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Childhood Brain Tumor Epidemiology: A Brain Tumor Epidemiology Consortium Review

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ABSTRACT

Childhood brain tumors are the most common pediatric solid tumor and include several histological subtypes. Although progress has been made in improving survival rates for some subtypes, understanding of risk factors for childhood brain tumors remains limited to a few genetic syndromes and ionizing radiation to the head and neck. In this report, we review descriptive and analytical epidemiology childhood brain tumor studies from the past decade and highlight priority areas for future epidemiology investigations and methodological work that is needed to advance our understanding of childhood brain tumor causes. Specifically, we summarize the results of a review of studies published since 2004 that have analyzed incidence and survival in different international regions and that have examined potential genetic, immune system, developmental and birth characteristics, and environmental risk factors.

INTRODUCTION

Brain and central nervous system (CNS) tumors are the most common solid tumor and the second leading cause of cancer death in individuals 0-19 years of age in the U.S. and Canada.(1, 2) The objective of this review is to summarize the descriptive and analytic epidemiology of childhood brain tumors (CBT) with a specific focus on studies from the past decade (since 2004) and to delineate future directions in CBT epidemiology research that are needed for progress in the field. We have included studies published primarily since 2004 pertaining to CBT descriptive and analytical epidemiology. We note that there is not a precise definition of CBTs and the tumor types included vary between studies, which can make them difficult to compare.

DESCRIPTIVE EPIDEMIOLOGY

There are >100 different histological subtypes of CNS tumors with the incidence of each varying by age and histologic subtype. Childhood CNS tumor incidence varies by country from

1.12-5.14 cases per 100,000 persons with the highest incidence in the U.S. (**Table 1**). CBTs are more common in males, though this varies by histologic type. In the U.S., Whites and Asians-Pacific Islanders have a higher CBT incidence than Blacks and American Indians/Alaska Natives, while Non-Hispanics have higher incidence than Hispanics. Subtype incidence and survival rates are reviewed below and in **Tables 1**-**2**.

Case ascertainment methodology, completeness, and standard populations used for age-adjustment of rates vary between cancer registries, making it challenging to compare statistics across registries. In addition, registries vary on when they began to include the reporting of benign brain tumors. For example, in the US registration of non-malignant tumors was not required by law, and therefore, limited prior to 2004. Final confirmation of CNS tumors can also vary by histological type and by region; even in the US, some tumors are not microscopically confirmed but are confirmed radiographically. However, across registries, the standard approach is to include both brain tumors and other CNS tumors in all statistics. Therefore all comparison statistics must be interpreted with these caveats in mind.

Glioma

Gliomas that arise from glial cells are the most common CBT.(3) Incidence and survival vary significantly depending on location and histologic type (reviewed below and in **Tables 1**-**2**).

Pilocytic astrocytoma

Pilocytic astrocytoma (World Health Organization [WHO] grade 1) is one of the most common CBTs, representing ~17% of all CNS tumors in 0-14 year olds.(4) Incidence rates in population based analyses range from 0.74-0.9 cases per 100,000 persons (**Table1**). These tumors are usually non-malignant, although some progress to higher grade tumors.(5, 6) Pilocytic astrocytomas have a high overall 10-year survival rate at >96%.(4)

Brain stem glioma

Brain stem tumors represent ~10% of all pediatric CNS tumors with the most common being diffuse intrinsic pontine glioma (DIPG).(7) DIPG prognosis is dismal with >90% of cases dying within 2 years of diagnosis.(8) These tumors are rarely biopsied, and as a result, their true incidence from cancer registry datasets is difficult to assess. (8)

All other glioma

Other glioma types are less common in children. Diffuse astrocytomas (WHO grade II) account for ~5% of all tumors in children aged 0-14 years, with a U.S. incidence rate of 0.28/100,000 (**Table 1**).(4) High grade astrocytomas (WHO grade III and IV) are less common, with incidence rates of 0.08 for anaplastic astrocytoma, and 0.14 for glioblastoma.(4)

Embryonal tumors

Embryonal tumors are theorized to develop in embryonic cells remaining in the CNS after birth. There are three major embryonal tumor types with distinct differences in age at diagnosis and survival: primitive neuroectodermal tumor (PNET), medulloblastoma (MB), and atypical teratoid/rhabdoid tumor (ATRT) (9) . Overall embryonal tumor incidence ranged from 0.28-0.80 cases/100,000 children aged 0-14 years (**Table 1**) with a 10-year relative survival rate of 55.5% (**Table 2**).(4)

Primitive neuroectodermal tumor (PNET)

Average annual age-adjusted incidence rates for PNET ranged from 0.08-0.21 cases/100,000 children. PNET survival improves with increasing age with U.S. population data from 2001-2006 showing 1-year survival rates of 31%, 88%, and 95% for children aged 0-1, 1-9, and 10-19 years, respectively.(10) Based on the 1993 WHO criteria, histologically similar tumors that are

classified as PNETs and MBs when they occur supratentorially and infratentorially, respectively.(11) Prior to this, tumors were considered PNETs regardless of tumor location.

Medulloblastoma (MB)

MBs are the most common embryonal tumors with average annual age-adjusted incidence rates ranging from 0.20-0.58 cases/100,000 persons. An analysis of U.S. population data from 2001-2006 reported 1-year survival rates of 52%, 90%, and 92% for children aged 0-1, 1-9, and 10-19 years, respectively.(10) Molecular analysis has identified four distinct MB subtypes that correlate strongly with survival.(12) No population-based studies of subtype specific survival have been reported, but in an international meta-analysis children with WNT tumors had a 95% 10-year overall survival. Children with SHH, group 3, and large cell anaplastic (LCA) tumors had 51%, 50%, and 32% 10-year survival, respectively.(13)

Atypical Teratoid/Rhabdoid Tumor (ATRT)

ATRT is a rare embryonal tumor that most commonly occurs in children <3 years old. Average annual age-adjusted incidence rates range from 0.07-0.14/100,000 persons.(14, 15) Prognosis is generally poor, though survival increases with age.(14-18) Overall, median survival is usually between 6-18 months.(16, 19-21) Most analyses show that ATRTs are more common in males (15, 16, 22) and among whites.(15, 23) A a systematic diagnostic approach for ATRT was not common until 2005; prior to that these tumors were frequently misclassified, mostly as MBs or PNET.(14)

ANALYTIC EPIDEMIOLOGY

GENETIC FACTORS

Cancer Syndromes

Established familial cancer syndromes (*gene*) that increase brain tumor susceptibility include: Neurofibromatosis type 1 (*NF1*), Neurofibromatosis Type 2 (*NF2*), tuberous sclerosis (*TSC1* or *TSC2* genes), Li-Fraumeni (*TP53* or *CHEK2*), Nevoid Basal Cell Carcinoma (*PTCH*), Turcot (*APC*), Cowden (*PTEN*), hereditary retinoblastoma (*RB1*), and Rubinstein-Taybi (*CREBBP*).(24-27)

Family history

Findings from studies of CBT risk among family members vary substantially. A 2008 review (28) including publications as early as 1959 reported that although most studies observed positive associations specific to brain tumors, there was borderline statistical evidence for an increased risk. Siblings of childhood CNS cancer cases consistently showed increased risks of developing a childhood CNS tumor, with a higher risk seen if both children had MB or PNET diagnoses. Risk was also reported to be higher among relatives if the index child was diagnosed at $\leq$4 years old. Children also had an increased risk of developing a nervous system tumor if a parent also had this tumor type. The SEARCH international brain tumor case-control study, which included 1200 CBT cases and 2,218 controls from Australia, Canada, France, Israel, Italy, Spain, and the U.S. reported no significant associations between CBTs and brain tumor history in close relatives were observed with odds ratios (ORs) of 0.8 (95% CI 0.5-1.3), 1.3 (95% CI 0.7-2.3), and 1.1 (95% CI 0.6-1.9) for astroglial (n=620), PNETs (n=244), and other CBT (n=324) subtypes, respectively.(29)

Parental age

Parental age at birth may serve as a marker for inherited somatic changes in aging parental germlines. Hemminki *et al*.(30) previously reported that offspring of older fathers (>40 years at the child's birth) were at increased CBT risk with no maternal age effect in a cohort study that included 1617 CBT cases diagnosed at ages 0-14 years. A more recent Swedish

analysis (31) of CNS tumors diagnosed in 0-4 year olds (n=977) indicated higher risks associated with paternal age >40 years after maternal age adjustment (incidence rate ratio (IRR)=1.69; 95% CI 1.21–2.35), particularly for astrocytoma. In contrast, Johnson *et al*. reported an increased childhood CNS tumor risk in association with maternal age after paternal age adjustment in a U.S. multistate record linkage study including >3500 cases ($OR_{per\ 5\ year\ age\ increase}$=1.08; 95% CI 1.03-1.14). Only astrocytomas and ependymomas were associated with an increased risk. The authors also reported stronger IRRs for children diagnosed at younger ages.(32)

Maternal genetic effects

Recent research has addressed the role of maternal genetic variation in genes that may influence the *in utero* environment. In spite of the potential importance of this mechanism in the etiology of CBTs, few assessments of maternal genetic effects have been performed. To our knowledge, there is only one small report that used a case parent triad study design (33) of the role maternal variation in xenobiotic detoxification genes and the risk of childhood MB (34) where it was reported that the maternal *EPHX1* rs1051740 genotype was associated with MB risk (RR=3.26; 95% CI 1.12-9.53). Larger studies are needed to explore the role of maternal genetic effects in CBT susceptibility.

IMMUNE SYSTEM

Allergic conditions (allergies, asthma, and eczema)

Studies consistently suggest inverse associations between adult gliomas and allergic conditions.(35) In children, a 2008 U.K. study including 575 cases diagnosed <15 years of age and 6,292 controls indicated that maternally reported asthma decreased CNS tumor risk (OR=0.75; 95% CI 0.58–0.97), particularly for MB/PNETs (OR=0.43; 95% CI 0.23-81).

However, this result was not confirmed in a participant subset for whom medical records were available (OR=1.20; 95% CI 0.74-1.94), which could be due to the diagnosis not being present or not being recorded.(36) CNS tumors were not associated with eczema (OR=0.94; 95% CI 0.74–1.18), but there was a significant inverse association for children with both asthma and eczema (OR=0.48; 95% CI 0.28–0.81).(37) A study of 272 matched case-control pairs reported an inverse association between CBTs diagnosed between 0-15 years old and asthma (OR=0.55; 95% CI 0.33–0.93), that was stronger for ependymoma (OR=0.15; 95% CI 0.18–1.21). No association with eczema was found. Overall, CNS tumor risk was increased with use of asthma controllers (e.g. inhaled corticosteroids) (OR=2.55; 95% CI 0.79-8.20) or asthma relievers (e.g. beta agonists) (OR=1.62; 95% CI 0.57-4.63).(38) Finally, CEFALO, a study conducted in Denmark, Norway, Sweden, and Switzerland that included 352 CBT cases diagnosed from 7-19 years and 646 controls, found no association with any atopic condition (asthma, wheezing, eczema, allergic rhinitis) (OR=1.03; 95% CI 0.70-1.34) and some evidence for reverse causality; an inverse association between CBTs and having a current (OR=0.76; 95% CI 0.53-1.11) but not past (OR=1.22; 95% CI 0.86-1.74) atopic condition was found.(39) Altogether, allergic conditions may protective factor for CBT development but further research is needed.

Markers of infectious exposures

Studies prior to 2004 of markers of infection and CBT risk have yielded mixed results (40-42). More recently, higher risks of CBTs among first-born children vs. those with higher birth order and lower risks among those who attended daycare as an infant have been reported. Altieri *et al*. compared the incidence of brain tumors in the Swedish Cancer Registry based on number of siblings, number of older siblings, and number of younger siblings.(43) When compared to cases diagnosed <15 years old with no siblings, the relative risk (RR) for cases with ≥3 younger siblings was increased for astrocytoma (RR=1.34), MB (RR=2.30),

ependymoma (RR=2.61), and meningioma (RR=3.71). Shaw *et al*. reported that CBT risk was elevated for having siblings (OR=1.4; 95% CI 0.9–2.3) and being at least second born (OR=1.7; 95% CI 1.2–2.4).(44)

Several studies suggest infectious exposures during older childhood increase brain tumor risk, while earlier infections reduce brain tumor risk. Harding *et al*. reported that children who had no social contact with other infants in the first year of life displayed an increased CNS tumor risk vs. those who had such early exposures (OR 1.37; 95% CI 1.08-1.75)(45), particularly among MB cases (OR 1.78; 95% CI 1.12-2.83). In addition, children who attended informal (OR=0.86; 95% CI 0.68-1.09) or formal (OR=0.93; 95% CI 0.68-1.26) day care showed slightly reduced risks vs. those reporting social contact only. Shaw *et al*. reported that CBT risk was reduced for subjects who attended daycare for >1 year or were breastfed (44), while Harding *et al*. found no association between breastfeeding and CBTs (OR=1.01; 95% CI 0.85-1.21).(46) Most recently, Andersen *et al*. reported that glioma (OR=2.93; 95% CI 1.57–5.50) and embryonal tumor (OR=4.21; 95% CI 1.24–14.30) cases had more frequent sick days with infections in the first 6 years of life vs. controls.(47) However, the timing of infections in relation to the first year of life vs. later in childhood was not evaluated. One common observation from these studies is that level of risk often varies by age at diagnosis and tumor type.

DEVELOPMENTAL AND BIRTH CHARACTERISTICS

Congenital Anomalies

Congenital anomalies (CA) and birth characteristics have been examined as putative risk factors for pediatric CNS tumors.(48-50) Among large studies, 45,200 children with CAs were identified in the Canadian Congenital Anomalies Surveillance System (CCASS) and matched to 45,200 children without CAs identified through the Ontario Birth Certificate File. The Ontario Cancer Registry was then used to identify 212 newly diagnosed cancers in the matched

cohorts. The authors observed a 2.5 fold increased CNS cancer risk in association with CAs that was stronger for children <1 year old (5.5 fold greater risk). Those with nervous system anomalies had an approximate 6-fold increased rate of primary CNS tumors. (51)

Using two population-based national birth registries in Sweden and Norway, Bjorge *et al*. linked birth and cancer registry data to examine risk of multiple pediatric cancer types in association with birth defects.(52) Specifically, children with nervous system malformations were at elevated risk of CNS cancers in both countries, particularly Norway.

Fisher *et al.* (53) linked data from the California Cancer Registry (CCR) to the Birth Defects Monitoring System for the period 1988-2004 among children aged 0-14 years. There were 4,869 children identified with cancer, among who 222 had a major birth defect. The authors reported a 1.87 (95% CI 0.6-5.79) and 1.80 (95% CI 1.28-2.53) fold elevated risks of CNS tumors among children with and without non-chromosomal and chromosomal anomalies, respectively.

A second study linking the CCR to California birth certificates examined birth anomalies and CNS tumor risk among children aged 0-14 years old between 1988-2006.(54) In this study, 4,560 newly diagnosed CNS tumors were identified of which 3,733 cases (82%) could be linked to the birth registry. Cases were then individually matched to four controls (n=14,932). MBs, and PNETs were more elevated in children with birth defects, with age-stratified analyses revealing stronger risks for younger children (OR=1.7; 95% CI 1.12-2.57 and OR=2.9; 95% CI 1.68-5.05 for children <2 and <1 year(s) old, respectively). This study was limited by the inability to capture birth defect information after hospital discharge.

Birth Characteristics

In one of the largest studies to date, Bjorge *et al*.(55) conducted a nested case-control study to examine fetal growth in relation to cancer development in Nordic children born between 1967-2010 using population-based birth registries. Each case (n=17,698) was matched to 10

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controls (n=172,422). Both higher birth weight ($RR_{\geq 4500\ g\ vs.\ 3000\text{-}3499\ g}$= 1.3; 95% CI 1.1-1.3) and increasing head circumference ($RR_{39\text{-}45cm\ vs.\ 33\text{-}36\ cm}$=1.7; 95% CI 1.2-2.3; p-trend <0.001) were associated with childhood CNS cancer risk. In a similar but smaller study including the same four Nordic nations, Schmidt *et al*. conducted a nested case-control study to examine the impact of fetal growth (including birth weight) on CNS tumor risk among children aged 0-14 years who were diagnosed with a CNS tumor between 1985 and 2006. This study matched 3,443 CNS cases identified from national cancer registries to 16,169 birth registry controls and found a significant gestational age adjusted association between birth weight >4500 grams and risk of all CNS (RR=1.27; 95% CI 1.03-1.55), and embryonal (RR=1.8; 95% CI 1.2-2.8) tumors but not other histological subtypes.

Milne *et al*. examined the relationship between fetal growth measured as proportion of optimal birth weight or length and CNS tumor development diagnosed between 1980-2004 in children aged 0-14 years.(56) Among >600,000 live births, 183 pediatric CNS tumors were identified. There were no statistically significant associations between fetal growth factors and CNS tumor development.

Using CCR data to examine birth characteristics and CNS tumor risk in children aged 0-14 years old between 1988-2006, MacLean *et al*. matched each child with a CNS tumor (n=3733) to four controls identified through the California birth certificate database, resulting in 14,932 controls.(57) There was an increased CNS cancer risk in the highest weight category (>4000 grams) among high grade gliomas, whereas among low-grade gliomas, those in the lowest weight category (<2500 grams) appeared to be protected against CNS tumors. This study indicates that separation of CNS subtype is warranted in studies of birth characteristics and CNS tumor risk.

Finally, in a 2008 meta-analysis, eight studies were identified that examined CBT risk in association with birth weight. Data from over 1.7 million children/young adults (0-18 years old) were analyzed, with 4162 primary diagnoses of astrocytoma, MB, or ependymomas combined.

Most cases were identified through cancer registries and the predominant study design was case-control. The authors found that high birth weight (>4,000 grams) was predictive of both astrocytoma (OR=1.38; 95% CI 1.07-1.79) and MB (OR=1.27; 95% CI 1.02-1.60) but not ependymomas, which was only examined in few studies.(58)

ENVIRONMENTAL EXPOSURES

Radiation exposure

High dose radiation to the head and neck for treatment of cancer or other conditions is an established CBT risk factor.(59) Radiotherapy for acute lymphoblastic leukemia is associated with a particularly high risk with several studies published in the 1990s (reviewed in (60)) showing increased brain tumor risks (gliomas, PNETs) in children who received prophylactic CNS irradiation (usually a cumulative dose of ~25 Gy). The latency between radiotherapy and subsequent brain tumor development has been estimated at 7-9 years with a higher risk for younger children.(60) It has also been broadly accepted for several decades that *in utero* diagnostic radiation exposure is associated with a small to moderate dose-dependent increase in childhood cancer risk, including brain tumors.(61) Recent studies examining ionizing and non-ionizing radiation exposure are reviewed briefly below with study details provided in **Tables 3** and **4**, respectively.

Ionizing Radiation. The Childhood Cancer Survivor Study reported that radiation therapy for a first primary cancer (most were leukemia) was associated with a significant 7.1 fold increased risk of a subsequent CNS tumor.(62)

A Danish study examined CBT risk associated with neonatal diagnostic X-ray exposure (vs. no exposure) and observed a 2-fold positive non-significant association.(63) A Swedish study of individuals born between 1975-1984 examined the association between medical record abstracted prenatal X-ray abdominal exposures and CBTs and found no increased risk overall

but an almost 2-fold increased risk for PNETs.(64) A U.S. study of MB/PNETs examined risks associated with maternally reported post-natal diagnostic X-rays and reported no significant associations for head, dental, or any X-ray exposure vs. no exposure.(65) A U.K. study reported associations between cancers and medical-record abstracted prenatal diagnostic radiation exposure. Based on 25 and 41 exposed CBT cases and controls, respectively, no significant association for prenatal or early infancy radiation exposure was observed.(66)

Two studies examined childhood/adolescence CT scans and subsequent brain tumor development. A U.K study employing a retrospective cohort study design that included 176,587 CT scan exposed individuals reported increased risks of subsequent brain tumor development for the exposed group.(67) An Australian study, that included ~11 million individuals, also reported significant positive associations between CT scan exposure and brain tumor development with risk generally decreasing with increasing age at first exposure, years since first exposure, and increasing calendar year of first CT scan.(68)

An ecological study conducted in Florida in response to an observed excess of childhood brain and other nervous tissue cancers in the 1990s found no evidence to indicate that the observed excess was related to nuclear plant installation in St. Lucie County in 1976.(69)

Non-Ionizing radiation. Sources of non-ionizing radiation that have been studied for their role in CBT risk predominantly include radio frequency/microwave (e.g. cell phones, AM and FM radio, televisions, microwaves) and extremely low frequency magnetic fields (ELF-MFs; e.g. power lines and electrical wiring) that are classified as possibly carcinogenic by the International Agency for Cancer Research.(70). Studies have shown no significant associations between non-ionizing radiation exposure and CBTs as summarized briefly below.

A South Korean case-control study examined associations between residential AM-radio transmission exposures and CBTs. No significant associations were observed by residential

distance to the AM radio transmitter or for estimated radio frequency radiation exposure (mV/m) for the 4th vs. 1st quartile.(71)

A 2008 meta-analysis that examined associations between residential magnetic field exposure and CBTs reported no significant associations in a number of different analyses.(72)

Kheifets *et al.* conducted a pooled analysis of 10 U.S. and European studies and found no evidence for an association between ELF-MFs and CBTs.(73)

A U.K. registry-based case-control study that examined maternal radiofrequency exposure from macrocell cellular phone base stations (masts) and mast proximity during pregnancy and offspring CBT risk reported no association for mother's exposure to masts during early pregnancy or for modeled power density birth address.(74)

CBTs and cellular phone use in 7-19 year olds was examined in a European multicenter case-control study (CEFALO); the authors reported no significant association between CBTs and regular cellular phone use vs. non-use.(75)

Maternal medical conditions and exposures

Medications. Medications containing amides or amines (e.g. barbiturates, antiepileptics, and antihistamines) may be converted to carcinogenic N-nitroso compounds (NOCs including N-nitrosamines and N-nitrosoamides) upon ingestion through reaction with dietary nitrate in the stomach. Two studies prior to 2004 did not find statistical evidence for an association between maternal exposure to nitrosable drugs and offspring CBTs.(76, 77) Likewise, a large study published in 2006 that included 1,218 CBT cases and 1,218 controls found little support for an association between CBTs and medications containing amines or amides (OR=1.01; 95% CI 0.82-1.24) overall or for astroglial (OR=1.01; 95% CI 0.78-1.31), PNET (OR=1.09; 95% CI 0.75-1.60), or other glial (OR=1.01; 95% CI 0.71-1.44) subtypes. No significant associations were found when data were analyzed by age group (≤5 vs. >5 years) or class of drugs (barbituates,

antiepileptics, antihistamines, neurally active drugs, diuretics, sex hormones, or antiemetics).(78)

A German case-control study of 399 CNS cases diagnosed between 1992-1994 and 2,057 controls evaluated associations between maternally reported medications and CBTs and found no significant associations between CNS tumors and diuretics/antihypertensives (OR= 1.65; 95% CI 0.73-3.74), "pain relievers" (OR=1.0; 95% CI 0.6-1.67), antinauseants or antiemetics (OR=1.15; 95% CI 0.68-1.96), or cold medications (OR=0.81; 95% CI 0.55-1.21). The authors also reported ORs of 1.23 (95% CI 0.71-2.12) and 0.92 (95% CI 0.68-1.24) for associations between offspring CNS tumors and high blood pressure/edema during pregnancy treated with and without drugs, respectively.(79)

A Taiwanese pregnancy cohort study examined maternal use of herbal medicines (Coptidis Rhizoma, An-Tai-Yin, Coptidis and Rhizoma & An-Tai-Yin, and other herbs) and reported an increased hazard ratio (HR) for brain tumors in association with Coptidis Rhizoma (HR=4.79; 95% CI 1.28-17.91).(80)

A Swedish registry based linkage study used medical record data to examine associations between maternal medication ascertained from medical records and offspring CBTs from 0-14 years. No significant associations were found for alimentary tract medicines (mainly antacids and laxatives), vitamins and iron, folic acid, diuretics, anti-infectives (antifungals, penicillin, antibiotics), analgesics (Aspirin/NSAID, Opioids, Paracetemol (acetaminophen), Antiemetics, antihistamines, neuroleptics), anti-asthmatics (oral and inhalation therapy). In contrast, maternal antihypertensives (OR=2.7; 95% CI 1.1-6.5) were positively associated with offspring CBTs, especially for β-blockers (OR=5.3; 95% CI 1.2-24.8).(81)

A German case-control study reported significantly increased risks for CNS tumors overall (OR=1.56; 95% CI 1.01-2.40), MB (OR=2.07; 95% CI 1.03-4.17), and astrocytoma (OR=2.26; 95% CI 1.09-4.69), but not ependymoma (OR=1.23; 95% CI 0.37-4.13) in association with maternal prenatal antibiotic use. For maternal antibiotic exposure including the

three months prior to pregnancy through pregnancy, the associations were less strong and not significant for CNS tumors overall (OR=1.37; 95% CI 0.92-2.05), MB (OR=1.79; 95% CI 0.92-3.48), astrocytoma (OR=1.79; 95% CI 0.87-3.70), or ependymomas (OR=0.95; 95% CI 0.28-3.17).(82)

Maternal antibiotic use during pregnancy was also examined in a Canadian case-control study that included 272 case-control pairs. Cases were diagnosed <15 years of age from 1980-1999. A non-significant positive association between CBTs and prenatal antibiotic exposure (OR=1.7; 95% CI 0.8-3.6) was reported.(44)

Maternal Nutrition

Prenatal vitamins/folic acid (FA). Relatively consistent evidence from earlier studies for a protective effect of prenatal vitamins on offspring CBT risk (reviewed by Goh and Koren (83)) has been reported. A 2007 German case-control study (79) reported no significant association between CBTs and maternally reported vitamin, folate and/or iron supplements (OR=1.07; 95% CI 0.85-1.34). A U.S. case-control study of 315 MBs/PNETs diagnosed from 0-5 years old from 1991-1997 reported no association for periconception (OR=1.2; 95% CI 0.8-2.1) or mid-pregnancy (OR=1.1; 95% CI 0.7-1.6) dietary folate intake when comparing the highest to lowest quartile of intake.(84) In a later report, the authors reported an OR of 0.7 (95% CI 0.4-1.0) for preconception multivitamin use. For dietary folate with supplements, the periconception and mid-pregnancy ORs for the highest vs. lowest intake quartile category ($\geq$380 μg vs. <267 μg) were 0.5 (95% CI 0.3-0.9) and 0.3 (95% CI 0.5-1.3) with a significant trend for increasing periconceptional intake (p=0.007).(85) A Swedish study reported a non-significant inverse association for FA supplementation (OR=0.6; 95% CI 0.3-1.1).(81)

A 2010 case-case study compared maternal FA supplement intake in nervous system tumors (n=44) vs. mesodermal tumor (n=155) cases diagnosed in children aged 0-14 years old during 2004-2006. The ORs for $\geq$ 400 vs. <400 μg/day were 0.34 (95% CI 0.10-1.06), 0.19

(95% CI 0.06-0.6), 0.57 (95% CI 0.33-0.99), and 0.94 (95% CI 0.79-1.14) for preconceptional, <21 days gestation, <36 days gestations, and any period, respectively. Multivitamin supplementation was also inversely associated with CNS tumors for 1st (OR=0.29; 95% 0.09-0.92), 2nd (OR=0.18; 95% CI 0.02-1.35), and any (OR=0.22; 0.07-0.68) trimester intake.(86) A 2012 Australian study of 327 CBT cases diagnosed from 0-14 years between 2005-2010 and 867 controls reported inverse associations during prepregnancy for maternal FA supplement intake (OR=0.68; 95% CI 0.46-1.01) and FA supplement without iron, vitamins B6, B12, C, or A intake (OR=0.55; 95% CI 0.32-0.93). No significant associations were found for FA supplement intake during trimester 1 or 2/3. Associations were also inverse for pre-pregnancy use for LGGs (n=109) and MBs/PNETs (n=47) for any FA vs. no FA supplement use.(87)

Finally, two ecological studies reported CBT incidence trends in association with mandatory population FA fortification of grain and cereal products. When CBT incidence before and after fortification (1985-1997 to 1998-2006) was compared in a Canadian study, IRRs for children aged 0-4 and 5-9 years old of 0.95 (95% CI 0.75-1.19) and 0.91 (95% CI 0.73-1.13), were found respectively.(88) A similarly designed U.S. study examined CBT incidence patterns from 1986-2008 for children diagnosed between 0-4 years old by comparing rates for those who were estimated to be *in utero* before vs. after fortification in 1998. Based on 573 pre- and 454 post-fortification CBT cases, the authors reported significantly lower incidence rates after fortification vs. before for PNETs (IRR=0.56; 95% CI 0.37-0.84) and ependymomas (IRR=0.7; 95% CI 0.51-0.97) but not other brain tumor types or overall. Trend analyses indicated that the data were consistent with a fortification effect for PNETs but not ependymomas.(89)

Dietary NOCs. Studies of rodents and non-human primates have provided evidence that maternal intake of dietary NOCs, particularly N-nitrosamides, induces brain tumors in offspring. However, their contribution to human CBTs is less clear. Direct NOC sources include nitrite-cured and smoked meat, fish, cheese and beer, while vegetables containing nitrites that can

undergo conversion to NOCs are an indirect NOC source (reviewed in (90)). A 2004 meta-analysis that included 1226 CBT cases and 1768 controls from seven studies reported a summary relative risk (RR) of 1.68 (95% CI 1.30-2.17) for the association between CBTs and maternal cured meat intake during pregnancy vs. no intake.(91) Since 2004, a study of 315 MB/PNET cases and 315 controls reported no overall association between maternal prenatal cured meat intake and offspring CBTs; however, maternal high cured meat intake in combination with low vitamin C intake increased risk (OR=1.5; 95% CI 1.0-2.3; p=0.08).(85) An international case-control study of 1,218 CBT cases and 2,223 controls diagnosed from ages 0-19 years old from 1982-1992 reported positive associations with ORs ranging from 1.8-2.5 across astrocytoma subtypes.(92) Finally, one study of 202 cases and 286 controls examined the association between maternal cured meat consumption and CBTs was modified by glutathione S-transferase (GSTs) genotypes, involved in NOC inactivation. Increasing risk with increasing frequency of maternal cured meat consumption in children without *GSTT1* ((OR=1.29; 95% CI 1.07-1.57) was reported.(93) Altogether, a causal connection between maternal intake of NOCs and CBTs is possible; however other nutrients as well as genetic factors may modify risk

Parental smoking and alcohol

Alcohol exposure *in utero* is a known toxin to the developing CNS. However, in agreement with earlier studies (94), a recent large case-control study did not support maternal consumption as a risk factor for offspring CBTs.(95)

The relation between maternal tobacco exposure and CBTs has been studied previously in case-control studies with no significant associations.(96-99) Only one recent prospective Swedish linkage study found an association with maternal smoking for CBTs (benign and malignant tumors, HR = 1.24; 95% CI 1.01-1.53).(100) A recent study assessed neonatal blood spots from 202 cases for genetic polymorphisms that metabolize tobacco-smoke chemicals and

reported that the *EPHX1* H139R polymorphism, one of nine polymorphisms that metabolizes polycyclic aromatic hydrocarbons, had a positive interaction OR for both maternal and paternal smokers with CBTs in offspring (p-interaction =0.02; 0.10).(101)

Parental occupation

Pesticide exposure. Although several studies suggest a causal relation between residential pesticide exposure and CBTs (reviewed in 2007 see (102)) (see also residential pesticides section below), results from studies of parental occupational exposure are less consistent. These inconsistencies could be due to: heterogeneous definition of "child" (ranging from 0 to 30 years old); difficulties in separating parental occupational exposure from residential use; generic definitions of pesticides (i.e., "pesticides" instead of a specific compound); and inconsistent definitions of exposure time windows.

In a Northern England cancer registry study (n=843 CNS tumors; aged 0-24 years old), no association between likely paternal occupational pesticide exposure (at the time of the child's birth) and childhood CNS tumor risk was found when comparing cases to other cancer controls in contrast to population controls where inverse associations were observed for all CNS tumors (OR=0.44, 95% CI 0.31-0.63) and astrocytomas (OR=0.48; 95% CI 0.27-0.87). However, the inverse associations disappeared when the results were stratified by urban vs. rural residence.(103)

In the U.S. Atlantic Coast Childhood Brain Cancer Study, 421 case-control pairs <10 years were analyzed.(104) A positive association was observed between paternal exposure to herbicides from both residential and occupational sources in the two years prior to the child's birth and astrocytoma (OR=1.8; 95% CI 1.1-3.1) with no evidence of an increased risk for fungicides or insecticides.

The Australian Study of Childhood Brain Tumors (Aus-CBT) included 256 cases and 819 controls aged 0-14 years old. Although the authors concluded that exposure to pesticides in

preconception as well as during pregnancy is associated with an increased CBT risk, the evidence was less clear for parental occupational exposure specifically. Only 13 fathers were classified as "exposed" to occupational pesticides in the year prior to pregnancy (OR=1.36; 95% CI 0.66-2.80).(105)

In a meta-analysis of this topic including studies published between 1985 and 2008, there was a significant positive association between CBTs and paternal (OR=1.40; 95% CI 1.20-1.62) but not maternal occupational pesticide exposure.(106) In a second meta-analysis of studies published between 1974-2010, a positive association between parents who had potential prenatal occupational pesticide exposure (including farm/agricultural workers, pesticide applicators, pesticide manufacturers, and others such as gardeners, greenhouse workers, etc.) and offspring brain tumors was reportd after combining all case-control (summary OR=1.30; 95% CI 1.11-1.53) or cohort (summary rate ratio=1.53; 95% CI 1.20-1.95) studies.(107)

ELF exposure. Previous studies examining the possible association between parental occupational ELF exposure in different exposure time windows and CBTs are inconsistent.(108) A recent U.K. registry-based case-control study of CNS tumors examined associations with likely paternal occupational exposure to the broad category of radiation or electromagnetic fields (EMF) applying an occupational exposure matrix to jobs reported on birth certificates.(109) No association was observed with all CNS tumors combined or for ependymomas, astrocytomas, PNETs, other gliomas, or other specified intracranial and intraspinal neoplasms.

A 2009 Canadian study of 548 incident CBTs (aged 0-14 years old) and 760 control subjects assessed potential associations with indicators of maternal occupational ELF exposure based on individualized exposure estimates or a job exposure matrix (JEM) applied to job history information collected during interview.(110) Positive associations between average ELF exposure ≥90th percentile (0.30 μT) but not cumulative or peak exposure in the two-year period prior to conception were observed for CBTs overall (OR=1.4; 95% CI 1.0-2.1) and astroglial

tumors specifically (OR=1.5; 95% CI 1.0-2.4). Positive associations between average ELF exposure ≥90th percentile (0.28 μT) during the pregnancy period were also observed for all CBTs (OR=1.5; 95% CI 1.1-2.2) and astroglial tumors (OR=1.6; 95% CI 1.1-2.5).

A German case-control study of 444 child CNS tumors (0-14 years) from the German Childhood Cancer Registry and 444 controls recruited through resident registration office files examined associations with preconceptional parental occupational exposure to ELF estimated using a JEM applied to lifetime occupational histories collected during interview.(111) No clear association was observed with preconceptional paternal occupational ELF exposure >0.2 μT (OR=1.06; 95% CI 0.84-1.34) or >1 μT (OR=1.19; 95% CI 0.81-1.75). Similarly, no association was observed with preconceptional maternal occupational ELF exposure >0.2 μT (OR=0.88; 95% CI 0.58-1.33).

Other parental occupational exposures. In recent analyses, a Taiwanese case-control study including 74 incident brain tumor cases <30 years old and 170 controls reported preliminary results that CBTs were associated with maternal preconceptional occupations for electronic parts and component manufacturing (OR=11.81, 95% CI 1.20-116.3) and the textile and garment industry (OR=7.25, 95% CI 1.18-31.0).(112) In contrast, analyses of the complete study of 202 CBT cases and 501 controls revealed no associations with parental (paternal or maternal) or personal occupation or industry for brain tumor risk overall, or with glioma specifically, nor with parental exposure to petrochemicals. A complete list of the industries/occupations studies is not included in the article. Selected industries/occupations studied included: agriculture, forestry, fishing; electricity, gas, and water; clerks; plant and machine operators and assemblers; construction; and craft and related trades workers.(113)

An Australian population-based case-control study examined associations between parental occupational exposure to engine exhausts and brain tumors in children aged 0-14 years.(114) A total of 306 CBT cases were examined with 950 controls. Estimates of paternal

and maternal exposure to diesel, petrol, and other exposures one and two years prior to birth and the year following birth were inferred based on a decision-rule approach. Significant positive associations for maternal (OR=2.03; 95% CI 1.09-3.81) and paternal (OR=1.38; 95% CI 1.02-1.86) diesel exhaust exposure any time prior to birth were observed. Paternal occupational exposure to petrol and other exhausts were also studied, however no significant association at any time before birth was found (OR=1.31; 95% CI 0.92-1.87). No associations between CBTs and occupational exposures to other exhausts were observed. Associations between CBTs and paternal occupational paint exposure were also examined with small positive associations reported for any paternal exposure prior to the child´s birth (OR = 1.32, 95% CI 0.90-1.92) or in the conception year (OR=1.25; 95% CI 0.69-2.28).(115)

In a case-control study of 1,218 CBT cases (0-19 years) and 2,223 controls in seven countries, there was a significant positive association between paternal preconceptional occupational exposure to polycyclic aromatic hydrocarbons (PAHs) and risk of all childhood brain (OR=1.3; 95% CI 1.1-1.6) and astroglial tumors (OR=1.4; 95% CI 1.1-1.7).(116) These results are generally consistent with previous studies on parental occupational PAH exposure.(117)

A South Korean study that linked birth to death records from 1995 to 2004, classified parental occupation (listed on birth certificate) as non-manual (e.g., legislators, professionals, office workers), manual (e.g., skilled agricultural, forestry and fishery workers, craft and affiliated craft workers, device and machine operators), and economically inactive (e.g., students, homemakers, soldiers). For CNS tumors, the HRs for paternal and maternal occupation were not significant (comparing manual and inactive work to non-manual work). Likewise, when stratified by paternal education level, paternal occupation was not associated with childhood CNS tumors.(118)

Lastly, a case-control study of 11,119 CNS tumors diagnosed aged <15 years from the Great Britain National Registry of Childhood Tumors and 11,039 matched controls from birth

records examined potential associations with 33 paternal occupational exposures as well as social class based on job title recorded at birth.(119) Significant positive associations were observed with "definite" paternal occupational exposure to animals (OR=1.40; 95% CI 1.01-1.96) and lead (OR=1.18; 95% CI 1.01-1.39) and a significant inverse association with metal working (oil mists) (OR=0.87; 95% CI 0.75-0.99). There was also a significant inverse association with paternal social class. Associations were also observed with paternal occupational exposures and specific CNS subtypes; however, they were somewhat sensitive to adjustment for paternal social class.

Residential pesticides

Pesticides are designed to act on the nervous system with some being carcinogenic in animal models.(120) Numerous studies have investigated the potential impact of use of household pesticides, pest extermination services on CBT development.(117, 121) Overall, these studies suggest positive associations with CBTs. In a meta-analysis, increased CBT risks in association with paternal pesticide use (herbicides, insecticides, and fungicides) in the home or garden during the prenatal (OR=1.48; 95% CI 1.22-1.80) or postnatal (OR=1.66; 95% CI 1.11-2.49) periods were reported.(106) A U.S. case-control study found that parental use of garden or lawn herbicides was significantly associated with childhood astrocytoma (RR=1.9; 95% CI 1.2-3.0) for children aged ≤10 years old but not PNETs and MBs.(104) However, another case-control study of PNET/MB reported an association with use of pesticides on the lawn during pregnancy (OR=1.6; 95% CI 1.0-2.5) or childhood (OR=1.8; 95% CI 1.2-2.8) for children aged ≤6 years old at diagnosis.(122)

Finally, a case-control study investigated genetic variation in the paraoxonase (*PON1*) gene that is involved in the organophosphorus insecticide metabolism and CBT risk. CBT risk increased with each *PON1-108T* allele the child carried in children exposed to residential insecticides (OR=2.6; 95% CI, 1.2-5.5) but not among unexposed children (OR=0.9; 95% CI,

0.5-1.6).(123) Research in an expanded study population also found the association with *PON1* (OR=1.8; 95% CI 1.1 to 3.0) and *FMO1*-9536A (*6) allele (OR=2.7; 95% CI 1.2-5.9) among pesticide exposed children exclusively.(124)

Summary and future directions.

Established CBT risk factors remain limited to ionizing radiation exposure and certain cancer syndromes. However, accumulating evidence suggests relatively consistent support from larger studies and meta-analyses for positive associations between advanced parental age, birth defects, markers of fetal growth, CT scans, maternal dietary NOCs, and residential pesticide exposure (summarized in **Table 5** and **Figure 1**).

A priority area for future CBT epidemiological research is the elucidation of both common and rare genetic risk variants that modify risk. Although it is well established that certain genetic syndromes strongly increase CBT risk, no genome-wide association studies that identify common risk variants were published at the time of this review. Identification of common genetic loci as well as potential parental genetic loci that modify CBT risk overall and by subtype will inform CBT biology. Identification of rare germline CBT risk variants through genome sequencing studies will also be an important future research priority.

With the exception of higher doses of ionizing radiation, no definitive environmental risk factors for CBT development exist. However, our review suggests that maternal dietary intake of NOCs, prenatal vitamin supplementation, and residential pesticide exposure may increase risk. Inherent limitations of case-control studies including small sample sizes, survey measurement error, and selection bias make it difficult to reach definitive conclusions. Finally, emerging evidence from two administrative data analyses suggests that exposure to CT scans increases brain tumor risk, emphasizing the importance of minimizing radiation exposure from diagnostic tests to the extent possible in children to mitigate cancer risk.

In summary, it is likely that the greatest gains in understanding of CBT etiology in the near future will come from genomic studies that identify genetic factors that modify CBT risk overall and by subtype. It will also be important to identify interactions between genetic and environmental factors and to conduct studies that integrate germline and somatic tumor sequence data to determine how germline variation influences tumor mutation profiles and prognosis. For progress in these areas to occur, a coordinated investment in systematic collection of clinically-annotated biospecimans (both tumor and normal) from a large number of CBT cases should be an international priority since cancer is a leading cause of death in children and CBTs have the highest cancer mortality rate among childhood cancers.(125) In the U.S. alone, there are >2000 children diagnosed each year with brain tumors representing a substantial population that could be approached for research participation during clinic visits where recruitment success has been shown to be higher.(126) A clear need also exists for increased international coordination to make samples available through standardized processes to all researchers with meritorious proposals. A step forward in this direction was recently achieved through funding of a biospeciman bank that will store samples from children diagnosed with cancer at a Children's Oncology Group Institution that includes 220 centers in North America, Saudia Arabia, Australia, New Zealand and Europe.(127)

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Table 1. Age-adjusted and age-specific incidence rates[a] per 100,000 persons, by histology, region, and gender

				Overall	0-4 years	5-9 years	10-14 years	15-19 years
Histologic Type	**Region (Surveillance System[b])**	**Years**	**Ages**	**Rate (95% CI)**	**Rate (95% CI)**	**Rate (95% CI)**	**Rate (95% CI)**	**Rate (95% CI)**
All CNS Tumors	Europe(128) (ACCIS)[c]	1988-1997	0-14	2.99	3.39 [d]	3.13	2.43	
	United States(4) (CBTRUS)	2006-2010	0-14	5.14 (5.05-5.22)				
	United States(4) (CBTRUS)	2006-2010	0-19	5.26 (5.19-5.33)	5.77 (5.63-5.93)	4.89 (4.75-5.03)	4.78 (4.64-4.91)	5.64 (5.5-5.78)
	Japan(129)	1989-2008	0-14	3.61	2.85	4.09	3.84	
	Kuwait(130) [e]	1995-2011	0-19	1.12				
	Denmark, Finland, Norway, and Sweden(131) [c]	1985-2006	0-14	4.20				
	Denmark(132) [e]	1980-1996	0-14	3.95	4.28			
Pilocytic Astrocytoma	United States(4) (CBTRUS)	2006-2010	0-14	0.90 (0.87-0.93)				
	United States(4) (CBTRUS)	2006-2010	0-19	0.82 (0.79-0.85)	0.96[c] (0.90-1.03)	0.91 (0.85-0.97)	0.26 (0.23-0.29)	0.58 (0.54-0.63)
	England(133) [c]	1995-2003	0-14	0.75				
Astrocytoma	Europe(128) (ACCIS) [c,f]	1988-1997	0-14	1.18	1.29 [d]	1.26	1.07	
	Japan(129)	1989-2008	0-14	1.32				
	Denmark, Finland, Norway, and Sweden(131) [c]	1985-2006	0-14	1.79				
	Denmark(132)	1980-1996	0-14	1.56	1.64			
Ependymoma/ Ependymal Tumors[f]	Europe(128) (ACCIS)[c]	1988-1997	0-14	0.34	0.54 [c]	0.23	0.17	
	United States(4) (CBTRUS)	2006-2010	0-14	0.28 (0.26-0.30)				
	United States(4) (CBTRUS)[g]	2006-2010	0-19	0.28 (0.26-0.29)	0.43 (0.39-0.48)	0.22 (0.19-0.25)	0.21 (0.18-0.24)	0.25 (0.22-0.29)
	Japan(129)	1989-2008	0-14	0.15				
	Denmark, Finland, Norway, and Sweden(131) [c]	1985-2006	0-14	0.42				
	England(133) [c]	1995-2003	0-14	0.25				
	Denmark(132) [e]	1980-1996	0-14	0.37	0.65			
Embryonal Tumors[h,i]	United States(4) (CBTRUS)	2006-2010	0-14	0.80 (0.77-0.84)				
	United States(4) (CBTRUS)	2006-2010	0-19	0.66 (0.64-0.69)	1.27 (1.20-1.35)	0.75 (0.70-0.80)	0.41 (0.38-0.46)	0.24 (0.21-0.27)
	Denmark, Finland, Norway, and Sweden(131) [c]	1985-2006	0-14	0.73				
	England(133)	1995-2003	0-14	0.28				
PNET	Austria(14)(ABTR)	1996-2006	0-14	0.21 (0.15-0.30)				
	England(133) [c]	1995-2003	0-14	0.08				
Medulloblastoma	Japan(129)	1989-2008	0-14	0.37				
	Austria(14)(ABTR)	1996-2006	0-14	0.58 (0.16-0.71)				
	England(133) [c]	1995-2003	0-14	0.20				
ATRT	Austria(14) (ABTR)	1996-2006	0-14	0.14				
	United States(4) (CBTRUS)	2006-2010	0-14	0.11 (0.10-0.12)				
	United States(4) (CBTRUS)	2001-2010	0-19	0.07 (0.07-0.08)				

[a]Rates are adjusted to population of region unless specified otherwise

[b]Differences in rates by region can be affected by differences in reporting practices and statistical methods of adjustment. For this reason, sources of data and differences in standard populations used for adjustment are provided.
[c]Adjusted to world standard population
[d]Incidence rate is for ages 1-4
[e]crude rates
[f]International Classification of Childhood Cancer (ICCC) group IIIa, based on the International Classification of Diseases for Oncology, 3rd Edition(134)
[g]Defined using the CBTRUS Brain and Central Nervous System Tumor Histology Groupings, based on *2007 WHO Classification of Tumours of the Central Nervous System(9)*
[h]ICCC group IIIb
[i]Includes PNET, Medulloblastoma, and ATRT
Note: AACIS = Automated Childhood Cancer Information System, CBTRUS = Central Brain Tumor Registry of the United States, ABTR = Austrian Brain Tumor Registry, CPBTC = Canadian Paediatric Brain Tumour Consortium

Table 2. Survival rates by histologic type and region.

					1 year	5 year	10 year
Histologic Type	**Region**	**Surveillance System**	**Years**	**Ages**	**Rate (95% CI)**	**Rate (95% CI)**	**Rate (95% CI)**
All CNS Tumors	Europe(128)	ACCIS	1988-1997	0-14		91 (60-62)	
	United States(4)	CBTRUS	2006-2010	0-14	85.2 (84.4-86)	72.3 (71.2-73.3)	68.2 (66.9-69.4)
	Sweden(135)		1984-2005	0-14		76	72
Ependymoma[a]	Europe(128)	ACCIS	1988-1997	0-14		53 (49-57)	
	United States(4)[b]	CBTRUS	1995-2010	0-14	93.6 (91.3-95.4)	72.2 (67.9-76.1)	62.8 (57.5-67.7)
	Sweden(135)		1984-2005	0-14		72	66
Astrocytoma [c]	Europe(128)	ACCIS	1988-1997	0-14		75 (73-76)	
	Sweden(135)		1984-2005	0-14		84	82
Pilocytic Astrocytoma	United States(4)	CBTRUS	2006-2010	0-14	98.7 (98.1-99.1)	97.2 (96.3-98.0)	96.2 (94.9-97.2)
Embryonal Tumors[d]	United States(4)	CBTRUS	1995-2010	0-14	79.9 (77.9-81.7)	62.1 (59.6-64.5)	55.5 (52.7-58.3)
PNET	Europe(128)[e]	ACCIS	1988-1997	0-14		49 (46-51)	
	United States(4)	CBTRUS	1995-2010	All ages	76.4 (72.9-79.6)	49.5 (45.3-53.6)	42.8 (38.4-47.2)
	United States(10)	SEER	2001-2006	<1	31 (9-58)	14 (2-39)	
	United States(10)	SEER	2001-2006	1-9	88 (81-93)	64 (54-72)	
	United States(10)	SEER	2001-2006	10-19	94 (82-98)	57 (41-70)	
	Sweden(135)		1984-2005	0-14		47	41
Medulloblastoma	United States(4)	CBTRUS	1995-2010	All ages	88.2 (86.5-89.7)	71.1 (68.5-73.5)	62.8 (59.7-65.8)
	United States(10)	SEER	2001-2006	<1	52 (30-70)	42 (22-61)	
	United States(10)	SEER	2001-2006	1-9	90 (86-93)	69 (58-78)	
	United States(10)	SEER	2001-2006	10-19	92 (85-96)	69 (58-78)	
	Sweden(135)		1984-2005	0-14		63	55
ATRT	United States(4)	CBTRUS	1995-2010	All ages	48.1 (40.3-55.5)	28.0 (20.7-35.7)	26.2 (18.8-34.3)

AACIS = Automated Childhood Cancer Information System, CBTRUS = Central Brain Tumor Registry of the United States, SEER = Surveillance, Epidemiology and End Results

[a]International Classification of Childhood Cancer (ICCC) group IIIa, based on the International Classification of Diseases for Oncology, 3rd Edition(134)

[b]Defined using the CBTRUS Brain and Central Nervous System Tumor Histology Groupings, based on *2007 WHO Classification of Tumours of the Central Nervous System(9)*

[c]ICCC group IIIb

[d]Includes PNET, Medulloblastoma, and ATRT

[e]ICCC group IIIc

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Table 3. Review of recent studies addressing ionizing radiation related risks and childhood brain tumors.

Study design/population	Subject number, Radiation measurement method	Radiation indicator	RR (95% CI)	Comment	Ref.
Cohort study of ≥5 years survivors of childhood cancer diagnosed between 1970-1986 in the U.S. and Canada.	166 CNS cases among 14,361 cohort members Medical record abstraction	Therapeutic radiation only for first primary childhood cancer vs. no exposure	OR=7.07 (2.76-18.1)[a]	Both glioma and meningioma risks were increased with a shorter interval following exposure for glioma vs. meningioma diagnoses. CBT diagnoses were not specifically reported.	(62)
Danish nested case-control study in children with an immaturity diagnosis born from 1977-1988. CBT cases were diagnosed from 0-19 years. Controls were randomly selected from the base cohort.	25 cases, 43 controls Medical record abstraction	Any newborn diagnostic X-ray exposure vs. none	OR=2.2 (0.6-8.8)[b]		(63)
Swedish registry linkage study of prenatal X-rays and CBTs. Subjects were born from 1975-1984. CBT cases diagnosed from 0-14 years were identified in the cancer registry. Controls were randomly selected from the Medical Birth Registrar matched to cases on sex and birth year.	512 CBT cases, 524 controls Medical record abstraction	Any prenatal abdominal X-rays vs. none	OR=1.02 (0.64-1.62)[c]	Risk estimates for subtypes: low grade astrocytomas (OR=0.72; 95% CI 0.38-1.42), high grade astrocytomas (OR=1.06, 95% CI 0.39-2.88), PNETs (OR=1.88; 95% CI 0.92-3.83), or ependymomas (OR=1.01; 95% CI 0.24-2.98)[c]. Risk estimates for non-abdominal prenatal X-ray exposures were not significant.	(64)
Case-control study of MBs and PNETs diagnosed 0-5 years from 1991-1997. Cases and controls were ascertained from the Children's Oncology Group and random digit dialing respectively. Controls were matched to cases on area code, race, and birth date (±6 months for cases diagnosed <1 year of age, ±1 year for cases diagnosed >1 year of age).	318 cases, 318 controls Maternal interview	Head X-ray not due to head injury exposure vs. none Post-natal head X-ray exposure vs. none Post-natal dental X-ray exposure vs. none Any post-natal X-ray exposure vs. none	OR=2.3 (0.91-5.7)[d] OR=1.2 (0.54-2.5)[d] OR=1.2 (0.54-2.5)[d] OR=1.2 (0.71-2.0)[d]		(65)
Case-control study of prenatal/early infancy diagnostic radiation exposure in 2,690 childhood cancer cases and 7,858 controls. Cases were from the United Kingdom Childhood Cancer Study (UKCCS). Two controls per case were ascertained from the population registrar matched on sex and date of birth (±1 month). Study subjects were born during 1976-1996.	25 exposed CBT cases, 41 exposed controls Medical record abstraction	Prenatal diagnostic radiation exposure vs. none Early infancy diagnostic radiation exposure vs. none	OR=1.06 (0.64-1.77)[e] OR=1.06 (0.64-1.77)[e]	Early infancy radiation exposure was not significantly associated with CBTs in analyses that considered no latency or a two year latency period.	(66)
Retrospective U.K. cohort of 176,587 individuals exposed to CT scans during childhood. Brain tumor cases were diagnosed from 6-45 years during 1985-2008.	135 cases Paper or film CT records were used to	CT scan exposure (mGy) Cumulative dose	ERR per mGy=0.023 (0.01-0.049) RR=2.82	No specific information was provided on CBTs.	(67)

	measure exposure and estimate dose	≥50-74 vs. <5 mGy	(1.33-6.03)		
Australian registry linkage study of the Medicare and the cancer registry that included 10.9 million individuals. Brain tumor cases were diagnosed through their early forties among 10.9 million individuals that included 680,000 CT scan exposed subjects during 1985-2005.	283 cases Australian Medicare administrative database	Any CT exposure vs. none Brain CT exposure vs. none Other CT scan vs. none	IRR=2.13 (1.88-2.41)[f] IRR=2.44 (2.12-2.81)[f] IRR=1.51 (1.19-1.91)[f]	The risk decreased with number of years since first exposure and with increasing calendar year of first CT scan for age at exposure age groups 1-4 and 5-9 years.	(68)
U.S. ecological study conducted in St. Lucie County, Florida. CBT cases diagnosed at ages 0-19 years during 1950-2000.	13 cases	SMR before (1956-1975) and after (1976-2000) the St. Lucie County nuclear power station installation in 1976 in St. Lucie County compared to two neighboring counties.	SMR_{before}=0.87 (0.35-2.20) SMR_{after}=0.96 (0.39-2.06)	SMRs were calculated using general U.S. population mortality rates.	(69)

RR=Relative Risk; GIS-Geographic Information Systems

[a]Adjusted for diagnosis group (leukemia, CNS, other)
[b]Adjusted for gestational age
[c]Adjusted for maternal age, parity, multiple birth, mother born in a Nordic country, gestational age at birth, mode of delivery, breech position, birth weight, birth head circumference, level of hospital, and hypertension during pregnancy; an unadjusted OR for ependymoma was reported due to the low number of cases.
[d]Adjusted for annual household income >$50,000, mother's education, age of child at interview
[e]Adjusted for child sex, age at diagnosis, UKCCS study region, birth weight, maternal age, early infancy radiation (1 year lag), early ultrasound scans (1 year lag)
[f]Adjusted for age, sex, year of birth, includes one year lag period

Table 4. Review of recent studies addressing non-ionizing radiation related risks and childhood brain tumors.

Study design/population	Subject number, Radiation measurement	Radiation indicator	RR (95% CI)	Comments	Ref.
South Korean case-control study of radio-frequency exposure from AM radio transmitters. CBT cases diagnosed <15 years. Case and control subjects were ascertained from the South Korean Medical Insurance Data System, Controls with respiratory diseases were matched to cases on age and sex at 1:1 ratio.	956 cases, 3,082 controls Residential addresses and GIS prediction program to estimate radio-frequency radiation	Residential distance to the AM transmitter <2 km vs. >20 km Estimated radiofrequency radiation exposure (mV/m) 4th vs. 1st quartile	OR=1.42 (0.38-5.28)[a] OR=0.77 (0.54-1.10)[a]	Radio-frequency radiation exposure was defined as "the highest exposure estimate among all the individual exposure estimates obtained from each transmitter established before the subjects' year of diagnosis'".	(71)
Meta-analysis of studies conducted in the U.S., Sweden, Taiwan, Denmark, Finland, Norway, United Kingdom, Germany, and Japan that examined residential magnetic field exposure (including distance to overhead power lines, wire codes, calculated magnetic fields, and magnetic field measurements (spot or long-term measurements)) and CBTs.	25-6,605 cases, 57-6,605 controls Distance to overhead power lines, wire codes, calculated magnetic fields, and measured magnetic fields (spot or long-term measurements)	Residential distance to power lines <50 m vs. ≥50 m (n=5 studies) Calculated magnetic field exposure ≥ 2 μT vs. < 2 μT (n=4 studies) Long-term measured exposure ≥2 μT vs. < 2 μT, the combined (n=4 studies) High vs. low wire code current configuration (n=3 studies) Very high vs. low wire current code configuration (n=3 studies) Spot measurement ≥2 μT vs. < 2 μT (n=3 studies)	OR= 0.88 (0.57-1.37) OR=1.13 (0.65-1.95) OR=1.14 (0.65-2.00). OR=1.08 (0.6-1.98) OR=0.83 (0.51-1.36) OR=1.13 (0.61-2.10)	Several influence analyses did not materially change the results and the funnel plot showed no evidence of publication bias. When considering only studies that reported higher doses (0.3 or 0.4 μT), the combined OR was 1.68 (95% CI 0.83-3.43). The authors concluded that they could not exclude the possibility of an increased risk at higher doses but for lower doses the analyses provided no evidence for an increased risk of CBTs.	(72)

Pooled analysis of 10 studies published in the U.S. and Europe between 1979-2010 examining associations between extremely low frequency magnetic fields (ELF-MF) and CBTs diagnosed 0-15 years.	7,770 cases, 10,883 controls Various	0.1-<0.2mT vs. < 0.1μT 0.2mT-<0.4 μT vs. < 0.1μT >0.4 μT vs. <0.1 μT	OR=0.95 (0.65-1.41)[b] OR=0.70 (0.40-1.22)[b] OR=1.14 (0.61-2.13)[b]	There was no evidence for dose-response and the results were consistently weak when subjected to numerous analyses.	(73)
U.K. registry-based case-control study of CBT cases diagnosed 0-4 years old from 1999-2001 who were ascertained from the National Cancer Registry. Controls were ascertained from the birth registry and matched to cases on sex and birth date.	251 CBT cases, 1,004 controls Three exposures were calculated: 1) distance from residential address at birth to macrocell mobile phone base station, 2) total power output across all base stations within 700m of residential address at birth, and 3) modelled power density for base stations within 1400 m at residential address at birth.	Distance from nearest base station (>1071.8 m vs. 0-612.0 m) Total power output (>4.743 kW vs. 0 kW) Modelled power density (≥-17.6965 vs. -70 to 26.4659 dBm^2)	OR=0.94 (0.65-1.36)[c] OR=0.84 (0.56-1.27)[c] OR=0.77 (0.53-1.12)[c]	Residential birth address served as a proxy for exposure address during pregnancy.	(74)
Multicenter case-control study (CEFALO) conducted in Denmark, Sweden, Norway, and Switzerland. Cases were diagnosed from 7-19 years during 2004-2008. Two controls per case matched on age, sex, and geographical region were ascertained from country population registries.	352 CBT cases, 646 controls Cell phone use ascertained through interviews and records where available	Regular use of cell phones vs. non-use	OR=1.36 (0.92-2.02)	In a subgroup analysis of individuals where phone operator data was available, an increased brain tumor risk was observed in association with length of mobile phone subscription but not amount of use.	(75)

[a]Adjusted for residential location, population density, and socioeconomic status of the community of residence
[b]Adjusted for age, study, sex
[c]Adjusted for percentage of population with education to degree level or higher and Carstairs deprivation score

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Table 5. Summary of evidence for risk factors for childhood brain tumors

	Exposure	Comment	Refs.
STRONG	Cancer Syndromes	Syndromes include: NF1, NF2, Tuberous sclerosis, Nevoid Basal Cell Carcinoma, Turcot, Cowden, hereditary retinoblastoma, and Rubinstein-Taybi syndrome	
	Ionizing radiation (therapeutic)	Recent studies of childhood cancer survivors continue to support an increased risk in association with therapeutic ionizing radiation treatment.	(59, 62)
SOME / SUGGESTIVE	Parental age	In support of a large study published in 1999 (> 1600 CBT cases), two recent large studies have also supported a parental age effect, particularly for astrocytoma. However, results are inconsistent with respect to maternal or paternal age.	(30-32)
	Birth defects	Four of four large recent studies reported increased risks, particularly for nervous system anomalies.	
	Fetal growth	Three recent studies including a meta-analyses of 8 studies reported consistent positive associations between CBTs and higher birth weight categories, while one smaller study reported no association of fetal growth measured as proportion of optimal birth weight. In positive studies, there is inconsistency between CBT subtypes. A positive association between head circumference and CBTs was reported in one study.	(55-58)
	Ionizing radiation (diagnostic)	Two large studies suggest that CT scans are associated with increased risk of brain tumors. Regarding X-rays, recent evidence suggests that prenatal X-rays of the abdomen have been associated with an increased risk of PNETs but not other types of CBTs. Other X-rays have not been associated with increased risk of CBTs.	(67, 68) (63-66)
	Folic acid/prenatal vitamins	Suggestive evidence for an inverse association with CBTs during preconception/early pregnancy from several studies for FA supplements with support from one of two ecological studies that examined childhood brain tumor incidence before vs. after FA fortification for PNETs.	(79, 81, 84-89)
	Maternal dietary NOCs	A meta-analysis of seven studies and two recent case-control studies support a positive association with one study providing evidence for a gene-environment interaction between *GSTT1*, a gene involved in inactivation of NOCs, and maternal consumption of cured meat.	(85, 91-93)
	Residential pesticides	A meta-analysis indicated overall positive associations between CBTs and both prenatal and postnatal exposure, however there is inconsistency between subtypes.	(104, 106, 117, 120-124)
WEAK / INSUFFICIENT	Maternal genetics	Positive evidence from one study for a role of the *EPHX1* gene involved in xenobiotic detoxification.	(34)
	Allergic conditions	Two studies reported consistent reduced risks for maternally reported asthma. One of these studies did not confirm this finding when using medical records to measure asthma history. A third study reported no significant association for atopic conditions (asthma, wheezing, eczema, allergic rhinitis) overall with some evidence for reverse causality.	(34, 37, 38)
	Markers of infection	Inconsistent evidence with findings varying based on sex, age at diagnosis, and tumor type.	(40-47)
	Maternal medications	Numerous medications have been examined including: diuretics/anti-hypertensives, pain relievers, anti-nauseants/anti-emetics, cold medications, antacids, laxatives, analgesics, anti-asthmatics, and anti-emetics, and herbal medicines, however most have been examined only in single studies. A 2006 review indicated no evidence for an association between medications containing amines/amides (barbiturates, anti-epileptics, and antihistamines) and CBTs. Two studies provided positive evidence for maternal use of antibiotics and CBT risk. On study indicated that certain herbal medicines were positively associated with CBTs.	(79-81, 136) (80, 82)
	Parental occupational exposures.	Inconsistent findings that could be due to difficulties in separating parental occupational exposure to pesticides from residential use, generic definitions of pesticides, and inconsistent definitions of time windows of exposure. However, two large meta-analyses support a positive association parental occupational pesticide exposure and offspring CBT risk. For parental occupational ELF exposure, studies are inconsistent. For various other parental occupational exposures (electronic parts, textiles, engine exhausts, petrochemicals, poly aromatic hydrocarbons, paints) there is limited study of the same exposure in different study populations and interpretations are limited due to small study sizes and the need for replication.	(103-107) (112-116, 118, 119) (109-111)

NONE / LITTLE	Family history	Overall, the evidence for a positive association is limited, suggesting that there is not a strong genetic component to most CBT cases.	(28, 29)
	Nuclear power plants	One report showed no evidence of an association.	(69)
	Non-ionizing radiation	There is an overall lack of association observed between several types of non-ionizing radiation (residential AM-radio transmission, residential magnetic field exposure, ELF-MF, maternal radiofrequency exposure from cell phone base stations and cell phone use among 7-19 year olds), but findings not replicated.	(69, 71-75)
	Parental alcohol and smoking	No evidence from one recent study of maternal alcohol consumption during pregnancy, in agreement with earlier studies. There is limited evidence for parental smoking as a risk factor for CBT development.	(71-75, 94-101)

FIGURE LEGEND

Figure 1. Summary of established and suspected risk factors related to childhood brain tumors. More established risk factors are listed in bold type. Suggested risk factors that are high-priority for validation are listed in non-bold type.

Figure 1