Review

Risk Factors for Childhood Brain Tumors

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Brain tumors are the second most common cancer in children after leukemia and constitute about 20% of all childhood cancers in the United States (1). The annual incidence is approximately 34 per million children under 15 years of age. The incidence may be rising; the U.S. National Cancer Institute reported an increase in the period 1973–1988 (1). With a 5-year relative survival rate of approximately 58%, brain tumors account for about 24% of the mortality from childhood cancer. Mortality rates have decreased in recent years (1), due to significant advances in neurosurgical and neurodiagnostic techniques and radiation therapy (2). However, children who survive their brain tumor are frequently cognitively impaired (3) or have endocrine deficiencies (4). Inasmuch as childhood brain tumors account for a large fraction of the mortality and morbidity from childhood cancer and of the deleterious late sequelae in survivors, an understanding of etiological factors leading to these tumors is crucial for the early detection of children at high risk and ultimately for prevention.

Several recent reviews exist in the literature on risk factors for childhood cancer (5–8), but none deals extensively with childhood brain tumors. The most recent review of risk factors for childhood brain tumors dates back to 1980 (9), and since then many papers have been published. A review of the risk factors for childhood brain tumors may assist in evaluating previous studies and initiating further research. Therefore, we reviewed the epidemiological studies on childhood brain tumors that appeared in the literature from 1974 to March 1992 (10–32). All investigations were case-control studies, and their designs are summarized in Table 1.

Methodological Issues

Spurious effects may be observed as the result of the design and conduct of case-control studies. Recall bias, interviewer bias, and multiple exploratory analyses may create effects that do not exist in reality. Many of the exposures studied in relation to childhood brain tumors can only be assessed by interview, and therefore, recall bias is a pertinent issue. Although none of the studies stated that the interviewer was blinded to case-control status, all used structured interviews which would reduce the possibility of interviewer bias. The issue of associations emerging by chance is pertinent, since most of the reviewed studies performed multiple exploratory analyses.

Case-control studies may also fail to detect real effects, for example, as a result of small sample size and crude measurement of exposure (33). These issues apply to the studies reviewed here since some were small and many categorized exposure only as “ever” or “never.” Real effects may also be masked when diseases with different etiologies are studied as one disease. All but two of the studies reviewed here combined all types of childhood brain tumors (Table 1). However, several histological types of brain tumors occur, the most common being astrocytomas and medulloblastomas, which comprise about 50% and 20%, respectively, of all brain tumors in children (34). Astrocytomas and medulloblastomas (now usually called primitive neuroectodermal tumors) differ in age-incidence curves, sex ratio, and cell of origin and thus may differ in etiology.

In summary, limitations of case-control studies can create associations that do not exist in reality or that mask true effects. Results of the reviewed studies have to be interpreted with caution in light of these limitations.

Suggested risk factors will be discussed in categories of nonoccupational factors, parental occupational factors, and familial factors. Nonoccupational and occupational risk factors may act before conception, leading to a new germinal mutation; during pregnancy, by affecting the embryo or fetus transplacentally; or after birth. Because most studies on occupational risk factors report data on the perinatal period only, the occupational findings discussed are for that period, unless stated otherwise. The familial factors studied, i.e., family history of cancer or neurological disorders, suggest a preexisting genetic susceptibility that increases the risk of a brain tumor in the child. Risk factors for other childhood cancers or adult brain tumors might also be associated with childhood brain tumors and will receive attention where appropriate.

Nonoccupational Risk Factors

Irradiation. The association between diagnostic X-rays in utero and the later development of cancer was first reported in 1956 by Stewart et al. (35, 36) and replicated in 1962 by MacMahon (37). The 1.5–2.0-fold increased risk of childhood cancer in these and later studies was similar for leukemia, central nervous system tumors, and other cancers. The association persisted after correcting for maternal age, birth order, abnormalities of pregnancy and delivery, and social class. Nonetheless, the concern arose that the X-rays may have been performed for a
maternal medical condition that increased the risk for childhood cancer. This possibility prompted studies of twins, since mothers of twins were usually X-rayed to confirm the twin pregnancy or determine fetal positions, rather than for medical conditions. In three twin studies, increased risk of the same magnitude as in singletons was observed, which was significant in two studies (38, 39) and of borderline significance in one (40). These results were taken as further evidence for the carcinogenic effect of in utero diagnostic X-rays.

Evidence that is not consistent with X-ray exposure in utero and subsequent childhood cancer also exists. For example, animal experiments do not provide evidence that in utero irradiation is more carcinogenic than irradiation of adult animals (41). No excess of cancer deaths in Japanese children under 10 years of age after in utero irradiation from the atomic bombs was noted (42), although these results are based on a small number of exposed children. The atomic bomb irradiation seems to have had a delayed effect, as the cancer incidence in adults who were exposed in utero is increased in a dose-response fashion (42).

According to a recent study (43), the observed childhood cancer risk decreased after the X-ray rate declined following the publication by Stewart et al. in 1956 (35). The authors state that the X-ray rate and cancer risk increased again in the early 1970s, but not significantly. Less frequent use of obstetric radiography and the lower radiation doses associated with modern techniques make the problem largely academic at present. In three recent studies of children, nearly all of whom were born after 1958, investigators observed no increased risk of brain tumors associated with maternal pelvic irradiation during pregnancy (21, 27, 31). However, the power to detect a 1.5-fold increase in risk was low in these studies.

Diagnostic X-rays in childhood have also been reported to increase the risk for childhood brain tumors. Preston-Martin et al. (21) observed a moderate risk of brain tumors after five or more full-mouth X-rays prior to 1964. Full-mouth X-rays were also a risk factor for brain tumors in adults, particularly when performed before 1945 (44–46). However, the radiation doses used today are several orders of magnitude lower than in the past and seem unlikely to pose any risk for brain tumors.

X-rays of the skull were also suggested to increase the risk for childhood brain tumors (27), but this is difficult to interpret since diagnostic films may be related to early symptoms of the tumor. Radiation doses for skull X-rays have also decreased over the years. The sensitivity of brain tissue to radiation-induced carcinogenesis is at most moderate, and the doses employed in the diagnostic techniques today would not be expected to lead to a measurable increase in risk (47, 48).

An association with exposure to therapeutic X-rays in childhood is more evident. Tinea capitis in childhood used to be treated with 1–2 Gy radiotherapy and was associated with a 7-fold increased risk of brain and nervous system tumors that occurred 6–29 years after therapy (48). It is unlikely that tinea capitis itself predisposed to brain tumors, since nonirradiated tinea capitis patients in another study were not at increased risk (49). Studies of patients treated for childhood cancer observed an excess of second cancers in the brain; a large fraction of these tumors were thought to be radiation associated (50–52).

In conclusion, children exposed to therapeutic doses of X-rays to the head are at increased risk for the development of brain tumors. The low dose and short exposure time of modern diagnostic X-rays probably do not increase the risk for the fetus or the child.

Drugs. The possibility that exposure to barbiturate medications could increase the risk for childhood brain tu-

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Table 1: Methodological characteristics of major studies reviewed

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Case group*</th>
<th>Upper age limit</th>
<th>No. cases</th>
<th>No. controls</th>
<th>Source cases</th>
<th>Source controls</th>
<th>Source exposure information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fahra (10)</td>
<td>1, 2</td>
<td>4</td>
<td>101</td>
<td>202</td>
<td>DC, HR</td>
<td>BC</td>
<td>BC</td>
</tr>
<tr>
<td>Hakulinen (11)</td>
<td>1</td>
<td>14</td>
<td>219</td>
<td>219</td>
<td>PBR</td>
<td>Maternity district</td>
<td>Maternity district</td>
</tr>
<tr>
<td>Gold (12-14)</td>
<td>1</td>
<td>19</td>
<td>75</td>
<td>150*</td>
<td>PBR</td>
<td>BC, HR</td>
<td>INT</td>
</tr>
<tr>
<td>Zack, Hicks (15, 16)</td>
<td>1, 2</td>
<td>15</td>
<td>52</td>
<td>156*</td>
<td>HR</td>
<td>HR, uncle, neighbor</td>
<td>INT</td>
</tr>
<tr>
<td>Kwa (17)</td>
<td>1, 2*</td>
<td>14</td>
<td>132</td>
<td>264</td>
<td>DC</td>
<td>BC</td>
<td>BC</td>
</tr>
<tr>
<td>Peters (18)</td>
<td>1, 3</td>
<td>9</td>
<td>92</td>
<td>92</td>
<td>PBR</td>
<td>Friend or neighbor</td>
<td>INT</td>
</tr>
<tr>
<td>Hemminki (19)</td>
<td>1</td>
<td>14</td>
<td>282</td>
<td>408</td>
<td>PBR</td>
<td>Maternity district</td>
<td>Maternity district</td>
</tr>
<tr>
<td>Sanders (20)</td>
<td>1, 3*</td>
<td>14</td>
<td>1161</td>
<td>112,840</td>
<td>DC</td>
<td>DC</td>
<td>DC</td>
</tr>
<tr>
<td>Preston-Martín (21)</td>
<td>1</td>
<td>24</td>
<td>209</td>
<td>209</td>
<td>PBR</td>
<td>Friend or neighbor</td>
<td>INT</td>
</tr>
<tr>
<td>Greenburg (22)</td>
<td>1, 3</td>
<td>15</td>
<td>51</td>
<td>154</td>
<td>PBR</td>
<td>RDD or area sample</td>
<td>INT</td>
</tr>
<tr>
<td>Johnson (23, 24)</td>
<td>1, 2, 3</td>
<td>14</td>
<td>499</td>
<td>998</td>
<td>DC</td>
<td>BC</td>
<td>BC</td>
</tr>
<tr>
<td>Wilkins (25)</td>
<td>1</td>
<td>14</td>
<td>491</td>
<td>491</td>
<td>DC</td>
<td>BC</td>
<td>BC</td>
</tr>
<tr>
<td>Naito a (26)</td>
<td>1</td>
<td>14</td>
<td>338</td>
<td>676</td>
<td>PBR</td>
<td>BC</td>
<td>INT</td>
</tr>
<tr>
<td>Howe (27)</td>
<td>1, 3</td>
<td>19</td>
<td>74</td>
<td>138</td>
<td>HR</td>
<td>Random population sample</td>
<td>INT</td>
</tr>
<tr>
<td>Giusti (28)</td>
<td>1, 3</td>
<td>14</td>
<td>200</td>
<td>200'</td>
<td>HR</td>
<td>HR</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>Wilkins (29)</td>
<td>1</td>
<td>19</td>
<td>110</td>
<td>191</td>
<td>HR</td>
<td>RDD</td>
<td>INT</td>
</tr>
<tr>
<td>Birch (30)</td>
<td>1, 2, 3</td>
<td>14</td>
<td>78</td>
<td>156</td>
<td>HR</td>
<td>GPR, HR</td>
<td>INT</td>
</tr>
<tr>
<td>Kujiyen (31, 32)</td>
<td>1*</td>
<td>14</td>
<td>163</td>
<td>163</td>
<td>HR</td>
<td>RDD</td>
<td>INT</td>
</tr>
</tbody>
</table>

* Case group codings: 1, malignant brain tumor; 2, malignant nervous system tumor, not in brain; 3, benign nervous system tumor.

* In these studies, brain tumors were one of several childhood cancers investigated.

* BC, birth certificate; DC, death certificate; HR, hospital record; GPR, general practitioner record; PBR, population-based registry; RDD, random digit dialing; INT, interview.

* The number of study subjects vary from 70 to 78 in these three studies. Two controls were matched to a case: a healthy control and a control with another type of cancer.

* The number of controls totaled 924 for 298 childhood cancers, i.e., another type of cancer.

* 100 noncancer controls and 100 controls with cancer outside the nervous system.

* These studies included only the most frequent type of childhood brain tumors, astrocytomas.
mors was used as anticonvulsants and in general anesthesia. Barbiturates could also increase cancer risk by modifying the metabolism of other carcinogens (56). Barbiturates are used as anticonvulsants and in general anesthesia.

The observed risk associated with in utero exposure to barbiturates in the study of Gold et al. (12) was based on only six discordant case-control pairs. Furthermore, the association was significant only in the comparison of patients with cancer controls and not in the comparison with healthy children. Preston-Martin et al. (21) noted increased risk for the offspring of mothers who underwent general anesthesia during pregnancy. Five of the six exposed mothers reported that a barbiturate was used as the anesthetic. Kuijten et al. (31) did not observe an association with general anesthesia, and two small cohort studies (57, 58) did not observe an increased risk for in utero exposure to barbiturates. Goldhaber et al. (59) assessed barbiturate exposure from prenatal medical records and found no evidence for an association with in utero exposure or with duration of use or trimester of exposure. Although the numbers of exposed cases and controls in most studies are too small to reach a definite conclusion, in utero exposure to barbiturates does not seem to increase the risk for childhood brain tumors.

Studies of exposure to barbiturates in childhood are difficult to interpret since barbiturates are frequently used to treat seizures which can be caused by an occult brain tumor. The associations observed for childhood exposure to barbiturates (59) and anticonvulsants (21) are likely to be related to seizures due to brain tumors. Two other studies with small numbers of exposed children did not observe significant associations (12, 27).

The authors of three large follow-up studies in cohorts of adults treated with phenobarbital for epilepsy (60–62) have reported a higher than expected occurrence of brain cancer. However, the seizures that were treated with phenobarbital may have been early symptoms of undiagnosed brain tumors. Slowly growing, intracerebral tumors have been reported to give rise to seizures 20 years or more before diagnosis of the tumor (63). In summary, the literature does not strongly support a role for barbiturates in the etiology of childhood brain tumors.

Kuijten et al. (31) observed a 2-fold increase in risk for brain tumors in the offspring of mothers who used antinausea medication during pregnancy. Most exposed mothers reported having used Bendectin, but the odds ratio for Bendectin alone was not significantly elevated. Recall bias may have played a role, because Bendectin has been the subject of adverse publicity. Studies of several childhood cancers other than brain tumors also observed an association with antinausea medication (64–66), whereas studies of other childhood cancers did not (67). In the only study to assess exposure from medical records, McKinney et al. (68) did not observe an increased risk of childhood cancer in general or of central nervous system tumors associated with Bendectin or other antinausea drugs, but the power to detect a 2-fold increase in the risk for central nervous system tumors was low. Bendectin has been taken off the market. However, if one of Bendectin's component drugs is carcinogenic, other drugs that contain this component might still impose risk.

In utero exposure to two classes of medication that contain N-nitroso compounds or their precursors, antihistamines and diuretics, was associated with increased risk for childhood brain tumors in one study (21) but not in another (31). The role of N-nitroso compounds in the etiology of childhood brain tumors will be discussed below.

A case-control difference of borderline significance was observed for the maternal use of marijuana during pregnancy in one study (31). Other studies of childhood brain tumors do not appear to have studied maternal marijuana use. Studies of acute nonlymphoblastic leukemia (66) and rhabdomyosarcoma (69) observed significant associations. The finding is biologically plausible, since marijuana is a teratogen and has been associated with several medical conditions in neonates (71–77). Thus, maternal marijuana use during pregnancy should be studied further.

Other Medical and Birth-related Factors. Head and neck trauma to the child was studied in several investigations. To limit the possibility of recall bias, only trauma that required medical attention or caused unconsciousness was studied. Howe et al. (27) observed a more than 3-fold increased risk associated with injuries to the head or neck that required medical attention. Preston-Martin et al. (21) observed a similar increased risk of borderline significance with head injuries requiring hospitalization but not for those that required less medical attention. Kuijten et al. (31) did not find an association with head injury that caused unconsciousness. The findings in children are based on small numbers and therefore preclude a definitive conclusion. Only larger studies with more detailed questions on head injuries will be able to detect an association if one exists. An association of serious head trauma and subsequent adult meningiomas was observed in two case reports (78, 79) and three case-control studies (44, 46, 80). It has been suggested that increased cell proliferation after head injury increases the likelihood of tumor development (81).

Howe et al. (27) noted significant increases in risk associated with growth problems during the developmental years. An explanation might be that the tumor interfered with growth, for example, by affecting growth hormone levels. Other groups do not appear to have studied growth problems.

Several birth and maternal characteristics have been studied as possible risk factors. In two studies, cases were first births more frequently than were controls (13, 28), although other studies found no association (21, 31, 82) or an inverse relation (27). There is no evidence that twins have a higher risk for brain tumors, since studies show a similar (83) or even a lower (82, 84, 85) incidence in twins compared to single births. Two studies indicated that the frequency of brain tumors in childhood increased somewhat with advancing maternal age at birth of the index child (82, 86), but other studies did not observe this (13, 28, 31). Maternal history of miscarriage or stillbirth was protective in one study (31), but others found no association with previous miscarriages (28), stillbirths (82), or abortions (21, 27). It is unlikely that any of these factors plays a role of major significance, since

1 L. L. Robison, personal communication.
the associations are weak (odds ratios of 2 or less), inconsistent, and without obvious biological plausibility. However, it is possible that one or more of these factors is related to a specific histological category of brain tumors.

The findings for higher birth weight in association with childhood brain tumors may be more plausible, since it has been suggested that the association of higher birth weight with increased risk of childhood cancer might be related to a greater number of cells in heavier infants (13). A greater number of cells would result from more cell divisions, which would increase the accumulation of genetic errors, in turn leading to a higher probability of neoplastic transformation (81). A higher birth weight of children with brain tumors has been reported in two studies (13, 31) but not in others (21, 27, 82). Other childhood cancers, including Wilms’ tumor, leukemia, and neuroblastoma, have also been associated with higher birth weight (87). However, higher birth weight may very well be a marker for another, not yet identified factor that is causally related to childhood cancer.

**Electromagnetic Fields.** Since 1979 several studies have investigated the possibility that children living in homes near power lines or other electric transmission facilities or in homes with elevated magnetic fields have an increased risk of cancer. Most of these studies investigated all childhood cancers as a group. Only three studies provide information on central nervous system tumors.

Wertheimer and Leeper studied the power line wiring configurations near the homes of 344 cases, including 60 with brain tumors, and 344 control families (88). The wiring configurations (visible characteristics such as proximity and size of wires and proximity to origin of current) were categorized based on the potential current flow and hence potential level of magnetic field exposure. A significant 2.4-fold increased risk of brain tumors was associated with living in homes with power line wiring configurations in the two highest current categories at birth or at death of the index child. Similar results were obtained for other childhood cancers. The study has been criticized for the lack of blinding to the case-control status. The individuals who assessed the wiring configurations were under the supervision of a panel of independent experts. Careful attention was paid to overcoming the weaknesses in the previous studies. The power line wiring configuration was studied for residences of 59 brain tumor cases and controls, and a significant 2-fold increased risk was associated with high current configuration. Magnetic fields in the residences were measured while all appliances were on and while they were off for only 25 brain tumor case-control pairs, due to a limited response rate, and no significant results were obtained. For all cancers combined, a significant association with high wire configuration but not higher measured magnetic fields was observed.

All three studies observed elevated odds ratios. This consistency is less apparent in studies on childhood leukemia and adult cancers (91). It is clear that the results of these studies have to be interpreted cautiously, since the small size in some studies and methodological limitations affect the precision of the observed association. The fact that an association was observed with crude measurement but not with more precise measurement in the Savitz study (90) casts doubt on a causal role of electromagnetic fields in the development of childhood brain tumors. It has been suggested, however, that wiring configuration may be a better marker for long-term past exposure than one or a few measurements made years after the presumed development of the cancer. Another possibility is that living close to power lines is a confounder of another risk factor.

Studies have also shown that offspring of fathers exposed to electromagnetic fields or employed as electrical workers might be at increased risk (24–26, 32, 92). Occupational exposure will be discussed later in this paper.

**N-Nitroso Compounds.** Preston-Martin et al. (21) observed that mothers of children with brain tumors were exposed more often during pregnancy to substances containing N-nitroso compounds or their precursors than mothers of controls. These findings seem to fit animal experiments well, since certain N-nitroso compounds, called N-nitrosoureas, are potent inducers of neurogenic tumors after transplacental administration to rodents (93). Nitrosamines, another group of N-nitroso compounds, are relatively weak carcinogens in rodent fetuses, but it has been suggested that the human fetus may be more susceptible (94).
\textbf{Parental Occupational Risk Factors}  

The first investigators to study parental occupation as a risk factor for childhood cancers observed an association with occupations likely to have hydrocarbon exposure. For fathers of children with brain tumors, the excess hydrocarbon jobs consisted of motor-vehicle related occupations (10). Most later studies could not confirm the association with paternal hydrocarbon exposure (11, 15, 17, 20, 26), although two did observe increased risk (14, 29). The risk for motor vehicle mechanics or related occupations also could not be replicated (11, 14, 17, 19, 23, 32). However, a research group observed a 2-fold increased brain tumor risk for children living at diagnosis in areas with high traffic density, a marker for potential exposure to motor vehicle exhaust (106).

The first study specifically confined to brain cancer observed a strong association in children diagnosed under 10 years of age with paternal employment in the aircraft industry (18). In an extension of this study, the authors found that this risk could be attributed to solvent exposure (107). Olshan et al. (22) tried to replicate this finding in a study of 52 children diagnosed under 15. They found no association overall but did observe a statistically nonsignificant 2-fold elevated risk for children diagnosed under 10. Hicks et al. (16) observed a significant risk for offspring of Air Force fathers among 52 brain tumor cases. However, this excess was based on only four exposed cases, whose fathers had jobs with different exposures. Two other studies found no association with the aircraft industry for children under 15 (23, 32).
While several studies have reported an increased risk of childhood brain tumors with paternal exposure to paints, others have not. Odds ratios of 7.0 and 2.6 were observed for self-reported occupational exposure to paint and occupation of painter, respectively (18, 19). Two studies found nonsignificantly elevated risks for a job cluster, of which painters were a substantial constituent (29), and for father's occupation as a painter after the child's birth (32). Several other investigators observed no increase in risk for fathers employed as painters (11, 23, 25, 27). Thus, the data on paternal paint-related exposures and risk of childhood brain tumors are inconclusive. Paternal occupational exposure to paint has also been associated with an increased risk for childhood leukemia (108) and acute nonlymphocytic leukemia (109). An International Agency for Research on Cancer working group concluded that occupational exposure as a painter is carcinogenic, but could not specify the agents or type of painting exposure responsible (110).

Brain tumors in children have been associated with paternal employment in agriculture in some but not all studies. In one study, an approximately 2-fold increased risk was observed for employment at the time of the child's birth (25); in two other studies a similar but not significant risk was found for employment before the child's conception, but not during the pregnancy or after the child's birth (29, 32). Two other studies found no association with fathers who were farmers (10, 19). Gold et al. (13) observed a risk for children living on a farm, which could be a surrogate for parental employment in the agricultural industry. Thus, paternal employment in agriculture has not been consistently associated with brain tumors. Childhood leukemia has also been associated with employment in agriculture (111). Furthermore, several studies on adult brain tumors observed increased risk in agriculture-related professions (112–115); one of these studies found that the increased risk was attributable to the use of insecticides and fungicides, some of which contain precursors of N-nitrosoureas (112). Children exposed to insecticides were at increased risk of brain tumors in one study (13), and paternal and child exposure to pesticides were risk factors for childhood leukemia in another (109).

Two studies observed an association with paternal exposure to ionizing radiation. One observed a 2-fold higher risk when exposure was classified by industry of employment but not when classified by occupation (26). The other study involving only 52 nervous system cancers also had inconsistent results (16): the association was present for occupations with less exposure but not for those with more exposure and was observed only in analyses by occupation and not in those by industry. Another study did not observe an association between ionizing radiation and childhood astrocytoma (32).

Two studies observed modest and statistically insignificant increases in risk associated with paternal electromagnetic field exposure (24, 26). Another study observed an insignificant increase in risk for probable exposure to electromagnetic fields but not for definite exposure (32). Electrical assembling, installing, and repairing occupations were associated with increased risks in one study (25). Two other studies could not replicate this finding (24, 32) but observed increased risk for subgroups of this category: occupation as a construction electrician at the birth of the child (24) and electrical and electronic re-pairmen in the preconception period (32). Wilkins et al. (92) identified a space-time cluster of six childhood primary intracranial tumor cases among offspring of parents employed at the same electronics firm (standard incidence ratio = 73.3; 95% confidence interval = 26.5–157.5). Some studies have shown an association between presumed occupational magnetic field exposure and leukemia (111, 117) and adult brain tumors (118, 119). Although the findings in the various studies of childhood brain tumors are somewhat erratic and may reflect chance observations from exploratory analyses, there is a certain consistency in the studies. A similarly arguable consistency was observed among the previously discussed studies concerning electromagnetic field exposure of the child.

Other paternal occupations and industries have been reported as possible risk factors, but the data are very limited. Kwa and Fine (17) observed an increased risk with paternal occupation as paper or pulp mill worker. Data from two other studies are consistent with an increased risk, although the findings were not statistically significant (26, 32). Two groups of researchers observed an association with paternal occupation of printer, which was significant and strong in one study, especially in the subgroup of graphic arts workers (23), and not significant in another (32). Another group did not observe an association (25). A strong association with machine repairmen was observed in one study (19); another study (14) observed an insignificant increased risk in the offspring of factory workers, machinists, or steelworkers. Others studying similar job groupings could not replicate these findings (17, 23, 25). In two studies, associations with paternal employment in the petroleum industry were reported, although neither was statistically significant (23, 26). Increased risks were also observed for self-reported exposure to chemical solvents (18), fathers employed as chemical and drug salesmen (23), fathers with probable heavy exposure to chemicals and petroleum products (23), workers in the construction industry (25), and fathers employed in metal-related occupations (25, 29). Parental occupational exposure to metals has also been associated with Wilms' tumor, acute nonlymphocytic leukemia, hepatoblastoma, and retinoblastoma (67, 109, 120, 121).

Maternal occupations are less frequently studied than paternal occupations. Excess risk was observed for factory workers (19), bakers (19), nurses (32), and women who used protective clothing or equipment at work (21), reported skin exposure to chemicals (18), or reported inhalation of chemicals, fumes, and dusts (18). Other studies did not observe excess risks (14, 26, 29) for these occupations or for any maternal occupation. In all studies, only a small number of women were employed in jobs with chemical exposures, and observed risk factors have been reported only once. Thus, at present there is no substantial evidence that maternal occupational exposure causes risk for brain tumors in the offspring.

In two studies, case parents were more likely to have completed higher education (32) or to hold white collar and professional jobs with no obvious carcinogenic exposure (20, 32). The association with higher education and professional occupation may reflect an increased incidence of childhood brain tumors in the higher social classes, as has been reported for some other childhood cancers (19, 20) and adult brain tumors (122). However,
two other studies on childhood brain tumors found reduced risk in the offspring of more educated parents (27, 29), and one study found no association with socioeconomic status (132). In summary, most data on parental occupational exposure are inconsistent and need replication. Most findings implicate work environments but provide little information about specific agents. For example, the carcinogenic agent in metal-related jobs may not be a metal at all, but rather substances used with metals, such as solvents. In addition, epidemiological studies may not be able to determine the time period of risk for each exposure since individuals tend to have the same jobs over time. Laboratory studies and molecular biology may help in determining the timing of exposure that confers risk. Agricultural exposures and exposure to paints and electromagnetic fields seem to be the most deserving of attention in future studies.

Familial Risk Factors

Family History of Cancer. Some inherited conditions, such as neurofibromatosis (124), tuberous sclerosis (125), nevoid basal cell syndrome (124, 126), Turcot syndrome (127), and Li-Fraumeni syndrome (128–131), are known to predispose to brain tumors in affected individuals. Apart from these conditions, there are numerous other case reports of familial brain tumor occurrences, suggesting a hereditary susceptibility. Hereditary cancer occurs at a younger than expected age (132). Thus, the occurrence of brain tumors in children may be a marker for a hereditary susceptibility in some families.

Several researchers studied the cancer incidence in families of children with brain tumors (31, 131, 133–137) (Table 2). 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 (133, 134) and the hematopoietic/lymphatic system (135), is also increased in some studies. The risk to the twin of a child with a brain tumor is difficult to assess due to small numbers. Two of the 11 sibling pairs of which both members had a brain tumor were like-sex twins in one study (134), and one identical twin pair, both with brain tumors, was observed among 25 twin pairs with at least one affected member (136).

The occurrence of nervous system tumors in parents of affected children was increased 5-fold in the study of Farwell and Flannery (135). However, the risk in first-degree relatives was not increased in the study by Giuffre et al. (28). In a study of childhood astrocytoma, cases were more likely than controls to have a first- or second-degree relative with cancer, a brain tumor, or breast cancer (31). The association was noted especially for children with brain tumors diagnosed before 5 years of age. In another childhood brain tumor study, no excess of brain tumors among relatives was observed, but cases were significantly more likely to have a first-degree relative with colon cancer (137). Relatives of adult brain tumor patients are at increased risk for a brain tumor in some studies (138–140) but not in another (141). One study observed an excess for cancer of any site, breast cancer, and lung cancer in relatives of adult male brain tumor patients (142).

Thus, most studies observed a modestly elevated risk for brain tumors or other cancers in relatives of brain tumor patients. Even a slightly elevated risk for family members of a series of brain tumor patients could imply a substantial genetic susceptibility for a proportion of patients (143). Furthermore, some brain tumors in children without positive family histories could be due to new germinal mutations. Under conditions of high mortality, especially in previous generations, few individuals who developed tumors at young ages will have produced offspring. Thus, the number of familial cases observed is an underestimate of the number of brain tumors that have a genetic origin. No malignancies were observed in a study of 385 offspring born to 205 survivors of childhood central nervous system tumors (144), but the length of follow-up of these families was short.

Cases with a genetic predisposition to cancer are not only expected to develop cancer at a younger than usual age but also to develop multiple tumors more frequently. For example, patients with hereditary retinoblastoma often have bilateral disease and develop second primary tumors more frequently than sporadic retinoblastoma patients (50, 51, 132). Similarly, multifocal brain tumors or a second primary tumor after a brain tumor may signal the presence of a hereditary syndrome. The multifocal occurrence of cerebral gliomas is well documented, with an estimated frequency of 5–6% (125), and provides additional evidence for a genetic etiology of brain tumors. Children with brain tumors are also at increased

<table>
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<th>Table 2</th>
<th>Cancer in family members of children with brain tumors</th>
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<tr>
<td>Author (reference)</td>
<td>Relative and tumor</td>
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<tr>
<td>Miller (131)</td>
<td>Sibling of child with brain tumor</td>
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<td>Draper (132)</td>
<td>Sibling of child with brain tumor</td>
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<td>Farwell (133)</td>
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<td>Parent of child with intracranial tumor</td>
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<tr>
<td>Kuijten (135a)</td>
<td>First- and second-degree relative of child with astrocytoma</td>
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<tr>
<td>Bondy (135)</td>
<td>First-degree relative of child with brain tumor</td>
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</table>

* Ratio of observed:expected cancers, based on incidence data (Draper, Miller, Farwell, Bondy), or ratio of case exposed/control unexposed:case unexposed/control exposed (Kuijten).
* RR, relative risk (Draper, Miller, Farwell, Bondy) or odds ratio (Kuijten).
* Ninety-five % confidence interval.
* d Tumors in relatives were not validated in this study.
* Including benign brain tumors.
risk for second tumors (50, 51), although the late effects of therapy for the first tumor probably account for a large fraction of the second malignancies.

In summary, several observations imply genetic factors in familial cases of central nervous system tumors other than those occurring within the known genetic conditions. If a genetic predisposition underlies these familial clusters, several genes probably are involved. A gene may be specific for glioma or medulloblastoma, since brain tumors occurring within a family are generally concordant with respect to these histologies (145). Specificity also occurs for medulloblastoma in the nevoid basal cell syndrome (124, 126). Case reports suggesting a gene for more specific types of glioma, such as for astrocytoma, glioblastoma, and oligodendroglioma, also exist (145). There are even rare reports of concordance of both tumor type and location, such as a father and son, both with low-grade astrocytomas in the rhombencephalon (146). Remarkable specificity is also suggested by the report of identical twins, each of whom expired from a glioma that consisted of two parts, one oligodendroglial and one astrocytic (147).

It is also possible that a less specific gene exists, predisposing to both glioma and medulloblastoma. Four sibling pairs with medulloblastoma in one sibling and glioma in the other are cited by Draper et al. (134), although it was not stated whether these tumors were histologically verified. The inherited condition neurofibromatosis also predisposes to gliomas and medulloblastomas, as well as other cancers (124, 148). A gene predisposing to brain tumors as well as other cancers is thought to explain the colon and brain tumor aggregation in Turcot syndrome (127) and the aggregation of several cancers in Li-Fraumeni syndrome (128–131). A similar gene with broad specificity could explain the mentioned aggregation of cancer at several sites in families of children with a brain tumor (31, 133–135, 137).

Although some evidence suggests the existence of genes predisposing to brain tumors, the mode of inheritance is not clear. Despite the large number of case reports of brain tumors in families, there are only a few documented examples of brain tumors in three or more generations or in extended family pedigrees. One report on a family with seven brain tumors (five proven gliomas) in three generations suggests autosomal dominant inheritance (149), and another study of an inbred family with 10 gliomas in five generations is consistent with autosomal recessive or possibly X-linked inheritance (150).

Theoretically, the clustering of brain tumors in these families is compatible with an environmental as well as a genetic etiology. However, the mathematical model of Khoury et al. (151) shows that for most environmental factors that confer an increased risk for disease of 10-fold or less, clustering of these factors among relatives leads to only a slight and often unmeasurable excess in aggregation of disease. This finding suggests that genetic factors may indeed play a major role in causing the observed familial aggregation. Nevertheless, family studies are needed to show that the pattern of inheritance fits a genetic model. Family studies can best be carried out in families of children with brain tumors, since results from the reviewed studies suggest that a childhood brain tumor is a marker of genetic susceptibility.

**Family History of Neurological Disorders.** Family history of other conditions has been associated with childhood brain tumors as well. Gold et al. (13) observed a significantly increased occurrence of epilepsy in siblings of cases, although this finding was based on only nine discordant pairs. Two other studies did not observe an increased incidence of epilepsy in first-degree relatives (28, 31). Thus, a causal role of a family history of seizures in the etiology of childhood brain tumors is not evident.

Kuijten et al. (31) observed a significantly increased occurrence of mental retardation in first- and second-degree relatives of cases. However, no distinction was made in the severity of retardation, and reporting bias may have played a role. In a recent study of adult gliomas, a nonsignificantly increased incidence of mental retardation in first- and second-degree relatives was observed (142). A significant excess of neurological disorders was observed in mothers of children with brain tumors in a study, which was attributable to migraine (30). In the study by Gold et al. (13), three cases and no control mothers had suffered a stroke early in life, but Kuijten et al. (31) did not observe an increased number of early strokes among first- or second-degree relatives of children with astrocytoma. Future studies should obtain more detailed information on family history of neurological disorders.

**Potential Use of Biomarkers**

Biological markers of internal dose and biologically effective dose could improve epidemiological studies, including those of childhood brain tumors. For example, ascorbate, N-nitroso metabolites, and N-nitroso DNA adducts can be measured in body fluids and would measure exposure more accurately than questionnaires. However, the evidence linking a specific substance or class of substances to childhood brain tumors is weak. A complication of using biomarkers to study childhood brain tumors is the possibility that exposures of the mother, father, and/or child might be etiologically relevant. Further research is needed to determine the most likely causal agents and the person (mother, father, or child) whose exposure is most likely to be causal, so that appropriate biomarkers can be chosen.

After biomarkers are chosen, their use in the study of childhood brain tumors will still be complicated by the case-control design of nearly all investigations. As etiological exposures were in the past, biomarkers that measure current exposure are problematic. Current adult diet reflects past adult diet fairly well (152), and therefore, biomarkers of dietary substances might be appropriate in case-control studies of adults. However, the most likely dietary risk factors for childhood brain tumors are childhood diet and maternal diet during pregnancy. Measurement of substances in body fluids several years later may not adequately reflect levels during the critical time period. Many women while pregnant take vitamin and mineral supplements and change their diet in other ways as well. Children’s diets also change dramatically as they get older. The problem of retrospective assessment of exposure could be overcome if specimens collected for other purposes were used. However, because of the rarity of childhood brain tumors, specimens would have to be available on very large populations to be useful. Because the exposures likely to be relevant are not substances routinely measured, stored specimens would be needed and only stable substances would be worth.
measuring. In summary, the use of biomarkers in the study of childhood brain tumors seems premature at present and presents problems of retrospective assessment of exposure.

Conclusion
We have discussed the results of epidemiological studies on risk factors for childhood brain tumors. The only factors that are consistently associated with an increased risk for childhood brain tumors are therapeutic cranial irradiation and certain genetic conditions.

The need for further research is obvious. With clear differences in their descriptive epidemiologies, the major tumor types, astrocytoma and primitive neuroectodermal tumor, are likely to differ etiologically. The separate study of these two tumor types is likely to be the most efficient way to resolve inconsistencies among previous observations and speed progress in identifying etiological factors.

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I. Review: Risk Factors For Childhood Brain Tumors


Risk factors for childhood brain tumors.

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