies (Wilkins et al., 1991; Kuijten et al., 1992; Mcken-Cowdin et al., 1998) all had elevated relative risks in relation to 'electrical work', and Mcken-Cowdin (1998) found an association with father's occupation as electrical worker, with an odds ratio of 2.3 (95%CI=1.3-4.0) for all histology types combined.

A later case-control study in Ohio by the same investigators (Wilkins and Lynn, 1996) has shown methodological improvements in terms of exposure assessment. Information about paternal occupation was obtained from telephone interview and analyses were limited to the 93 cases and 166 individually-matched controls. Paternal occupational exposure to EMF was inferred from a list of job titles likely involving EMF exposure based on published dosimetry studies. Notably elevated OR values were found in association with any paternal welding (OR=3.8; 95% CI: 0.95-15.55) in the one-year preconception period, and welding is associated with higher than average exposure to measured magnetic fields. Small increases in risk were also found for paternal jobs associated with EMF exposures, and the OR values ranged from 1.12 to 1.31.

Although a few studies have also investigated maternal occupational EMF exposures, the number of mothers with an occupation before and during pregnancy in the studies has generally been too small to allow meaningful analyses. A case-control study (Sorahan et al., 1999) of childhood cancers and maternal occupational exposure to magnetic fields was conducted in the United Kingdom; women were first classified based on occupations which possibly involved electric and magnetic fields exposure. Mother's occupation as a sewing machinist during the preconception and pregnancy periods was not a risk factor for all brain tumors combined. However, the relative risk for mothers who definitely held work in the textile industry (other than sewing machinist) before conception with likely EMF exposure was significantly elevated (RR=1.44, 95%CI= 1.03-2.01). Another case-control study in Taiwan (Ali et al., 2004)

also found that brain tumors were more common in children of mothers who had worked in electronic parts and components manufacturing (OR=7.3, 95% CI: 1.4–37.0). Mcken-Cowdin et al. (1998) found an all tumor odds ratio of 2.4 (95%CI=1.0-5.6) for mothers employed in the broadcasting and entertainment industries (motion picture, radio, television, or theater) during the preconception period and an odds ratio of 1.5 (95%CI=1.0-2.1) for those whose tasks included office machine operation (stenography, typing).

Only one of the 12 studies used a JEM to assess EMF exposure. Feychting et al. (2000) conducted a cohort study in Sweden to examine the association between parental exposure to MF and the risk of cancers in their offspring. Information about parental occupations was linked to a JEM developed for a male population. In that study, no association between CBT and maternal occupational mean MF exposure before conception was observed, and a decreased risk of brain tumors was found for paternal MF exposure above 0.3μT (RR=0.5; 95%CI: 0.3-1.0). However, the study was limited by the fact that the JEM developed for male workers may not have been completely applicable to women workers, and because about 40% of the mothers could not be included in the analyses because no measurements were available for them. Therefore, opportunities for exposure misclassification remained and may have lead to a dilution of the risk estimates. Furthermore, studying total CBT as a single entity may mask or attenuate a causal association.

Conclusion

The association between CBT and parental employment in occupations or industries involving EMF exposure is inconsistent, and most studies did not find a significant positive association, but it is not sufficiently persuasive to conclude that there is no real association. The ability of epidemiologic study to assess the relationship between cancer risk and exposure to EMF is very dependent upon the quality of the exposure assessment. In the majority of previous studies, the ELF-MF levels were inferred from occupations or job groups (e.g., electrical occupations) or from job exposure matrices (JEMs) based on MF measurement data. However, reliance on job titles or job groups alone may not be the most accurate method for estimating ELF-MF exposure; the use of electrical equipments in the course of the work and the presence of such equipments in the work environment could be equally or more important.

The results from *in vivo* and *in vitro* studies of EMF are inconsistent. Although a carcinogenic mechanism has not yet been identified, one possible hypothesis has been proposed that ELF-MF may cause cancers through radical pair mechanism (Juutilainen et al., 2006). Further, using a single summary exposure metric, such as geometric or arithmetic mean, may not be appropriate. Others may be relevant also to capture transient or intermittent exposure; the latter may have a greater potential to cause genotoxic effects than the average metric (Skyberg and Vistnes, 1993; Nordenson et al., 1994).

Exposure assessment in community-based case-control study

The validity of an occupational epidemiologic study is judged to a large extent by the quality of the exposure assessment. High quality assessment would include detailed work history from company records, and exposure information, including personal exposure measurement results. This type of information, however, is usually not available in community-based case-control studies. In most previous community-based CBT studies, parental occupational exposure assessments were mainly focused on job titles or job groups or parental occupational exposures were assessed using general JEMs. The approaches of using population-specific JEM, job-specific questionnaires (JSQs), and the so-called expert method (Infante-Rivard et al., 2005) have never been used in CBT studies. Each occupational exposure assessment approach has advantages and difficulties associated with its implementation, and investigators should choose the exposure assessment approaches that best fit their study design according to study purpose and the limited available resources.

Job title or job group

Job title or industry is often used as a surrogate for workplace exposure to potentially hazardous agents, and can be obtained from records or questionnaires. Job titles can be combined with similar exposures into groups. This approach is relatively inexpensive, and may provide suggestions leading for further research. The first study published on paternal occupation and CBT has used this approach, which found that children of fathers with high potential for exposure to hydrocarbon-related jobs were at higher risk of CBT (Fabia and Thuy, 1974). However, job title or job group approach has

several limitations. It does not take into account the variety in exposure levels and work environments within each job and thus may reduce the likelihood of finding true associations. In addition, it does not consider gender differences in tasks performed (Stewart and Herrick, 1991; Messing et al., 1994), possibly resulting also in a reduced sensitivity to risk detection. Furthermore, groups of jobs may actually be quite heterogeneous in the likelihood or intensity of their exposure to the agent of interest.

Job exposure matrix

An another approach to assign exposure is to use a job exposure matrix (JEM), which can provide an objective way of evaluating exposures for groups of workers. A JEM lists a wide range of occupations and/or industries on one axis and a wide range of exposure agents on the other; it can be somewhat costly and time-consuming to develop, but once created they are generally easy and cheap to use. Job titles, which are routinely collected in occupational epidemiological studies, are converted into specific workplace exposures. It may be a valid alternative to exposure assessment when individual exposure measurement is economically infeasible (Checkoway et al., 1989). The main drawback of JEMs is the inability to determine inter-individual differences within the same occupation resulting in greater non-differential misclassification of exposure than with expert method (explained below) (Plato and Steineck, 1993). This has been shown to attenuate the risk estimates toward one, thereby decreasing the statistical power.

Although existing JEMs are a practical way of assessing occupational exposures, one must consider several factors when choosing a general JEM for a study, including the specific place and time, the study population, the purpose for which the JEM was constructed, and the exposures and occupations included in the JEM. For example, an EMF JEM developed in Sweden based on men's jobs may not be appropriate for the Quebec and Ontario CBT study, when the goal is to assess occupational ELF-MF exposures in women.

Job-specific questionnaires

Questionnaires are frequently the sole source of occupational exposure information in retrospective population-based epidemiologic studies, and recall bias (in particular nondifferential) is always a concern. In order to improve the recall of details about job tasks, job specific questionnaires (JSQs) have recently been developed, first by Gerin and Siemiatycki (1991). These are the basis for the expert assessment of exposure for broad variety of substances. The method was later modified in order to reduce costs (Stewart et al., 1996) by incorporating it into a computer-assisted personal interview (Stewart et al. 1998).

JSQs include detailed exposure-specific questions allowing researchers to stimulate a worker's memory and gather valuable information on past exposures that might otherwise have been forgotten. They are often developed by experts who have the ability to determine which jobs have potential for exposure to agents of interest, and which specific tasks may lead to exposure. A JSQ begins with general questions about

the type of workplace and type of work usually done, and then proceeds to a series of questions that elicit standardized information about specific job tasks and the time spent at them, specific exposures related to these tasks, and the environment in which they were conducted.

JSQs, similar to JEMs, also assign specific chemical exposures to the subjects. However, compared with JEMs, JSQs allow for individualized exposure assessment, highlighting exposure variability among subjects with the same or similar jobs, which can decrease misclassification and increase study power (Reinier et al., 2004). Furthermore, task-based interview to prompt subject to recall products and chemicals rather than checklist format could reduce the opportunity for recall bias (Reinier et al., 2004). However, subjects may have difficulty remembering occupational events in detail, particularly the jobs held a long time ago. Furthermore, this approach relies heavily on intensive training of the interviewers, and is also relatively more expensive than the use of JEMs or job titles.

Expert assessment of exposure

Expert assessment involves the use of job specific questionnaires or interviews, combined with an evaluation by trained experts, such as occupational hygienists, chemists, and other professionals, for the purpose of inferring occupational exposures individually. It is premised on the notion that working environments are not stable and always change over time, and if each subject's actual environment can be considered, the validity of exposure information will be considerably improved. Based on a variety

of information sources, including the subject's detailed job description, technical documentation, and consultants who are experts in one or another industry, experts can make educated guesses as to the possible chemical and physical exposures experienced by the subject and code exposures with the level, frequency, as well as of their degree of confidence that the exposure occurred (Infante-Rivard et al., 2005). This approach has generally been considered the best possible retrospective exposure estimation method (McGuire et al., 1998) compared with other less elaborate methods of collection of occupational exposure data—such as self-reported exposure, JEM, and in some situation, even better than exposure measurements, which are also prone to error due to spatial and temporal variation in exposure concentrations. Although this method has the advantage of improved exposure measurement, it has some limitations. It is extremely expensive, time consuming and relies on the quality of occupational history and rare expertise that may not always be available (Siemiatycki et al., 1981).

Conclusion

Each method has its strengths and limitations. Self-report based on the exposure description has a higher sensitivity, but subjects may be less likely to know specific substances and this method may be subject to possible recall bias; JEM based on job title description is objective, as well as easy and cheap to use, but it is affected by its inability to determine inter-individual differences within the same job tile; although the expert method based on comprehensive review of individual data is often considered as the best approach, it is time-consuming and costly. A high sensitivity and specificity would indicate that the exposure assessment approach classifies

individuals into the same exposure category (exposed/not exposed) as the gold standard, and has a lower misclassification, which is desired by all studies. However, investigator should choose the exposure assessment approaches that best fit their study design according to study purpose, exposure prevalence, and the limited available resources.

Study objectives

This study is a secondary data analysis of two population-based case-control studies conducted in Ontario and Quebec, Canada, which assess the association between a number of possible risk factors including occupations of the parents and the development of brain tumors in the offspring. The goal of this study is to evaluate whether mothers' occupational exposure to ELF-MF, immediately before and during pregnancy, is associated with an increased risk of childhood brain tumors, using individual exposure estimations or a job exposure matrix based on ELF-MF sources, work environments and duration of exposure. The details of the study population and general method are described below.

Methods

Two Canadian studies were pooled; case and control selection, as well as data collection and exposure assessment methods are described separately for each study.

Case selection

Québec study

Details of this study have been described elsewhere (Shaw et al., 2006). This study was restricted to tumors occurring within the brain as defined in the International Classification of Disease for Oncology, Second Edition, using site codes C71.0–C71.9, plus cerebral meninges (C70.0), meninges undefined (C70.9), optic nerve (C72.3), pituitary gland (75.1), craniopharyngeal duct (75.2) and pineal gland (75.3). Brain tumors were classified according to the 1996 International Classification of Childhood Cancers second edition (ICCC-2) (Kramarovaet al., 1996) as: astroglial tumors (includes optic nerve gliomas); primitive neuroectodermal tumors (PNET, consists mostly of medulloblastoma), other gliomas (includes oligodendroglioma); ependymomas (includes chorid plexus papilloma); other specified intracranial (includes craniopharyngioma, pineoblastoma/cytoma, and ganglioglioma), and other unspecified intracranial tumors (includes intracranial germ cell tumors). Primary, malignant brain tumor cases were recruited from tertiary care centers designated by governmental policy to hospitalize and treat children with cancer in the province. Tumor specimens were reviewed by pediatric neuro-pathologists. Due to budgetary constraints between 1980 and 1993 a random sample of one-third of all brain tumor cases diagnosed before 10 years of age was selected (n = 130). Between 1995 and

1999, all first primary, malignant brain tumor cases diagnosed in Québec before 15 years of age were invited to participate (n = 142). Because cancer care is covered under a universal health plan for all Canadian residents, we believe a negligible number of children, if any, were treated outside the province. Children who were adopted, who lived in foster families, whose families spoke neither French nor English, who were not resident in Canada, or whose parents were both unavailable for interview were excluded. The response rates for cases from 1980–1993 to 1995–1999 were 94.0% and 82.7%, respectively. The response rates for cases from 1980-1993 and 1995-1999 were 94.0% and 82.7%, respectively. Differences in response rates between the study periods are likely due to slightly different methods in recruiting subjects: in the earlier study period cases were recruited by the research team, while in the more recent study period cases were first approached by hospital personnel to determine interest in the study.

Ontario study

In Ontario, cases were children under the age of 15 years who were first diagnosed between October 1997 and December 2002 at five pediatric oncology centers throughout the province (Toronto (HSC), Hamilton, London, Ottawa and Kingston), and who resided in the province at the time of diagnosis. Tumor specimens and pathology reports were reviewed by a reference pediatric neuro-pathologist. They were classified according to the WHO criteria with assigned histology codes which are convertible to the morphology codes for the histological types using the third edition of the ICCC (Steliarova-Foucher et al, 2005). The resulting classification is as follows:

astroglial tumors (8000, 9380–9382, 9400, 9401, 9411, 9420, 9440, 9441), PNET (9470–9473), ependymomas (9390-9392 and 9394), other gliomas (9450), and other intracranial neoplasms (9350, 9360-9362, 9364, 9503 and 9505). ICCC-3 provides continuity with ICCC-2. During that period, 325 eligible cases were identified, among whom, 40 refused to participate, and 9 could not be traced; thus, 276 interviews (85%) were completed.

Control selection

Québec study

Population-based controls (1:1 ratio) were matched to the cases on sex and age at diagnosis in the calendar year of diagnosis (i.e., a case aged 4 in 1995 was matched to a child of the same age free of disease in 1995). Between 1980 and 1993, controls were chosen from continuously updated family allowance files, which contain information on all children living legally in Canada. From 1995 to 1999, controls were chosen from the continuously updated provincial health insurance agency files where current information on all families living in Québec is maintained to provide universal medical care coverage. These sources of data were the most complete census of children available during the study periods. According to the expected distribution of cases, ten potential controls per case were randomly chosen from the lists. Similar exclusion criteria as the cases were also made for controls. The response rates for controls from 1980-1993 and 1995-1999 were 83.8% and 90.4%, respectively. Address information provided for control subjects was more accurate in the latter phase of the study.

Ontario study

In Ontario, population-based controls, frequency-matched to the cases by age categories (0-1, 2-4, 5-9, 10-14 years) at diagnosis and region of the province (using postal code areas), were randomly chosen from the Property Assessment Files of the Ontario Ministry of Finance. These files include information on all residents living legally in the province and were the only data for Ontario that enabled age-stratified sampling. In total, 722 families with an eligible child were identified, 30 percent refused to participate, and 488 (67%) completed the telephone interview.

Date collection

Both studies were approved by the ethics committee of each of the institutions involved and the respective provincial agencies overseeing access to information regulations. An informed consent was obtained from all study participants.

Québec study

Soon after sending a letter introducing the general purpose of the study, trained interviewers contacted the parents to schedule an appointment for an interview, which was eventually administered by telephone using structured questionnaires. One such questionnaire addressed general risk factors and potential confounding factors; another structured questionnaire was used to collect a detailed job history from the age of 18 years and on, until the end of pregnancy. It included the job title and dates on this job, the type of industry, and its name and address. For each job held by the mother from 2

years before pregnancy and up to birth of the index child, a semi-structured questionnaire was also used to probe for more detailed information related to the company's activities, the raw materials and final product, presence of any electrical equipment or ionizing and non-ionizing radiation sources, personal protective equipment, and a detailed open-ended description of the woman's typical activities at work. Finally, for frequent job titles and/or jobs with a significant potential for occupational exposures (e.g., nurse, sewing machine operator, hairdresser, waitress, cook, textile dry cleaner, knitting and weaving operator), a job-specific questionnaire was administered that probed more deeply into the specific tasks, the time spent at them, specific exposures related to these tasks, and the environment in which they were conducted.

Ontario study

A structured questionnaire was administered on the phone by a trained interviewer to gather information on a number of suspected risk factors including occupational history for all full and part-time (on average, a minimum of 20 hours of work per week) jobs outside the home that each parent had held for at least 6 months; the collected information included job title and dates on this job, the main task performed, the type of industry and its name and address.

Exposure assessment

Québec study

The so-called expert method for assessing exposure has been described in detail elsewhere (Infante-Rivard et al., 2005) and is based on the assessment of individually reported exposure data by expert chemists or hygienists. The Quebec study had collected detailed parental occupational exposure information, but experts were not available to code all the ELF-MF exposure due to budget cost limitation. However, an estimation method and exposure matrices of maternal occupational exposure to ELF-MF by sources and work environments or job titles had been developed by the Québec research group (Deadman and Infante-Rivard, 2002), for a study of childhood acute lymphoblastic leukemia (ALL) in the same province, carried out at approximately the same time. These matrices were constructed by an expert using values associated with electrical equipment and work environment, as published in the literature or based on available actual measurements. These matrices included ELF-MF estimates for 111 sources, 59 work environments, and 61 job titles. Based on this method, a pilot study was conducted (Claire Infante-Rivard, personal communication) to compare estimates of occupational ELF-MF exposure obtained by an educated but not considered-as-expert-observer and an expert, using 75 case and 75 control mothers coming from Québec CBT data. Results showed that a trained non-expert using the published matrices from the ALL study could produce almost similar estimates of maternal occupational exposure to ELF-MF as those of an expert. In particular, for 95% of the estimates, an estimate by the non-expert would be between 0.2 μT lower, and 0.2 μT

greater, than an estimate by the expert. (results available on request from the corresponding author) (results available on request from Claire Infante-Rivard). Therefore, in the Québec study, for each job held by a mother during the 2 years before pregnancy up to birth, one educated but not considered-as-expert-observer was trained by the expert to recognize and classify the ELF-MF sources, the potential for exposure in the work environment, and the duration of exposure. That observer assigned a weekly time-weighted average (TWA) exposure based on the published values in the matrices (Deadman and Infante-Rivard, 2002). A TWA was calculated as the product of the magnetic field intensity of each identified source by the duration of exposure for this source; any remaining work time was multiplied by the background field level assigned to the specific work environment. The sum of products across all exposed sources and duration as well as environment and duration were divided by the total weekly hours spent at work. However, there was no useful information in the published matrix for about 18% jobs in the CBT study; for these cases, the educated observer consulted the expert and a decision was made to assign a TWA by extrapolating exposure level from other sources in the matrix having similar electrical operations.

Each job was coded according to the seven-digit Canadian Classification and Dictionary of Occupations (CCDO) 1971 (Department of Manpower and Immigration, 1971) and industry was coded according to the three-digit Standard Industrial Classification (SIC) 1980 (Statistics Canada, 1980).

Ontario study

Although essential occupational information (job tile and task as well as duration) was available from the Ontario study, it was substantially less detailed than in the Québec study. Therefore, we developed a job-exposure matrix for ELF-MF (available on request) for the Ontario study, derived from exposure information in the Québec childhood brain tumor database. In the Ontario data, there was often not enough information provided in the questionnaire to code at the same detailed level as in the Québec study; therefore, all jobs involving similar duties and similar work as those held by the mothers in the Québec study were grouped together using the first four-digits of the CCDO code. A similar grouping was done for the industries according to the first two-digits of the SIC code. The four-digit occupation codes formed a list of 121 occupation groups, and the 2-digit industry codes formed a list of 47 industry groups. An exposure information table was generated from the Québec data, which included a list of 4-digit occupation and 2-digit industry combinations and the estimated time-weighted average exposure for each combination. These occupation and industry code combinations resulted in a total of 181 cells compiled into the JEM; each cell contained information on total number of workers for each job code, the mean value of ELF-MF, as well as the minimum and maximum value. For example, based on the individual exposure estimations of Québec childhood brain tumor data, the range of TWA for 5 mothers who worked as secretaries (coded 4111) in the health and social service industry (coded 86) was 0.21-0.32 μT, the mean TWA value for this job code (411186) was 0.26 μT, and the minimum and maximum values were 0.21 μT and 0.32 μT, respectively.

Before linking the JEM to the work histories from the Ontario data, each job held by a mother and the industry in which it was held during the 2 years before pregnancy and during the pregnancy were also coded to the four-digit CCDO (1971) and the two-digit SIC (1980); coding was blind to the case-control status. A mean TWA value was assigned to each combination of occupation and industry code. However, there were approximately 25% jobs which could not be linked to a cell in the JEM. For these jobs, if the occupation code was the same but the industry code was different as that in an existing JEM cell, a mean exposure value from the same occupation title but in a different industry was assigned; if, on the other hand, the occupation code could not be found in the JEM, we extrapolated the mean exposure value from the closest job type within the matrix using the questionnaire data describing the job task to confirm the assigned category.

Statistical analysis

In the Québec study individual matching was done on age and sex; in the Ontario study frequency matching was based on geographic region and age groups (in years, 0-1, 2-4, 5-9, 10-14). Because the studies used different matching strategies, unconditional logistic regression models were used with the pooled data adjusting for the variables: study center, sex, and age at diagnosis of the child (in years, 0-1, 2-4, 5-9, and 10-14). Since matching variables such as area of residence could not be taken into account in unmatched analysis, matched conditional analyses were also performed for the subset studies. For Quebec study (individually matched), strata were defined by

matched sets; for Ontario study (frequency matched), strata were defined by geographic region, and/or age group (in years, 0-1, 2-4, 5-9, 10-14). Since result comparisons from matched conditional analyses and unmatched analyses for the same subset of study participants were similar, results from unmatched analyses were reported. The use of X-ray pelvimetry, a known risk factor for CBT, was not adjusted in the model, because it was explored in the subset analyses with Quebec data and did not indicate that this was a potential confounder which may be due to the substantially lower radiation doses than in the earlier time. Two other potential confounders: maternal age and education level did not materially modify the odds ratio associated with exposure and thus were also not included in the model.

Five maternal job or industry categories involving ELF-MF exposure that were previously found to be associated with CBT were created for this analysis: electrical workers, sewing machine operators, office machine operators, food and beverage preparers, and broadcasting and entertainment industries (Sorahan et al., 1999; McKean-Cowdin et al., 1998; Ali et al., 2004). An additional 35 industrial and 44 occupational categories (Table 2 and 3) were examined in a secondary analysis. Because many of the sub-categories were based on small numbers, odds ratios were reported only for categories with at least five exposed cases.

Analyses were conducted on three ELF-MF exposure metrics, as was previously done in the childhood leukemia study (Infante-Rivard and Deadman, 2003): cumulative exposure, average exposure, and peak exposure. Cumulative exposure (expressed as

exposure microTesla-days, (μT-days)) was calculated as the sum across all jobs of the product of the TWA for each job held times its duration. For example, if a mother held a job during 2 years before pregnancy with an intensity value of 0.2 μT and worked 150 days, changed her job to another job code with an intensity level of 0.16 μT, and worked 100 days, that mother's cumulative exposure for magnetic fields is (0.2×150+0.16×100) =46 μT-days. Average exposure (i.e., cumulative exposure divided by the duration of exposure) in this case is (46 μT-days /250) =0.18 μT. Cumulative and average exposures were classified into, at or above the 90th percentile of the distribution, and below the 90th percentile, among all study women (working and nonworking). This cut-point was selected based on previous studies; first, a meta-analysis of residential exposures in which a moderately increased risk of childhood brain tumors was observed only among children exposed at high level (residential magnetic fields exposure above 0.3 or 0.4 μT) (Mezei et al., 2008); and second, the fact that 0.4 μT is a level above which residential magnetic fields were associated with childhood leukemia (Ahlbom and Feychting, 2001). The peak exposure for an occupation was measured as weekly TWA and dichotomized at 0.4 μT, for this same reason.

Using these three exposure metrics, analyses were conducted in two time windows: the first was for the 2 year period before pregnancy, reflecting the continuity of jobs over this period of time, and the second was for the pregnancy period. For tumor-specific analyses, cases were classified into 3 major histological types: astroglial

tumors, PNET, and other gliomas, including ependymomas, oligodendrogliomas, and other unspecified gliomas.

Statistical analyses were conducted by using SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA), as well as the Stata software (StataCorp 1997).

Results

The distribution of tumor types was quite similar between the two studies (Table 5). The distribution of all characteristics was similar between cases and controls in the Québec study. In the Ontario study, this was also the case except for the age and sex distributions of study subjects. The level of education was lower in the Québec study, reflecting in part the fact that recruitment in this study dates back further than in the Ontario study. In the pooled data, child's age differed markedly between cases and controls carrying the impact of these distributions being different between the cases and controls in the Ontario study.

Of the five maternal job or industry categories where an association with childhood brain tumors was previously suggested (see above), we found a elevated risk among children of mothers employed as sewing machine operators for all brain tumors combined (OR=2.3, 95% CI=1.0-5.4), as well as for astroglial tumors (OR=2.3, 95% CI=0.8-6.3) and other gliomas (OR=2.9, 95% CI=0.8-11.7) (Table 6). An elevated risk for other gliomas was also found for mothers working as food and beverage preparers (OR=2.9, 95% CI=1.4-6.3). There was no increased risk associated with the categories secretaries and typists or broadcasting and entertainment industries. Although risk of childhood brain tumors in the offspring of electrical workers has also been suggested to be increased, there was only one exposed case and results were not reported in the table.

Where at least five cases were exposed, analyses of other occupation and industry groups were carried out. A statistically significant association was observed for other gliomas in the food and beverage service group (OR=2.6, 95% CI=1.2-5.5). Elevated risk for other gliomas was also found for mothers working as nurses (OR=2.1, 95% CI=1.0-5.0) or for all tumors combined in the health services group (OR=1.3, 95% CI=1.0-1.8). No other associations between childhood brain tumors and maternal occupations or industries before birth were observed.

Median ELF-MF levels were similar for cases and control groups in each study when using cumulative and average metrics among all women and among working women (Table 7). Compared to Québec study, the Ontario median levels for the cumulative metric were slightly lower before conception and slightly higher during pregnancy; the median levels for the average metric were similar in both studies.

For the 2 year period before pregnancy, the absolute number of women considered exposed for any of the three ELF-MF exposure metrics was somewhat higher in the Québec than in the Ontario study, despite a similar number of cases and a smaller number of controls (Table 8). The ORs in the Quebec study were slightly lower than those observed in the Ontario study for cumulative and average exposure metrics. We did not find any association with maternal occupational ELF-MF exposure in either study. During the entire pregnancy period, the ORs were similar as those observed for the period before conception for each exposure metric. However, when considering histological subgroups for both studies together (Table 9), an elevated risk for

astroglial tumors was associated with the average exposure metric (OR=1.5, 95% CI=1.0-2.4) before conception. During the entire pregnancy period, a significantly elevated risk was also observed for the average metric with astroglial tumors and all tumors combined (OR=1.6, 95% CI=1.1-2.5, and OR=1.5, 95% CI=1.1-2.2, respectively).

No significant interactions between maternal ELF-MF exposure and age at diagnosis of the child were found in the analysis.

Discussion

Summary of findings

In this study, we did not find strong associations between childhood brain tumors and mothers being potentially exposed to ELF-MF before and during pregnancy through their occupations or the industries in which they worked. Except for sewing machine operators, most categories of occupations or industries with a higher ELF-MF exposure had only one subject. However, children of sewing machine operators had an OR indicative of a two-fold increase in the risk of all tumors combined as well as for astroglial tumors and other gliomas. A similar observation was also reported in the childhood leukemia study (Infante-Rivard and Deadman (2003). We used three exposure metrics (cumulative, average, and maximum level) to further analyze quantitative occupational ELF-MF exposure. There was some evidence that an elevated risk was observed for astroglial tumors with average exposure metric before conception. During the entire pregnancy period, a significantly elevated risk was also observed for astroglial tumors and all tumors combined with the average metric.

Comparison of results to previous findings

Only one previous epidemiologic study has examined the risk of CBT related to maternal quantitatively occupational MF exposure. Feychting et al. (2000) conducted a cohort study in Sweden to examine the association between parental exposure to MF and the risk of cancers in their offspring. Information about parental occupations was linked to a JEM developed for a male population. In that study, no association

between CBT and maternal occupational mean MF exposure before conception was observed. However, the study was limited by the fact that the JEM developed for male workers may not have been completely applicable to women workers, and because about 40% of the mothers could not be included in the analyses because no measurements were available for them. Further, studying total CBT as a single entity may mask or attenuate a causal association.

Since potential biological mechanisms through which ELF-MF may cause carcinogenic effects have not yet been identified, the relevant exposure metrics for the effect of ELF-MF are speculative. Whereas we used three metrics, others may be relevant also to capture transient or intermittent exposure; the latter may have a greater potential to cause genotoxic effects (Skyberg and Vistnes, 1993; Nordenson et al., 1994) than the exposure estimated by our three metrics. In this study, the risk estimates for all the three metrics were fairly consistent across the duration before conception and the entire pregnancy.

All other previous epidemiologic studies have evaluated an association between CBT risk and maternal occupational exposure using job titles or groups. One such study was conducted in the United Kingdom; women were first classified based on occupations which possibly involved electric and magnetic fields exposure. Mother's occupation as sewing machinist preconception and during pregnancy was not a risk factor for all brain tumors combined. However, the relative risk for mothers who definitely held work in the textile industry (other than sewing machinist) before

conception with likely EMF exposure was significantly elevated (RR=1.44, 95%CI= 1.03-2.01). These results are compatible with our findings for sewing machine operators and all brain tumors combined.

Mckean-Cowdin et al. (1998) found an all tumor OR of 2.4 (95% CI=1.0-5.6) for mothers employed in the broadcasting and entertainment industries (motion picture, radio, television, or theater) during the preconception period, and an OR of 1.5 (95% CI=1.0-2.1) for those whose tasks included office machine operation (stenography, typing), as well as an OR of 1.6 (95% CI=1.1-2.5) for astroglial tumors among those working as food preparers. For the categories secretaries and typists and broadcasting and entertainment industries, no significantly increased risks were observed in our study; however, we observed a similar result among those working as food and beverage preparers for other gliomas.

Kuijiten et al. (1992) observed an increased risk of astrocytoma for mothers working as nurses (OR of 2.2 (95%CI=0.7-8.1)), and the risk was higher for children diagnosed before age four. On the other hand, Olsen et al. (1991) also reported an OR of 1.4 ($P<0.05$) for all tumors combined among children of women working as nurses. We also found an increased risk for all tumors combined and astrocytoma for mothers working as nurses, in the health service industries, employed as teachers or working in the finance and insurance industries. Working as a nurse or in health services also involves potential exposure to chemicals or solvents, which may themselves be risk factors for childhood brain tumors (Cordier et al., 1997; and Feingold et al., 1992).

Misclassification of exposure

In most epidemiologic studies of the association between CBT and parental occupational exposures, the retrospective exposure assessment poses a significant challenge and misclassification of exposure is a common concern. In this study, we used two exposure assessment methods: individual exposure estimations and a job exposure matrix; the potential misclassification biases are discussed for each method.

To our knowledge, this study is the first to use individual exposure estimations (Québec study) based on the main determinants of exposure such as sources, work environments, as well as duration, to examine associations between maternal ELF-MF exposure and childhood brain tumors. Nevertheless, some misclassification has likely occurred, and possibly more so when the information collected from mothers was not detailed enough to accurately estimate the exposure duration. In addition, reliance on published ELF-MF levels associated with source and work environment, as found in the matrices we used, may have limitations since some sources or environments may have many published values, while others may have few or none. Furthermore, the published measurements may have been taken at a different time from that when the actual exposure occurred, and magnetic fields exposure within occupations may well have changed over time due to increased use of electrical equipments or improved manufacturing processes. However, this exposure assessment was not adjusted for possible effects due to the era in which the job was held because there is little or no specific information available on the change of magnetic fields with time for the various sources or environments. For sources or environments where there were no

published values, estimated levels were assigned by an expert based on reviewing of the measurement campaigns conducted in the province of Québec. This method of assigning values to estimate magnetic fields exposure has also been employed in other studies (De Roos et al., 2001; Infante-Rivard and Deadman, 2003).

We believe that the JEM for ELF-MF, derived from individual exposure information from the Québec data was probably the more feasible approach to estimate Ontario's occupational exposures due to the minimal available information. However, since some jobs involve a lot of different tasks with widely varying levels of exposure, based on the individual assessment, an average exposure level was used for these job titles. This could have resulted in greater non-differential misclassification of exposure than for individual estimation (Plato and Steineck, 1993). Furthermore, the fact that we used the Québec ELF-MF values for job titles with very few subjects, to assign them to the Ontario data, may have resulted in unstable exposure estimates. Nevertheless, a JEM based on sources, work environments, and duration, in contrast with JEMs based solely on source measurements without considering work environments, is expected to improve the precision of exposure estimates (Kelsha et al., 2000). Although the reliability of the JEM constructed from the Québec population but applied to the Ontario population was not be evaluated, Québec and Ontario both are in central Canada, have similar economies and are quite similar with respect to types of industrial practice. There were approximately 25% jobs in the Ontario data for which occupation and industry information was not sufficient to find a correspondence in the Québec data. For these cases, we extrapolated the mean

exposure value from the closest job type within the matrix using the job task description to confirm the assigned category. This could be an additional source of non-differential misclassification in our data.

Other Bias

Recall bias

Interviews of mothers were the primary source of information about maternal occupations during the three-year period before birth, which certainly introduces the possibility for recall bias. For the Ontario center, a specific JEM was used to code exposures; a JEM is much less not susceptible to differential recall of exposures and tends to have less misclassification of exposure than self-reported exposures (Siemiatycki et al., 1989; Coughlin and Chiazze, 1990). For the Quebec center, a trained and knowledgeable individual coded exposure but this individual is not considered an expert. In this context, there is strong reliance on the quality of the occupational history. In order to improve the recall of details about job tasks, job specific questionnaires (JSQs) have been developed; these include detailed exposure-specific questions to simulate a worker's memory and gather valuable information on past exposures that might otherwise have been forgotten. However, subjects may have difficulty remembering occupational events in detail, particularly the jobs held a long time ago. Further, it is impossible to determine whether cases reported their work histories in a different way than controls which would lead to misclassification of exposure.

Selection bias

Two population-based case-control studies were conducted in central Canada, and information was obtained from about 85% of the identified cases. In the Quebec study, controls were selected to be a random sample from the general population, and the response rates were extremely high, and from 1980-1993 and 1995-1999 were: 83.8% and 90.4%, respectively; thus, selecting of subjects was in essence independent of exposure status, eliminating the possibility of selection bias occurring. On the other hand, in the Ontario study, the response rate was only 67% among eligible controls, indicating a greater likelihood of selection bias. One previous CBT study suggested that socioeconomic status played a role in selection of participating controls due to the association between CBT and higher education level. It might be expected that those mothers who were more educated would be more likely to respond than the general population.

Potential confounders

We were unable to assess the effect of home exposure to ELF-MF since this variable was not measured; however, the proportion of nonworking women, mother's age and education level were quite similar between cases and controls in each study reducing the potential for marked differential home exposures between the mothers of cases and controls. The use of X-ray pelvimetry, the only clearly established environmental cause for CBT, was explored in the subset analyses with Quebec data. However, it did not indicate that this was a potential confounder which may be due to the substantially lower radiation doses than in the earlier time.

The current study did not examine the effect of paternal occupational ELF-MF exposure before preconception. Potential biological mechanisms through which EMF may cause carcinogenic effects by maternal or paternal exposure has not yet been identified, although several previous studies have suggested an association between CBT and paternal employed as an electrical worker or welder. However, maternal exposures are likely more important for fetal exposure than paternal, and thus should receive somewhat more attention. The other unmeasured confounders, such as known chemical carcinogens (solvents), could be associated with occupational magnetic fields and thus potentially confound the effects estimated in this study. Several studies suggested (review, McCann et al., 1993) that combined exposure to EMF with a known carcinogen may enhance the carcinogenic potential of EMF. The effects of these unmeasured confounders need to be explored in the future studies.

Other limitations

One limitation of the current study was the lack of power to detect small differences due to the small number of histological types of cases and the small number of mothers with an occupation before and during pregnancy. The power of the study may have been reduced further due to the misclassification of exposure as already discussed; however, we attempted to increase efficiency of our exposure estimates by introducing two more valid exposure assessment methods.

The current study was also limited by its inability to determine which exposure metric is more relevant in association with CBT. Since there is still lack of an accepted carcinogenic mechanism of ELF-MF, and using a single summary exposure metric may not be appropriate, three different exposure metrics were chosen as the representative exposure metrics: cumulative exposure, average exposure, and peak exposure. However, these three types of exposures may not be representative of the other aspect of exposures, such as transient exposures or the intermittency of exposure, which may have greater potential to cause genotoxic effects (Nordenson et al, 1994; Skyberg and Vistnes, 1993).

Conclusion

Results are suggestive of a possible association between maternal occupational ELF-MF exposure and certain brain tumors in their offspring. Future studies should confirm this association with improved exposure assessment. Ideally, home exposure should also be evaluated carefully, in addition to detailed work histories. Furthermore, it would be interesting to explore modification of effects by chemical factors and ELF-MF exposure.

In future studies, questions on occupational histories should obtain as much detailed as possible, including job title, industry, tasks, work hours and duration, source and distance, as well as frequency and use of personal protection equipment. Further, it would be better to assess exposure on an individual basis rather than inferring exposure indirectly. Although expert assessment offers some theoretical advantages over using population JEM to analyze specific exposures, it is time-consuming and costly as well as relies on the quality of occupational history. However, if there are clear main determinants of exposure existed, and if there is also detailed information on these determinants are available in the literature, a trained non-expert could produce almost similar estimates as those of an expert but at a lower cost, such as the method used to assess ELF-MF exposure in Quebec center. Further, the JEM used in Ontario center based on sources, work environments and duration, in contrast to the JEMs based on just source measurement data without regard to work environment, were expected to improve the precision of exposure estimates. These two methods

have not been used before and will need to be applied by others to determine their validity.

Different and specific exposure scenarios may have a different potential to cause carcinogenic effects. Although no such clue was provided in our data from the use of three exposure metrics, other aspects of exposure, in particular, transient or intermittent exposure, should also be taken into account in future studies.

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Table1. Epidemiologic studies of CBT and parental potential occupational EMF exposure.

Reference (place)	Study design	Source of occupational exposure data	Exposure assessment (F=father M=mother)	Histology	No of case/control	Time frame	EMF exposures or surrogates	No of exposed cases	Risk estimates (95% CI)
Ali et al. (2004, Taiwan)	C-C	Interview	Job groups (F,M)	Brain tumors	74/417	Preconception	Electronic parts and components manufacturing (M)	4	7.3 (1.4-37.0)
McKinney et al. (2003, UK)	C-C	Interview	Job groups (F, M)	Central nervous system	687/7629	Preconception	Occupations related to EMF exposure (F)	35	1.04 (0.72-1.47)
							Occupations related to EMF exposure (M)	39	0.95 (0.67-1.32)
Cordier et al. (2001, International)	C-C	Interview	Job groups (F, M)	Brain tumors	1218/2223	Before birth	electrical work (F)	98	1.1 (0.9-1.5)
							electrical work (M)	22	1.3 (0.7-2.2)
Feychting et al. (2000, Sweden)	Cohort	Censuses data	JEM (F, M)	Brain tumors	162	Preconception	MF≥0.26uT (M)	7	1.1 (0.5-2.4)
							MF≥0.30uT (F)	10	0.5 (0.3-1.0)
Sorahan et al. (1999, Great Britain)	C-C	Interview	Job titles and groups (M)	Brain tumors	NA	Preconception	Sewing machinist	52	1.13 (0.74-1.73)
							Textile industry work (other than sewing machinist) with likely EMF exposures	98	1.44 (1.03-2.01)

Table1. Continued

Reference (place)	Study design	Source of occupational exposure data	Exposure assessment (F=father M=mother)	Histology	No of case/control	Time frame	EMF exposures or surrogates	No of exposed cases	Risk estimates (95% CI)
						Pregnancy	Sewing machinist	5	1.17 (0.33-4.11)
							Textile industry work (other than sewing machinist) with likely EMF exposures	15	1.72 (0.75-3.97)
McKean-Cowdin et al. (1998, California and Washington, USA)	C-C	Interview	Job groups (F, M)	Brain tumors	504/801	Preconception	Electrical workers (F)	34	2.3 (1.3-4.0)
							Office machine operator (M)	63	1.5 (1.0-2.1)
							Broadcasting and entertainment industry (M)	14	2.4 (1.0-5.6)
						Pregnancy	Electrical workers (F)	25	2.5 (1.3-4.8)
							Office machine operator (M)	14	1.2 (0.7-2.0)
				Astrocytoma	308/801	Before birth	Food preparers (M)	40	1.6 (1.1-2.5)
Wilkins and Wellage (1996, Ohio, USA)	C-C	Interview	Job titles and groups(F)	Brain tumors	94/166	Preconception	Jobs associated with EMF exposure	11	1.3 (0.6-3.0)
							Welder	6	3.8 (0.95-15.6)

Table1. Continued

Reference (place)	Study design	Source of occupational exposure data	Exposure assessment (F=father M=mother)	Histology	No of case/control	Time frame	EMF exposures or surrogates	No of exposed cases	Risk estimates (95% CI)
						Pregnancy	Jobs associated with EMF exposure	9	1.03 (0.45-2.39)
							Welder	5	2.50 (0.67-9.31)
Kuijten et al. (1992, Philadelphia, USA)	C-C	Interview	Job groups (F, M)	Astrocytoma	163/163	Preconception	Definite EMF (F)	19*	1.10 (0.4-3.1)
							Probable EMF (F)	27*	1.70 (0.7-4.4)
							Electrical assembling, installing, repairing (F)	18*	1.0 (0.4-2.8)
							Electrical repairing only (F)	9*	8.0 (1.1-356)
						Pregnancy	Definite EMF (F)	17*	0.90 (0.3-2.6)
							Probable EMF (F)	21*	1.60 (0.6-4.5)
							Electrical assembling, installing, repairing (F)	12*	1.0 (0.3-3.7)
							Electrical repairing only (F)	6*	5.0 (0.6-237)

Table1. Continued

Reference (place)	Study design	Source of occupational exposure data	Exposure assessment (F=father M=mother)	Histology	No of case/control	Time frame	EMF exposures or surrogates	No of exposed cases	Risk estimates (95% CI)
Wilkins et al. (1991, Ohio, USA)	C-C (Cancer cluster)	Interview	Job groups (M, F)	Brain tumors	NA	Before diagnosis	Electronic components manufacturer	6	73.3 (26.5-157.5)
Johnson and Spitz (1989, Texas, USA)	C-C	Birth certificate	Job groups (F)	Central nervous system	499/998	At birth	Industries involving potential EMF	25	1.6 (0.96-2.8)
							Electronics manufacturing	7	3.6 (1.04-12.2)
Nasca et al. (1988, New York, USA)	C-C	Interview	Job groups (F, M)	Central nervous system	338/676	At Birth	Electricians, electronics workers, and power linemen (F)	15	1.7 (0.8-3.6)
Wilkins and Koutras (1988, Ohio, USA)	C-C	Birth certificate	Job groups (F)	Brain tumors	491/491	At birth	Structural work: Electrical assembling, installing, repairing	19	2.7 (1.2-6.1)
							Machinery industry: Electrical assembling, installing, repairing	16	3.6 (1.3-10.0)
							Bench occupations: assembly and repair of electrical equipment	4	1.0 (0.3-3.7)

Abbreviations: NA, not available; C-C, case-control; JEM, job exposure matrix; * number of discordant pairs; EMF, electromagnetic frequencies.

Table 2. Job categories applied to this study according to 1971 Canadian Classification and Dictionary of Occupations (CCDO).

Job categories	CCDO code
Managers and Administrators	1119-1179
Life scientists	2133
Engineers (industry and technology)	2145&2165
Computer Programmers	2183
Economists	2311
Social workers	2331-2339
Lawyers and related	2343 & 2349
Other social workers	2391 & 2399
Teachers and professors	2711-2799
Doctors and dentists	3111&3113
Nurses and therapists	3130-3139
Nurse and nurse assistant	3131,3134 & 3135
Other health workers	3151-3159
Artists	3313-3332
Writers	3351
Coaches, Trainers and Instructors	3710
Clerical workers	4111-4199
Secretaries and typists	4111&4113
Electronic Data-processing Equipment operators	4143
Telephone Operators	4175
sale workers	5130-5199
Food and Beverage Preparers and servers	6120-6125
Cooks and chefs	6121
Lodging workers	6130&6133
Personal service workers	6143-6147
Pressing workers	6165
Janitors, Char workers, and Cleaners	6191

Table 2. Continued

Job categories	CCDO code
Other service workers	6198
Farmers and related	7115-7199
Food and Beverage processors	8213-8228
Textile Winding and Reeling processors	8265
Other processors	8296
Electrical and electronic fabricators	8534
Textile, fur, and leather fabricators	8550-8569
Sewing Machine Operators	8563
Rubber and plastic fabricators	8573
Other fabricators	8595&8599
Construction workers	8711&8791
Materials Packaging and related	9317 & 9318
Typesetting and composing workers	9511
Pumping and pipeline equipment operators	9537
Sound and Video Recording and Reproduction Equipment Operators	9555
Photographic Processors	9591
Not elsewhere classified	9919

Table 3. Industry categories applied to this study according to 1980 Standard Industrial Classification (SIC)

Industry title	SIC code
Agricultural	01
Fishing and Trapping	03
Food and Beverage	10 & 11
Tobacco Products	12
Plastic Products	16
Leather and Allied Products	17
Textile and Clothing	18 & 24
Furniture and Fixture	26
Printing and Publishing	28
Transport Equipment	32
Electrical and Electronic Products	33
Chemical and Chemical Products	37
Other Manufacturing	39
Construction	40 & 42
Transportation	45
Communication	48
Other Utility	49
Wholesail and retail	52-69
Finance and Insurance	70-74
Real Estate Operation	75
Insurance and Real Estate Agent	76
Business Service	77
Government Service	81-83
Educational Service	85
Health and Social Service	86
Lab or research unspecified	87
Office unspecified	88
Food and Beverage Service	92
Amusement and Recreational Service	96
Personal and Household Service	97
Membership Organization	98
Other Service	99
No specific industry	00

Table4: Job exposure matrix of extremely low frequency magnetic field values based on exposure information in the Québec childhood brain tumors database.

Occupation code*	Industry code[$]	Mean	Min	Max	No
1119	81	0.174	0.174	0.174	1
1130	77	0.100	0.100	0.100	1
1135	70	0.231	0.231	0.231	2
1136	77	0.321	0.209	0.432	2
1141	64	0.210	0.210	0.210	1
1142	92	0.276	0.276	0.276	1
1149	77	0.010	0.010	0.010	1
1171	70	0.097	0.092	0.101	2
1171	77	0.103	0.080	0.172	4
1174	77	0.210	0.210	0.210	3
1174	81	0.210	0.210	0.210	1
1179	45	0.336	0.336	0.336	3
1179	98	0.080	0.080	0.080	1
2133	86	0.180	0.180	0.180	1
2145	77	0.374	0.374	0.374	1
2165	77	0.162	0.131	0.177	3
2183	77	0.202	0.202	0.202	2
2311	77	0.247	0.247	0.247	1
2331	86	0.131	0.131	0.131	2
2333	86	0.140	0.140	0.140	6
2339	86	0.104	0.104	0.104	1
2343	77	0.080	0.080	0.080	2
2391	86	0.254	0.254	0.254	1
2399	81	0.140	0.140	0.140	1
2399	86	0.146	0.080	0.212	2
2711	85	0.087	0.087	0.087	2
2731	85	0.063	0.060	0.075	6
2731	86	0.080	0.080	0.080	2
2733	85	0.078	0.014	0.126	9
2792	96	0.062	0.062	0.062	4
2795	86	0.062	0.062	0.062	2
2797	85	0.256	0.233	0.308	5
2799	85	0.063	0.063	0.063	2
3111	86	0.152	0.140	0.200	5
3113	86	0.309	0.309	0.309	1
3130	86	0.140	0.140	0.140	1
3131	86	0.164	0.090	0.217	23

Table4. Continued

Occupation code*	Industry code[$]	Mean	Min	Max	No
3135	86	0.140	0.140	0.140	2
3137	86	0.258	0.153	0.300	10
3139	81	0.103	0.103	0.103	2
3139	86	0.140	0.140	0.140	1
3151	60	0.217	0.155	0.246	7
3152	86	0.201	0.200	0.202	2
3156	86	0.213	0.180	0.282	4
3157	86	0.309	0.309	0.309	4
3159	60	0.264	0.262	0.266	6
3159	86	0.140	0.140	0.140	1
3313	17	0.113	0.113	0.113	1
3330	48	0.200	0.200	0.200	1
3332	96	0.065	0.030	0.100	2
3351	28	0.385	0.385	0.385	1
3351	77	0.236	0.236	0.236	1
3710	96	0.226	0.226	0.226	1
4111	1	0.278	0.278	0.278	1
4111	32	0.226	0.226	0.226	1
4111	42	0.289	0.289	0.289	1
4111	54	0.111	0.111	0.111	1
4111	64	0.186	0.084	0.332	4
4111	70	0.229	0.229	0.229	1
4111	74	0.269	0.269	0.269	1
4111	77	0.230	0.080	0.363	42
4111	81	0.231	0.220	0.244	5
4111	83	0.238	0.219	0.271	5
4111	85	0.224	0.083	0.301	3
4111	86	0.255	0.211	0.321	11
4111	96	0.083	0.083	0.083	1
4113	75	0.267	0.267	0.267	1
4113	77	0.277	0.273	0.283	3
4130	70	0.197	0.168	0.217	5
4131	64	0.234	0.234	0.234	1
4131	71	0.250	0.250	0.250	1
4131	77	0.236	0.207	0.291	13
4131	83	0.186	0.186	0.186	1
4133	60	0.280	0.280	0.280	2
4133	64	0.280	0.243	0.302	8
4133	65	0.280	0.280	0.280	1
4133	70	0.279	0.207	0.347	21

Table4. Continued

Occupation code*	Industry code[$]	Mean	Min	Max	No
4133	77	0.289	0.200	0.322	12
4135	70	0.130	0.123	0.136	2
4135	76	0.138	0.130	0.153	3
4139	77	0.153	0.153	0.153	1
4143	77	0.253	0.210	0.355	7
4153	77	0.113	0.113	0.113	1
4161	77	0.131	0.131	0.131	1
4161	85	0.143	0.100	0.225	6
4171	77	0.186	0.080	0.285	7
4173	77	0.430	0.083	0.757	4
4175	48	0.103	0.103	0.103	1
4192	76	0.107	0.107	0.107	1
4193	45	0.262	0.262	0.262	1
4193	77	0.281	0.229	0.334	2
4195	77	0.332	0.332	0.332	2
4197	39	0.115	0.115	0.115	1
4197	64	0.238	0.238	0.238	1
4197	88	0.240	0.080	0.302	25
4197	82	0.260	0.260	0.260	1
4199	61	0.231	0.200	0.262	2
4199	65	0.253	0.253	0.253	1
5130	61	0.231	0.231	0.231	1
5130	64	0.231	0.231	0.231	1
5131	45	0.306	0.306	0.306	1
5133	52	0.890	0.890	0.890	1
5133	53	0.139	0.139	0.139	2
5133	57	0.389	0.389	0.389	1
5135	54	0.233	0.233	0.233	1
5135	64	0.197	0.182	0.200	6
5135	65	0.207	0.200	0.214	4
5137	60	0.100	0.100	0.100	1
5137	64	0.216	0.216	0.216	1
5141	69	0.190	0.190	0.190	1
5170	72	0.315	0.315	0.315	1
5170	76	0.247	0.247	0.247	1
5171	48	0.230	0.230	0.230	1
5171	76	0.256	0.256	0.256	1
5191	59	0.146	0.146	0.146	1
5199	96	0.200	0.200	0.200	1

Table4. Continued

Occupation code*	Industry code$	Mean	Min	Max	No
6120	92	0.201	0.201	0.201	2
6121	92	0.291	0.152	0.450	15
6123	92	0.207	0.207	0.207	1
6125	92	0.220	0.150	0.320	22
6130	92	0.068	0.068	0.068	1
6133	97	0.140	0.140	0.140	1
6143	97	0.391	0.119	0.506	5
6143	99	3.000	3.000	3.000	1
6144	99	0.010	0.010	0.010	3
6147	86	0.226	0.226	0.226	1
6147	97	0.226	0.209	0.259	6
6165	24	0.985	0.985	0.985	2
6191	97	0.120	0.120	0.120	2
6191	99	0.120	0.030	0.218	7
6198	92	0.138	0.138	0.138	4
6198	97	0.138	0.138	0.138	1
7115	1	0.105	0.105	0.105	1
7183	1	0.101	0.101	0.101	1
7191	1	0.127	0.112	0.133	3
7195	1	0.050	0.050	0.050	1
7195	96	0.010	0.010	0.010	1
7198	1	0.076	0.076	0.076	1
7199	1	0.082	0.082	0.082	1
8213	10	0.404	0.404	0.404	3
8215	60	0.629	0.629	0.629	1
8215	92	0.629	0.629	0.629	1
8217	3	0.103	0.103	0.103	1
8223	10	0.100	0.100	0.100	1
8228	10	0.181	0.100	0.344	3
8265	18	0.469	0.469	0.469	1
8296	12	0.100	0.100	0.100	1
8534	33	0.587	0.587	0.587	1
8550	24	0.250	0.250	0.250	1
8551	26	0.630	0.630	0.630	1
8553	24	0.288	0.288	0.288	1
8553	48	0.193	0.193	0.193	1
8562	26	0.012	0.012	0.012	1
8563	17	0.776	0.776	0.776	2
8563	24	0.776	0.284	0.925	23

Table4. Continued

Occupation code*	Industry code[$]	Mean	Min	Max	No
8566	24	0.250	0.250	0.250	1
8568	17	0.250	0.250	0.250	1
8568	24	0.250	0.250	0.250	1
8569	24	0.250	0.250	0.250	4
8573	16	0.100	0.100	0.100	1
8595	37	0.100	0.100	0.100	1
8595	39	0.344	0.344	0.344	1
8599	16	1.763	1.763	1.763	1
8599	17	0.250	0.250	0.250	1
8599	39	1.016	1.016	1.016	1
8711	40	0.060	0.060	0.060	1
8791	49	0.198	0.198	0.198	1
9317	10	0.100	0.100	0.100	1
9317	11	0.231	0.100	0.363	2
9317	18	0.450	0.450	0.450	1
9317	24	0.450	0.450	0.450	2
9317	37	0.100	0.100	0.100	1
9318	10	0.100	0.100	0.100	1
9318	16	0.175	0.175	0.175	1
9318	24	0.213	0.175	0.250	2
9318	39	0.175	0.175	0.175	1
9511	28	0.333	0.333	0.333	1
9537	49	0.235	0.229	0.241	2
9555	96	0.131	0.131	0.131	1
9591	99	0.178	0.126	0.229	2
9919	87	0.158	0.080	0.320	5

* 1971 Canadian Classification and Dictionary of Occupations (Manpower and Immigration, 1971);

[$] 1980 Standard Industrial Classification (Statistics Canada, 1980)

Table 5. Socio-demographic characteristics of cases with childhood brain tumors and controls by study center.

	Québec		Ontario		Pooled	
	Cases (n=272)	Controls (n=272)	Cases (n=276)	Controls (n=488)	Cases (n=548)	Controls (n=760)
Child age (yrs) [a]						
<2	22 (8.1)	21 (7.7)	42 (15.2)	17 (3.5)	64 (11.7)	38 (5.0)
2-4	99 (36.4)	100 (36.8)	57 (20.7)	65 (13.3)	156 (28.5)	165(21.7)
5-9	121 (44.5)	121 (44.5)	93 (33.7)	188 (38.5)	214 (39.1)	309 (40.7)
≥10	30 (11.0)	30 (11.0)	84 (30.4)	218 (44.7)	114 (20.8)	248 (32.6)
Child's sex						
Male	160 (58.8)	160 (58.8)	155 (56.2)	247 (50.6)	315 (57.5)	407 (53.6)
Female	112 (41.2)	112 (41.2)	121 (43.8)	241 (49.4)	233 (42.5)	353 (46.4)
Maternal age at child's birth (yrs)[b]						
<35	253 (93.4)	257 (94.5)	241 (87.3)	414 (84.8)	494 (90.3)	671 (88.3)
≥35	18 (6.6)	15 (5.5)	35 (12.7)	74 (15.2)	53 (9.7)	89 (11.7)
Race [c]						
White	254 (93.4)	263 (96.7)	241 (88.6)	448 (92.0)	495 (91.0)	711 (93.7)
Non-white	18 (6.6)	9 (3.3)	31 (11.4)	39 (8.0)	49 (9.0)	48 (6.3)
Mother's level of education [d]						
None or primary school	12 (4.4)	6 (2.2)	3 (1.1)	1 (0.2)	15 (2.8)	7 (0.9)
Secondary school	133 (48.9)	148 (54.6)	68 (24.9)	118 (24.2)	201 (36.7)	266 (35.1)
College or university	127 (46.7)	117 (43.2)	202 (74.0)	369 (75.6)	329 (60.5)	486 (64.0)
Employment						
2 years before pregnancy						
No	57 (21.4)	59 (22.1)	55 (20.9)	99 (20.4)	112 (21.1)	158 (21.0)
Yes	210 (78.6)	208 (77.9)	208 (79.1)	386 (79.6)	418 (78.9)	594 (79.0)
During pregnancy						
No	96 (36)	90 (33.7)	73 (27.8)	133 (27.4)	169 (31.9)	223 (29.6)
Yes	171 (64.0)	177 (66.3)	190 (72.2)	352 (72.6)	361 (68.1)	529 (70.4)
Type of tumor						
Astroglial tumors	120 (44.1)		119 (43.1)		239 (43.6)	
PNET	80 (29.4)		65 (23.6)		145 (26.5)	
Other gliomas[e]	42 (15.4)		39 (14.1)		81 (14.8)	
Other tumors	30 (11.0)		53 (19.2)		83 (15.1)	

[a] Age at diagnosis for cases, age at interview for controls; [b] Mother's date of birth missing for one case in Québec study; [c] Race missing for 4 cases and 1 controls in Ontario study; [d] Mother's education missing for one control in Québec study and 3 cases in Ontario study; [e] Other gliomas include: ependymomas, oligodendrogliomas, and other unspecified gliomas; PNET, primitive neuroectodermal tumors.

Table 6. Adjusted Odds ratios (OR)[a] of childhood brain tumors for selected maternal occupational and industries during the 3-year period before birth according to main histological subgroups.

Occupations/Industries	Controls (n=760)	All tumors (n=548)		Astroglial tumors (n=239)		PNET (n=145)		Other gliomas[b] (n=81)	
	No	No	OR (95% CI)	No	OR (95% CI)	No	OR (95% CI)	No	OR (95% CI)
Occupations									
Secretaries & typists	72	54	1.1 (0.7-1.6)	25	1.1 (0.7-1.9)	13	1.0 (0.5-1.8)	8	1.1 (0.5-2.4)
Sewing machine operators	8	16	2.3 (1.0-5.4)	7	2.3 (0.8-6.3)	3	1.5 (0.4-5.8)	3	2.9 (0.8-11.7)
Food and beverage preparers	35	32	1.3 (0.8-2.2)	9	0.8 (0.4-1.6)	10	1.5 (0.7-3.2)	10	2.9 (1.4-6.3)
Food and beverage processors	8	8	1.4 (0.5-3.9)	3	1.2 (0.3-4.6)	3	2.2 (0.5-8.6)	1	1.2 (0.1-9.8)
Textile, fur, and leather fabricators	19	19	1.1 (0.6-2.2)	8	1.0 (0.4-2.4)	5	1.1 (0.4-3.0)	3	1.1 (0.3-3.8)
Material packagers	6	11	2.2 (0.8-6.2)	6	2.8 (0.9-9.2)	3	1.8 (0.4-7.8)	1	1.5 (0.2-12.8)
Nurse and assistant	37	25	1.1 (0.6-1.7)	11	1.1 (0.5-2.2)	6	0.9 (0.4-2.2)	7	2.1 (1.0-5.0)
Clerk	240	166	1.0 (0.8-1.3)	82	1.2 (0.9-1.6)	34	0.7 (0.4-1.0)	23	0.9 (0.5-1.4)
Sale workers	36	29	1.1 (0.7-1.9)	11	0.9 (0.5-1.8)	8	1.3 (0.6-2.8)	3	0.7 (0.2-2.2)
Teachers & professors	45	33	1.1 (0.7-1.7)	14	1.1 (0.5-2.0)	11	1.3 (0.6-2.6)	5	1.2 (0.5-3.2)
Lawyer and related	7	6	1.5 (0.5-4.6)	2	1.1 (0.2-5.5)	2	1.8 (0.4-9.3)	1	1.9 (0.3-15.6)
Managers and administrators	76	40	0.8 (0.5-1.2)	16	0.8 (0.5-5.5)	12	1.0 (0.5-2.0)	9	1.4 (0.6-3.0)
Industries									
Broadcasting and entertainment	32	18	1.0 (0.5-1.7)	10	1.2 (0.6-2.4)	4	0.7 (0.2-2.2)	1	0.3 (0.1-2.5)
Food and beverage industries	10	12	1.6 (0.7-3.8)	5	1.5 (0.5-4.6)	4	2.4 (0.7-8.3)	1	0.9 (0.1-7.4)
Textile and clothing	15	22	1.6 (0.8-3.1)	10	1.5 (0.7-3.5)	6	1.5 (0.5-4.0)	3	1.3 (0.3-4.6)
Wholesale and retail	63	54	1.3 (0.9-1.9)	26	1.4 (0.9-2.4)	13	1.2 (0.6-2.2)	11	1.7 (0.4-3.4)
Finance and insurance	51	31	0.9 (0.6-1.5)	19	1.4 (1.8-2.4)	5	0.5 (0.2-1.3)	6	1.1 (0.5-2.8)
Health service	107	89	1.3 (1.0-1.8)	39	1.3 (0.9-2.0)	23	1.3 (0.8-2.2)	15	1.5 (0.8-2.7)
Office unspecified	11	12	1.2 (0.5-2.8)	7	1.6 (0.6-4.2)	4	1.3 (0.4-4.1)	1	0.7 (0.1-5.4)
Food and beverage service	36	37	1.4 (0.8-2.2)	11	0.9 (0.4-1.8)	10	1.3 (0.6-2.8)	10	2.6 (1.2-5.5)
Business service	93	67	0.9 (0.6-2.2)	28	0.8 (0.5-1.3)	17	0.8 (0.4-1.4)	12	1.1 (0.6-2.1)
Educational service	62	37	0.9 (0.6-1.4)	18	1.0 (0.6-1.8)	10	1.0 (0.5-2.1)	4	1.5 (0.5-4.7)
Transportation	9	6	1.0 (0.4-2.9)	5	2.0 (0.7-6.2)	0	-	0	-
Government service	29	17	1.0 (0.5-2.8)	6	0.8 (0.3-2.0)	3	0.6 (0.2-2.2)	3	1.2 (0.4-4.2)

[a] ORs were calculated adjusted for child's age, sex, and study center; [b] Other gliomas include: ependymomas, oligodendrogliomas, and other unspecified gliomas; PNET, primitive neuroectodermal tumors.

Table 7. Median levels of maternal occupational exposure to extremely low frequency magnetic fields for each center.

	Québec		Ontario		Pooled	
	All women	Only working women	All women	Only working women	All women	Only working women
Before conception						
Cumulative exposure (μT-days)						
[Median (min, max)]						
cases	106.5 (0, 1095.0)	145.1 (2.4, 1095.0)	102.2 (0, 1237.7)	138.7 (0.2, 1237.7)	102.2 (0, 1237.7)	141.9 (0.2, 1237.7)
controls	102.2 (0, 1286.6)	146.0 (2.2, 1286.6)	100.0 (0, 1237.7)	131.4 (4.8, 1237.7)	102.2 (0, 1286.6)	139.0 (2.2, 1286.6)
Average exposure (μT)						
[Median (min, max)]						
cases	0.2 (0, 3.0)	0.2 (0, 3.0)	0.2 (0, 1.7)	0.2 (0, 1.7)	0.2 (0, 3.0)	0.2 (0, 3.0)
controls	0.2 (0, 1.8)	0.2 (0, 1.8)	0.2 (0, 1.7)	0.2 (0, 1.7)	0.2 (0, 1.8)	0.2 (0, 1.8)
During pregnancy						
Cumulative exposure (μT-days)						
[Median (min, max)]						
cases	21.3 (0, 247.9)	49 (0.2, 247.9)	36.2 (0, 457.8)	54.3 (1.1, 457.8)	27.3 (0, 457.8)	50.3 (0.2, 457.8)
controls	24.2 (0, 266.4)	50.8 (0.3, 266.4)	34.2 (0, 457.8)	60.1 (0.5, 457.8)	29.3 (0, 457.8)	50.2 (0.3, 457.8)
Average exposure (μT)						
[Median (min, max)]						
cases	0.1 (0, 0.9)	0.2 (0, 0.9)	0.1 (0, 1.7)	0.2 (0, 1.7)	0.1 (0, 1.7)	0.2 (0, 1.7)
controls	0.1 (0, 1.8)	0.2 (0, 1.8)	0.1 (0.1, 1.7)	0.2 (0, 1.7)	0.1 (0, 1.8)	0.2 (0, 1.8)

Table 8. Adjusted Odds ratios (ORs) for childhood brain tumor associated with maternal occupational exposure to extremely low frequency magnetic fields for each study center and for both centers together.

	Québec			Ontario			Pooled
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]	OR (95% CI)[b]
	2 year period before pregnancy						
Cumulative exposure ≥90th percentile (≥214.8 μT-days)	40	37	1.1 (0.7-1.8)	24	29	1.5 (0.9-2.9)	1.3 (0.9-2.0)
Average exposure≥90th percentie (≥0.30 μT)	46	40	1.2 (0.7-1.9)	23	28	1.5 (0.8-2.7)	1.4 (1.0-2.1)
Maximum exposure (≥0.4 μT)	19	14	1.4 (0.7-2.8)	11	23	0.8 (0.4-1.8)	1.1 (0.7-1.8)
	During pregnancy						
Cumulative exposure ≥90th percentile (≥73.6 μT-days)	31	30	1.1 (0.6-1.8)	32	36	1.7 (0.9-2.8)	1.4 (0.9-2.0)
Average exposure ≥90th percentile (≥0.28 μT)	43	38	1.3 (0.7-1.9)	34	36	1.8 (1.0-2.9)	1.5 (1.1-2.2)
Maximum exposure (≥0.4μT)	14	12	1.2 (0.5-2.6)	12	18	1.2 (0.5-2.5)	1.2 (0.7-2.1)

[a] ORs were calculated adjusted for child's age and sex; [b] ORs were calculated adjusted for child's age, sex, and study center.

Table 9. Adjusted Odds ratios (ORs)[b] for childhood brain tumors for maternal occupational exposure to extremely low frequency magnetic fields according to main histological subgroups.

	Controls (n=760)	Astroglial tumors (n=239)		PNET (n=145)		Other gliomas[b] (n=81)	
	No	No	OR (95% CI)	No	OR (95% CI)	No	OR (95% CI)
	2 year period before pregnancy						
Cumulative exposure ≥90th percentile (≥214.8 μT-days)	66	28	1.3 (0.8-2.1)	17	1.2 (0.7-2.2)	11	1.6 (0.8-3.2)
Average exposure≥90th percentile (≥0.30 μT)	68	34	1.5 (1.0-2.4)	14	0.9 (0.5-1.6)	11	1.5 (0.8-2.9)
Maximum exposure (≥0.4 μT)	37	14	1.3 (0.6-2.3)	7	1.0 (0.4-2.3)	3	0.8 (0.2-2.7)
	During pregnancy						
Cumulative exposure ≥90th percentile (≥73.6 μT-days)	66	29	1.4 (0.9-2.3)	15	1.2 (0.6-2.2)	11	1.7 (0.8-3.3)
Average exposure≥90th percentile (≥0.28 μT)	74	38	1.6 (1.1-2.5)	17	1.1 (0.6-2.0)	12	1.6 (0.8-3.1)
Maximum exposure (≥0.4 μT)	30	15	1.6 (0.8-3.1)	5	0.9 (0.3-2.3)	1	0.3 (0.1-2.4)

[a] ORs were calculated adjusted for child's age and sex, and study center; [b] Other gliomas include: ependymomas, oligodendrogliomas, and other unspecified gliomas; PNET, primitive neuroectodermal tumors.

Appendix

Appendix A: Certificates of Human Ethics Approval