Review

Childhood Brain Tumors and Exposure to Tobacco Smoke

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Abstract

Brain tumors are the second most common cancer in children after leukemia, yet the etiology of childhood brain tumors remains unknown. Tobacco smoke contains several dozen compounds that are known to be carcinogens. Among these are N-nitroso compound precursors, principally tobacco-specific nitrosamines. Although smoking has not been identified as a significant risk factor for the development of brain tumors in adults, fetuses and infants have incompletely formed blood-brain barriers that may allow the passage of carcinogenic tobacco metabolites into the central nervous system and initiate the formation of neural tumors. In this review, we present data from case-control and cohort studies published between 1971 and 1995 that examined the relationship between parental smoking during pregnancy and childhood brain tumors (CBTs). The majority of these studies found little association between CBTs and maternal smoking before or during pregnancy or between CBTs and maternal exposure to passive smoke during pregnancy.

Introduction

Brain tumors account for 20% of all incident cancer cases and deaths in children. With an incidence rate of 3 per 100,000 children per year, CBTs are the second most common cancer after leukemia in those under age 20 years, and yet the etiology of CBTs remains uncertain (1). In epidemiological studies conducted to date, established risk factors, including genetic predisposition and exposure to ionizing radiation, and suspected risk factors such as head trauma have accounted only for a small proportion of incident cases. Despite recent dramatic improvements in diagnostic, surgical, and treatment techniques, mortality rates have declined only modestly in the past 3 decades. Currently, only about 60% of children survive 5 years after the initial diagnosis (1). Many of these survivors face cognitive deficits, paralysis or paresis, visual losses, hormone deficiencies, primary tumor spread, or second malignancies (2–5) and ultimately die from their disease. Depending on tumor location, only 4–27% of CBT patients reported no deficits 5 years after initial surgery (5). Epidemiological investigation into the etiology of CBTs will lead to primary prevention of this disease if preventable risk factors are observed and proper education follows.

Tobacco smoke contains several dozen compounds that are known to be carcinogens. Among these are precursors to NOCs, principally tobacco-specific nitrosamines (6, 7). In several reports, analyses of placental and umbilical cord tissues of human fetuses exposed to maternal smoking have confirmed the passage of tobacco metabolites and carcinogens across the placenta (8–11), and animal studies have demonstrated that certain NOC and NOC precursors (nitrosamides) are effective nervous system carcinogens in various species, especially when exposure is transplacental (12). In another report, exposure of male rats to ethylnitrosourea before mating was found to increase the incidence of neurogenic tumors in offspring (13). Thus, nitrosamines such as ethylnitrosourea and possibly also nitrosamines, such as the tobacco-specific nitrosamines in tobacco smoke, and its metabolites may have mutagenic effects on germ cells as well as on the developing fetus, possibly leading to subsequent childhood malignancies. In fact, reports from three case-control studies have noted positive associations between maternal smoking during pregnancy and various childhood cancers with ORs between 1.6 and 2.9 (14–16).

In a recent review of the literature that examined risk factors for adult brain tumors (17), most studies found little relationship between active smoking and brain tumors (18–27), or they found that elevations in risk (OR = 1.2–1.8) were either not significant (23, 25, 27) or confined to subjects’ use of unfiltered cigarettes (25). One cohort study that examined the relationship between passive smoke exposure and adult brain tumors demonstrated a significantly elevated risk (one-tailed \( P = 0.004 \)) among nonsmoking women whose husbands smoked (RRs between 3.0 and 6.3, varying by numbers of cigarettes smoked/day; Ref. 28). Another study that examined passive smoke exposure and adult brain tumors found no elevation in risk for the development of gliomas but found a significantly elevated risk for meningiomas, especially among women (RR = 2.7; 95% CI = 1.2–6.1) (27). The relationship between smoking and adult brain tumors has been variable in epidemiological studies to date, and compared with adults, a greater effect of smoking on the central nervous system of fetuses and infants is possible because of the immature blood brain barrier.

This report reviews English language case-control and cohort studies on CBTs and exposure to tobacco smoke that were published between 1971 and 1995. Several analyses have looked specifically at parental smoking and CBTs with variable results (14–16, 29–41). Overall, most reports have shown no strong associations between CBTs and maternal smoking before conception (ORs between 0.4 and 0.9) or during pregnancy (ORs between 0.9 and 1.6; Refs. 14, 32, 36–41). One smaller
study reported an OR = 5.0 (P = 0.22) for the association between continued maternal smoking during pregnancy and CBTs (30). A few analyses have shown positive associations between paternal smoking or living with a smoker during pregnancy and CBTs (ORs between 1.5 and 2.2; Refs. 16, 31, 38, 40). All of the reviewed case-control studies examined smoking before and/or during pregnancy and the development of subsequent CBTs. Only three reports (37, 38, 40) considered effects of early childhood passive exposure to tobacco smoke (ORs between 0.64 and 2.9 for maternal and paternal smoking by histological type and site of brain tumor) despite other analyses that have shown positive associations between passive exposure to tobacco smoke as an adult or child and various malignancies, including brain tumors (27, 28, 42–44).

Case-Control Studies

The case-control studies reviewed below are presented in Table 1 and in the text by order of publication date. A distinction is made between maternal and paternal smoking before pregnancy and during pregnancy. ORs and 95% CIs or P values are presented as available in the original publications.

An exploratory case-control study was conducted in Baltimore (MD) between 1965 and 1975 (30). The study data included 84 CBT patients who were diagnosed by age 19 years and two control groups totaling 151 children. CBT patients were identified from hospital records and tumor registries of 15 Baltimore hospitals. Population-based control subjects were 73 children with no known malignant disease selected from Maryland birth certificates and matched to CBT patients on gender, date of birth (±1 year), and race. Hospital control subjects consisted of 78 children with malignancies other than brain tumors who were matched to CBT patients on gender, age, race, and date of age at diagnosis. Parents of cases and controls were interviewed regarding a variety of prenatal and family history topics, including maternal smoking habits. The role of maternal smoking before pregnancy with the index child yielded no differences between CBT patients and either set of control subjects. An increased risk of CBTs was reported for mothers who continued smoking during pregnancy compared with mothers who quit smoking during pregnancy (OR = 5.0; P = 0.22). Nonsmokers were excluded from this analysis.

A population-based case-control study conducted in Los Angeles (CA) identified 209 CBT patients through the Los Angeles County Cancer Surveillance Program who were <25 years old at the time of diagnosis (1972–1977; Ref. 31). Control subjects (n = 209) who were neighbors or friends of CBT patients were identified by patients’ mothers and individually matched to CBT patients on gender, race, birth year (±3 years), and socioeconomic status. Telephone interviews were conducted with mothers of CBT patients and control subjects. Results showed no association between maternal smoking during index pregnancy and CBTs, but they did reveal an elevated OR of 1.5 (one-sided P = 0.03) for case mothers living with a smoker during pregnancy as compared with control mothers.

A Swedish case-control study examined the effects of maternal smoking during pregnancy and the risk of childhood cancer (14). Maternal smoking information was collected from parents of 305 cancer patients, including 43 brain/nervous system tumor patients and 340 control subjects who were children with insulin-dependent diabetes mellitus. Both cancer patients and control subjects, ages 0–16 years, were regularly treated at 37 pediatric departments throughout Sweden and were frequency matched by gender and date of diagnosis (1976–1981).

The analyses showed no association between maternal smoking during pregnancy and CBTs.

A case-control study of CBTs in children under age 15 years at the time of diagnosis was conducted in Great Britain between 1980 and 1983 (32, 35, 45). The data from this report were taken from a larger study conducted by the Inter-Regional Epidemiological Study of Childhood Cancer, which was established to investigate etiologies of childhood cancers. CBT patients (n = 78) were identified in three Health Service regions of Great Britain (West Midlands, Yorkshire, and North Western) through pediatric oncology centers and cancer registries. Two sets of control children were matched individually to cases by gender and age (within 6 months). General practitioner controls were selected randomly for each case from each general practitioner’s roster of patients. Hospital controls were selected from children admitted to the hospital for minor illnesses or accidents. Interviews in either the home or hospital were conducted with mothers and fathers or other relatives, as available. No association was noted between mothers’ and fathers’ smoking before or during pregnancy.

A case-control study was conducted in Ontario, Canada, between 1977 and 1983 (33). The report included 74 CBT cases diagnosed through age 19 years and who were identified mainly in the two Toronto hospitals that treated most CBT patients in the area. The 138-population-based control subjects were matched to cases by gender and date of birth (within 2 years). The fathers of the potential control subjects were identified from a random sample of the Ontario government adult population lists. A list of the men’s children was generated by telephoning a sample of men from these lists and asking them the ages of their children. From this list, two control subjects/case were selected randomly. Biological mothers were interviewed in person for 95% of CBT patients and 92% of control subjects. When possible, fathers also were interviewed (39% CBT patients and 31% control subjects). Exposures were classified as “ever” versus “never” exposed to maternal and/or paternal smoking during pregnancy. ORs were adjusted for age at the time of diagnosis. No significant positive associations were noted between maternal/paternal smoking and CBTs.

CBT patients were under age 15 years at the time of diagnosis in 1980–1986 in a case-control study of 163-matched pairs that investigated risk factors for astrocytoma, the most common form of CBT (34). Cases were identified from tumor registries of eight hospitals in Pennsylvania, New Jersey, and Delaware. Control subjects were selected by random digit dial and were matched to cases on age (within 1–3 years depending on age), gender, race (black or non-black), and telephone exchange. The study revealed no elevated risk for parental smoking during pregnancy.

A case-control study was conducted in Denver (CO) that examined prenatal exposure to parental smoking and childhood cancer (15). Cases were 48 CBT patients. Patients, ages 0–14 years, were diagnosed between 1976 and 1983 and were identified through the Colorado Central Cancer Registry and through the medical records of hospitals that did not report to a cancer registry. Random digit dial was used to select 196 control subjects who were individually matched to patients by age (±2 years) and telephone exchange. In-person or telephone interviews were conducted with parents. Maternal smoking during pregnancy was reported by trimesters and showed no association with CBTs (ORs ranged between 0.8 and 1.0). Analysis of paternal smoking in the absence of maternal smoking yielded an OR of 1.9 (95% CI = 0.9–4.2). However, adjustment for the fathers’ educational levels reduced the OR to 1.6 (0.7–3.5).
### Table 1  Childhood brain tumors and parental smoking: summary of case-control and cohort studies

<table>
<thead>
<tr>
<th>Year published, 1st author, years of diagnosis, CBT patients, control subjects, study location</th>
<th>CBT patients/ control subjects/ cohort (n)</th>
<th>Matching criteria</th>
<th>OR (95% CI)* Maternal smoking (Ever vs. never)</th>
<th>OR (95% CI)* Paternal smoking (Ever vs. never)</th>
<th>% of direct paternal interviews</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>1979, Gold (1965–1975)</td>
<td>84</td>
<td>Hospital controls: individually matched on gender, race, date and age at diagnosis. Population controls: 7.0</td>
<td>During pregnancy:</td>
<td>Hospital controls: 5.0 (P = 0.22)</td>
<td>Did not examine effects of paternal smoking. ORs compare mothers who continued to smoke during pregnancy to mothers who quit during pregnancy. Nonsmokers are not included in calculations.</td>
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<tr>
<td>1982, Preston-Martin (1972–1977)</td>
<td>209</td>
<td>Individually matched on gender, date of birth (± 1 yr), race</td>
<td>During pregnancy: 1.1 (one-sided P = 0.42)</td>
<td>During pregnancy: 1.5 (one-sided P = 0.03)</td>
<td>All data obtained from mothers of CBT patients/ control subjects. No dose response data presented. Paternal OR reflects mother living with any smoker during pregnancy.</td>
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<tr>
<td>1986, Sjørenfeldt (1978–1981)</td>
<td>43</td>
<td>Frequency matched by date of diagnosis and gender</td>
<td>During Pregnancy: 1.0 (1–9 cigarettes/day)</td>
<td>0.86 (10+ cigarettes/day)</td>
<td>Study examined effects of maternal smoking during pregnancy and risk of childhood cancer. Analysis included 305 cancer patients of whom 43 were diagnosed with brain or nervous system tumors.</td>
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<tr>
<td>1986, McKinney (1980–1983)</td>
<td>78</td>
<td>Individually matched on gender and age (± 3 yrs), socioeconomic status, gender, race</td>
<td>During pregnancy: 1.1 (0.52–2.4)</td>
<td>1.0 (0.53–2.4)</td>
<td>No association found for parental smoking before or during pregnancy. No dose-response effect.</td>
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<tr>
<td>1989, Howe (1977–1983)</td>
<td>74</td>
<td>Individually matched by age and gender</td>
<td>During pregnancy: 1.4 (0.70–3.0)</td>
<td>1.8 (0.62–2.1)</td>
<td>31%</td>
<td>Both mothers and fathers were interviewed when control possible. Did not examine dose response.</td>
</tr>
<tr>
<td>1990, Kuitjen (1980–1986)</td>
<td>163</td>
<td>Individually matched by age, ethnicity, telephone area code and prefix</td>
<td>During pregnancy: 1.0 (0.6–1.7)</td>
<td>0.8 (0.5–1.3)</td>
<td>Both mothers and father were interviewed when possible. Mother provided proxy interview if father was unavailable.</td>
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<tr>
<td>1991, John (1976–1983)</td>
<td>48</td>
<td>Individually matched by age (± 3 yrs), gender, telephone prefix</td>
<td>Before pregnancy: 0.9 (0.4–2.1)</td>
<td>1.9 (0.9–4.2)</td>
<td>Study examined effects of parental smoking on various childhood cancers. Analysis included a total of 223 cancer patients of whom 48 were CBT patients.</td>
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<tr>
<td>1993, Gold (1977–1981)</td>
<td>361</td>
<td>Individually matched by age, gender, mother’s ethnicity, area code, telephone prefix</td>
<td>Ever smoked: 0.92 (0.71–1.2)</td>
<td>1.1 (0.82–1.4)</td>
<td>No dose-response effect.</td>
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* OR: Odds Ratio; CI: Confidence Interval

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Table 1 Continued

<table>
<thead>
<tr>
<th>Year published, 1st author, years of diagnosis, CBT patients, control subjects, study location</th>
<th>CBT patients/ control subjects/ cohort (n)</th>
<th>Matching criteria</th>
<th>OR (95% CI)* Maternal smoking (Ever vs. never)</th>
<th>OR (95% CI)* Paternal smoking (Ever vs. never)</th>
<th>% of direct paternal interviews</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994, McCredie (1985–1989) CBT patients: New South Wales Central Cancer Registry Control subjects: Electoral roll</td>
<td>82</td>
<td>Frequency matched by age (± 1 yr) and gender</td>
<td>Mother only before pregnancy: 0.4 (0.1-1.3) During pregnancy: 0.9 (0.5-1.8)</td>
<td>Father only before pregnancy: 2.0 (1.0-4.1) During pregnancy: 2.2 (1.2-3.8)</td>
<td>55% Increased paternal risk confined to data supplied by mother (proxy); not in data directly from father. No dose-response effect.</td>
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<tr>
<td>1994, Filippini (1985–1988) CBT patients: 8 hospitals Control subjects: Random selection from records of National Health Service Italy</td>
<td>91</td>
<td>Individually matched by age, gender, and residence</td>
<td>At any time: 1.2 (0.8-1.9) During pregnancy: 1.7 (0.8-3.8)</td>
<td>Nonsmoking mother exposed to passive smoke during pregnancy: 2.2 (1.1-4.5) &gt;2 h/day</td>
<td>45% Statistically significant dose-response relationship found for increasing levels of passive smoke exposure (P for trend = 0.02)</td>
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<tr>
<td>1994, Bunin (1986–1989) CBT patients: Children’s Cancer Group, including 33 hospitals Astrocytoma patients: Random digit dial United States, Canada Control subjects: Random selection from Electoral roll</td>
<td>82</td>
<td>Frequency matched by race, birth yr, and telephone area code and prefix</td>
<td>Ever (astrocytoma/PNET): 1.1 (0.7-1.6) During pregnancy (astrocytoma/PNET): 1.0 (0.6-1.7) Passive exposure during pregnancy (astrocytoma/PNET): 0.9 (0.6-1.5)</td>
<td>Ever (astrocytoma/PNET): 1.1 (0.7-1.6) During pregnancy (astrocytoma/PNET): 1.0 (0.6-1.7)</td>
<td>Adjustment made for proxy vs. direct paternal interview. No dose response effect. Astrocrytomias adjusted for income level.</td>
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<tr>
<td>1994, Cordier (1985–1987) CBT patients: 13 hospitals Control subjects: Random sample from region from national population census in France supplemented with random sample from regional municipal telephone directories</td>
<td>109</td>
<td>Frequency matched by birth yr</td>
<td>During pregnancy: 1.6 (0.7-3.5) Active or passive exposure during pregnancy: 1.5 (0.8-2.8)</td>
<td>OR adjusted for age, sex, maternal age. Examined the effects of childhood exposure to passive smoke and found a statistically significant elevated risk: 2.3 (1.1-4.6)</td>
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<tr>
<td>1995, Norman (1984–1991) CBT patients: Tumor registries Control subjects: Random digit dial</td>
<td>540</td>
<td>Frequency or individually matched by gender, birth yr, and age at diagnosis</td>
<td>Before pregnancy: 0.82 (0.64-1.0)* During pregnancy: 0.98 (0.72-1.3)*</td>
<td>Before pregnancy: 1.1 (0.84-1.3)* During pregnancy: 1.2 (0.90-1.5)*</td>
<td>77% No dose-response effect.</td>
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<tr>
<td>1971, Neutel (1958–1961) CBT patients: Ontario death certificates and cancer clinics; direct follow-up of British subjects. Cohort: 10 Ontario hospitals (1958–1961); all births in England and Wales (3/5/58–3/9/58)</td>
<td>84,947</td>
<td></td>
<td>During pregnancy: RR = 1.6 (0.56-4.6) (none or &lt;1 pack/day vs. ≥1 pack/day)</td>
<td>Did not examine effects of paternal smoking.</td>
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<tr>
<td>1992, Pershagen (1982–1987) CBT patients: Swedish Cancer Registry Medical Birth Registry</td>
<td>81</td>
<td></td>
<td>During pregnancy: RR = 0.9 (0.48-1.6) (&lt;10 cigarettes/day)</td>
<td>Did not examine effects of paternal smoking</td>
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<td></td>
<td></td>
<td></td>
<td>During pregnancy: RR = 1.1 (0.55-2.1) (≥10 cigarettes/day)</td>
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</table>

*95% CI or P values are presented as available in original papers.

†McKinnney paper presents smoking data and a brief description of methods; Birch paper presents the methods of the study in more detail.

© Adjusted for age at diagnosis or selection for controls.

‡Exposure to sidestream smoke during pregnancy.

§First OR not adjusted; second OR adjusted for father’s educational level.

| SEER, Surveillance, Epidemiology and End Results. |

★Smoked <1 pack/day.

☆Smoked ≥1 pack/day.

☆Adjusted for maternal race.

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A population-based case-control study included questions on parental smoking in relation to CBTs (37) and included 361 CBT patients under age 18 years who were diagnosed between 1977–1981. The patients were obtained from eight Surveillance, Epidemiology and End Results program registries, and 1083 population-based control subjects were matched to cases by age, gender, mother’s ethnicity, and area code and telephone exchange. Information on pregnancy and maternal smoking was obtained directly from the mother. Information on paternal smoking was obtained directly from fathers in 71% of interviews. The results indicated no significant increased risk with smoking exposure was found for any category.

A population-based case-control study of CBTs diagnosed in children 0–14 years old was conducted in New South Wales from 1985 through 1989 (38). Cases (n = 82) were identified from the New South Wales Central Cancer Registry, and mothers of 164 control subjects were identified from a random sample of the Electoral Role of women 20–55 years old. Control subjects were matched to CBT patients by age (± 1 year) and gender. In-person interviews were conducted with mothers of CBT patients and control subjects, and telephone interviews with fathers were conducted for 55% of CBT patients and 37% of control subjects. No association was found between mothers smoking either before or during pregnancy and CBTs. After adjustment for father’s educational level, the father’s smoking status before and during pregnancy resulted in elevated ORs of 2.0 (95% CI = 1.0–4.1) and 2.2 (95% CI = 1.2–3.8), respectively. However, this increased risk was found only among fathers who were not interviewed but who had data provided by the mother (ORs were 5.5 and 4.2 for fathers who smoked before and during pregnancy) and not among fathers who were interviewed directly (ORs were 1.0 and 1.1). No dose-response effect was seen when data were stratified by frequency of use of cigarettes.

A population-based case-control study was conducted in Italy to examine the effects of maternal tobacco smoking and maternal passive smoke exposure during pregnancy (16). CBT patients (n = 91) were identified from neurosurgery departments, pediatric oncology centers, and outpatient radiology clinics of eight major hospitals. All CBT patients had been diagnosed with a primary brain tumor between 1985 and 1988, were under age 15 years at the time of diagnosis, and were residing in one of three provinces of Northern Italy. Control children (n = 321) were randomly selected from computerized records of the Regional Health Service that provides coverage to children from the same area. The control children were individually matched to CBT patients on age, gender, and residence, and their parents were interviewed. The study found a somewhat elevated risk estimate for CBTs with maternal smoking during pregnancy (OR = 1.7; 95% CI = 0.8–3.8). They also reported a dose-response relationship with CBTs for passive smoke exposure (P trend = 0.02) with light smoke exposure, > 2 h/day, (OR = 1.7; 95% CI = 0.8–3.6) and heavy smoke exposure, > 2 h/day, (OR = 2.2; 95% CI = 1.1–4.5) among nonsmoking mothers.

A case-control study was conducted to investigate risk factors for the two most common types of CBTs, astrocytic glioma and PNET (41). Children with astrocytic gliomas (n = 155) and children with PNET (n = 166) who were under age 6 years and diagnosed between 1986 and 1989 were identified through the Children’s Cancer Group. A pediatric oncology cooperative group of 33 hospitals in the United States and Canada. Controls (n = 321) were selected by random digit dial and matched individually to cases by race, birth year, and telephone area code and prefix. Mothers, and fathers when available, were interviewed by telephone. Analyses were adjusted for case-control differences in demographic characteristics and whether the father’s interview was direct or by proxy. This study found no association between CBTs and maternal or paternal smoking during pregnancy or CBTs and maternal exposure to passive smoke during pregnancy.

A case-control study was conducted in the Ile de France (Paris Region) to analyze risk factors for CBTs (40). A total of 109 CBT patients under age 16 years and who were diagnosed between 1985 and 1987 were selected from a review of records from 13 hospitals. Population controls (n = 113), frequency matched by year of birth to CBT patients, were selected from a sample of the national census. They were supplemented by a random sample of controls from municipal telephone directories of the region. All interviews were conducted at the home of mothers of CBT patients or control subjects. ORs from data analyses were adjusted for child’s age at the time of diagnosis (or interview for controls), sex, and mother’s age at the child’s birth. The study found increased, yet nonsignificant, elevations in risk for maternal smoking during pregnancy (OR = 1.6; 95% CI = 0.7–3.5) and for maternal exposure to active or passive smoke during pregnancy (OR = 1.5; 95% CI = 0.8–2.8). The study also revealed a significantly elevated risk of CBT for childhood exposure to passive smoke (OR = 2.3; 95% CI = 1.4–4.6).

Data from a large, population-based case-control study were analyzed to investigate the relationship between prenatal exposure to tobacco smoke and CBTs (39). A total of 540 CBT patients under age 20 years, diagnosed between 1984 and 1991, were identified from population-based tumor registries in 19 West Coast counties that included Seattle, WA (13 counties), San Francisco, CA (5 counties), and Los Angeles, CA (1 county). Control subjects (n = 801) were selected through random digit dial in each geographical region to obtain a case:control ratio of 1:2 in San Francisco and Seattle and a 1:1 ratio in Los Angeles. All mothers of cases and controls were interviewed in person, and fathers were interviewed in person (31%) or by telephone (69%). The data were analyzed first by individual geographical site, and later the three sites were combined and unconditional logistic regression analyses were conducted with adjustment for gender, age at the time of diagnosis (or reference date of control subjects), birth year of the index child, and maternal race. No association was found between maternal or paternal smoking before pregnancy. Maternal smoking during pregnancy did not increase the risk of CBTs in this data set. No significant increased risk for CBT was found for paternal smoking during pregnancy in the absence of maternal smoking or maternal exposure to passive smoke from any source.

Cohort Studies

Only two cohort studies have included data specifically addressing the relationship between maternal smoking during pregnancy and CBTs (29, 36). The results are presented in Table 1 (Section II) and in the text by publication date. No data on paternal smoking were available in these studies.

A prospective study that included combined data from Ontario and Great Britain examined the relationship between maternal smoking in pregnancy and childhood cancers (29). Infants (n = 89,302) who survived at least 7 days after birth in Ontario between 1959 and 1961 and in England and Wales
during March 3–9, 1958, were included in the population base. CBT patients (n = 28) were identified from Ontario death certificates and cancer clinics and from direct follow-up of British study participants. Maternal smoking data were obtained from detailed prenatal and postnatal medical histories. For all data combined, a RR of 1.6 (95% CI = 0.56–4.6; based on person-years of observation) was found for smokers of ≥1 pack/day when compared with nonsmokers and smokers of <1 pack/day.

In Sweden, a cohort of 497,051 children who were born between 1982 and 1987 was available through the Swedish Medical Birth Registry (36). Data on smoking habits were obtained from mothers through prenatal interviews conducted by midwives during the first trimester. All cancer cases reported through 1987 were identified through the Swedish Cancer Registry and included 81 children with tumors of the nervous system. The study found no association between maternal smoking during pregnancy and nervous system tumors in offspring. In addition, no significant dose-response effect was found for increasing levels of maternal smoking.

Discussion
In summary, results linking parental smoking and CBTs have been consistently negative for maternal smoking but mixed for maternal exposure to passive smoke during pregnancy. Nearly all of the case-control and cohort studies that examined CBTs in relation to maternal smoking either before or during pregnancy showed no elevated risk estimates. The effects of paternal smoking or maternal exposure to passive smoke during pregnancy were more variable; four of the nine studies that examined passive smoke exposure during pregnancy reported ORs between 1.5 and 2.2.

Initially, it seems unlikely that a relationship between passive smoke exposure and CBTs would exist when no relationship has been demonstrated between active smoke exposure during pregnancy and CBTs. The variation in methodology and data analysis among studies could partially explain the differences in outcome. The four studies that reported elevated risks for paternal smoking relied entirely on data supplied by the mother (31, 40), contained small numbers of CBT patients (29), or noted significant discrepancies between directly reported and proxy data (38). The use of proxy data for paternal smoking was of concern in many of these reports. Prior studies that have examined the extent of agreement between subjects’ and surrogates’ report of smoking habits have found consistent agreement as to whether subjects smoked but less agreement on the amount smoked (46–48). Thus, the accuracy of dose-response effects is difficult to interpret when the studies are reliant on proxy data. Another report demonstrated that passive smoking histories also are unreliable (49). When subjects were asked to report their passive smoke exposure in a given time period (i.e., during pregnancy) on two separate occasions, their responses were inconsistent. Although it is difficult to eliminate recall bias associated with reporting of passive smoke exposure in retrospective studies, overall bias can be reduced by directly interviewing subjects (i.e., fathers) whenever possible.

Statistical analysis of active and passive smoke exposure in most studies in this review used nonsmoking mothers as the referent group. The mother’s passive smoke exposure was not considered, and therefore, the referent group may not represent an unexposed group. This misclassification would underestimate any relationship between smoking and CBTs. The studies that used mothers neither actively nor passively exposed to smoke during pregnancy as their referent group tended to report a higher risk for CBT associated with passive exposure to smoke (15, 16, 37–40).

For recall possibly could have played a role in all of these studies because interviews were conducted up to 20 years after the smoke exposure of interest. Studies that examined maternal smoking histories have found them to be accurate when compared with biochemical markers or the use of daily diaries for report of smokers’ habits (50). In retrospective case-control studies, it is not possible to verify past smoke exposure by biochemical means because of the unavailability of markers that accurately measure past smoke exposure levels. To date, few reports are available that assess whether women with affected children over- or underreport their smoking exposures compared with mothers of unaffected children, although one study noted no differences in reporting retrospective smoking histories between women with positive or adverse pregnancy outcomes (51).

Small sample size and crude measurements of exposure could have resulted in analyses with insufficient power to detect real effects had they existed. Many of the studies had <200 cases, making detection of small elevations in risk less likely.

Different histological classifications of CBTs were combined in all but three of these reports, and various histological tumor types may have different etiologies. In reports to date, no significant elevated risk for CBTs related to smoking has been found for any histological type; however, this again may be due to small sample size and the lack of power to detect smaller elevations in risk. Future studies should enroll larger numbers of subjects to increase power and ability to stratify by tumor type.

The effect of childhood exposure to smoke and the incidence of CBTs has not been addressed adequately in studies to date. As discussed, only three of the studies reviewed examined early childhood smoke exposure with one report of a significantly elevated risk (OR = 2.3; 95% CI = 1.1–4.6; Ref. 40) for childhood smoke exposure and CBT. Most reports reviewed did not differentiate the effects of in utero versus early childhood exposure to smoke. Also, none incorporated information about the child’s own smoking history. Several studies include children diagnosed with CBTs in their late teens and early 20s; thus, they may have personal smoking histories of >10 years. Future work should be designed to control for postnatal personal and passive smoke exposure.

Although the relationship between smoking and CBTs is not entirely clear, given the results of studies conducted to date, it is highly unlikely that a dramatic association exists. On the basis of these same studies, we cannot rule out a very modest association between CBTs and passive smoke exposure. Because it is difficult to obtain accurate information about the degree of smoke exposure in retrospective studies, we do not recommend additional epidemiological work that focuses solely on tobacco smoke exposure and CBTs. Instead, because recent studies have shown possible relationships between dietary NOCs and CBTs (52), smoking histories should be included as part of the total assessment of a subject’s exposure to NOCs.

References
Childhood brain tumors and exposure to tobacco smoke.
M A Norman, E A Holly and S Preston-Martin