A Meta-Analysis of Parental Smoking and the Risk of Childhood Brain Tumors

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Abstract

Objective: Previous studies regarding the association between parental smoking and the risk of childhood brain tumors (CBT) have reported inconsistent results. We performed a meta-analysis to summarize evidence on this association and to quantify the potential dose-response relationship.

Methods: A systematic literature search was conducted in the Medline and Embase databases. The summary relative risks (RRs) with 95% confidence intervals (CIs) were calculated. Dose–response meta-analysis was also performed for studies that reported categorical risk estimates for a series of smoking exposure levels.

Results: A total of 17 studies fulfilled the inclusion criteria. In the meta-analyses, the summary RRs (95% CIs) of CBT for maternal smoking during pregnancy, paternal smoking during pregnancy, maternal smoking before pregnancy, and paternal smoking before pregnancy were 0.96 (0.86–1.07), 1.09 (0.97–1.22), 0.93 (0.85–1.00), and 1.09 (1.00–1.20), respectively. Dose-response meta-analysis also showed no significant association between parental smoking and the risk of CBT.

Conclusions: Findings from our meta-analysis indicate that parental smoking may not be associated with a risk of CBT.

Introduction

Childhood brain tumors (CBT) are one of the most common types of cancers in infants and children (behind hematological malignancies) and they account for approximately 20 to 25% of total primary pediatric tumor diagnoses [1]. Their 5-year survival ranges from >90% to <10% for various histological subtypes [2]. A small percentage of these tumors are found in the setting of an identifiable cancer predisposition syndrome, such as neurofibromatosis and melanoma–astrocytoma syndrome [3]. However, for most sporadic cases, little is known about the genetic or environmental etiologies.

Cigarette smoking is a major cause of illness and death worldwide. The first phase of Global Adult Tobacco Survey (GATS) reported that a high percentage of men smoke, women begin smoking early, and few successfully quit smoking [4]. It has been hypothesized that some cancers may begin during the early stages of fetal development [5]. The exposure to environmental cigarette smoke during pregnancy could lead to DNA mutations and cytogenetic damage and has been shown to act as a transplacental carcinogen in animal studies [6–8]. Increased levels of carcinogenic tobacco-specific nitrosamines could be detected in the urine samples of newborns and the amniotic fluid in early pregnancy of parents who smoked cigarettes during pregnancy [9–11]. Therefore, parental smoking, which is relatively frequent, may play a role in tumorigenesis of CBT and require further exploration.

However, epidemiological studies on a possible association between parental smoking and the risk of CBT have provided no definitive answers. Overall, the published literature remains inconclusive and inconsistent. For example, a Sweden cohort study and an Italian case–control study suggested a positive association between maternal smoking during pregnancy and the risk of CBT [12,13], whereas a UK case–control study reported a negative association between them [14]. Because of the relatively small number of cases included in the individual studies, we performed a comprehensive meta-analysis to summarize the evidence on whether parental smoking is associated with the risk of CBT.

Methods

Search Strategy

We conducted a literature search (up to January 2014) of Medline and Embase for studies examining the association between parental smoking and the risk of CBT. The search terms were (case-control OR cohort OR epidemiolog*) AND (cancer OR carcinoma OR neoplasms OR tumor OR tumour) AND (parental smoking OR maternal smoking OR paternal smoking).
An estimation of potential publication bias was evaluated by estimates were computed after the omission of each study in turn. Influence analysis was performed, in which the summary location, histological subtype, number of cases and publication year. We also conducted analyses stratified by study design, study population (n = 8); no data on CBT (n = 3); lack of sufficient data to calculate RR and 95% CIs (n = 2); adult patients included (n = 1). A manual search of references cited by these papers yielded 2 new eligible articles. Therefore, we finally included 17 articles [12–14,24–37] in the meta-analysis.

Results

Study Characteristics

The 17 studies were published between 1986 and 2013, involving a total of 5,098 cases. Of these studies, 6 were conducted in North America [25,32–36], 6 in Europe [12–14,27,29,37], 2 in Australia [24,26], 2 in China [30,31] and 1 was multi-centered [28]. 2 studies were cohort studies [12,26], and 15 were case-control studies [13,14,24,25,27–37]. Of the 17 studies, 16 had information on maternal smoking during pregnancy [12–14,24–30,32–37], 7 had data on maternal smoking before pregnancy [13,14,24,28,30,33,34], 9 on paternal smoking during pregnancy [24,25,27,29,30,32–34,36], and 7 on paternal smoking before pregnancy [13,14,24,28,30,31,33]. 8 studies considered all brain cancers together only [24–26,30,31,34,36,37], 1 considered astrocytoma only [35], and 8 considered several subtypes of CBT and provided separate analyses for these cancer subtypes [12–14,27–29,32,33]. In 12 of the 15 incident case-control studies, controls were matched for age and sex [13,14,24,25,27–31,33,34,36]. The numbers of cases and controls or cohort, types of CBT, exposure assessment method, and outcome ascertainment were shown in Table 1.

Quantitative synthesis

The pooled RRs between parental smoking and the risk of CBT were not statistically significant and close to unity (RR = 0.96, 95% CI 0.86–1.07 for maternal smoking during pregnancy; RR = 1.09, 95% CI 0.97–1.22 for paternal smoking during pregnancy; RR = 0.93, 95% CI 0.85–1.00 for maternal smoking before pregnancy; RR = 1.09, 95% CI 1.00–1.20 for paternal smoking before pregnancy) (Figures 2 and S1).

In the stratified analysis by study region, histological subtype, number of cases, and publication year, no significant associations were observed in any of the categories (Tables 2–5).

Dose-response analysis

Using a restricted cubic splines model, we did not find a curvilinear association between parental smoking and the risk of CBT (P = 0.619, 0.638, 0.924, and 0.749 for non-linearity, respectively). The summary RRs of CBT for an increase of 10 cigarettes per day were 0.98 (95% CI 0.92–1.04; P = 0.506 for linear trend), 1.04 (95% CI 0.98–1.11; P = 0.196 for linear trend), 0.95 (95% CI 0.89–1.02; P = 0.179 for linear trend), and 1.02 (95% CI 0.96–1.07; P = 0.598 for linear trend) for maternal...
smoking during pregnancy, paternal smoking during pregnancy, maternal smoking before pregnancy, and paternal smoking before pregnancy, respectively (Figures 3 and S2).

**Influence analysis**

In the influence analysis, the influence of each study on the pooled RR was examined by repeating the meta-analysis while omitting each study, one at a time. The study-specific RRs ranged from the lowest values of 0.91 (95% CI 0.83-0.99), 1.06 (95% CI 0.94-1.21), 0.91 (95% CI 0.93-0.99), and 1.08 (95% CI 0.99-1.19) to the highest values of 0.99 (95% CI 0.89-1.10), 1.12 (95% CI 0.98-1.27), 0.96 (95% CI 0.85-1.08), and 1.11 (95% CI 1.00-1.24) for maternal smoking during pregnancy, paternal smoking during pregnancy, maternal smoking before pregnancy, and paternal smoking before pregnancy, respectively (Figure S3).

**Evaluation of heterogeneity**

For maternal smoking during pregnancy, low to moderate between-study heterogeneity was observed for the pooled RRs (I² = 28.2%, 95% CI 1.6%-60.7%) and several subgroup results, including cohort studies (I² = 59.0%), studies conducted in Europe (I² = 65.2%, 95% CI 16.3%-85.5%), Ependymomas (I² = 28.9%, 95% CI 0.0%-73.8%), studies of cases > 300 (I² = 42.2%, 95% CI 0.0%-75.7%), and studies published after 2000 (I² = 50.1%, 95% CI 0.0%-77.7%).

For paternal smoking during pregnancy, there was no obvious heterogeneity between studies, except for Astrocytomas (I² = 52.1%, 95% CI 0.0%-84.2%); for maternal smoking before pregnancy, moderate heterogeneity was observed for studies conducted in Europe (I² = 51.6%); for paternal smoking before pregnancy, no heterogeneity was found in any of the categories.

**Publication bias**

There was no evidence of significant publication bias according to the Begg and Egger tests (Figure 4; Begg, P = 0.528, Egger, P = 0.790 for maternal smoking during pregnancy; Begg, P = 0.348, Egger, P = 0.420 for paternal smoking during pregnancy; Begg, P = 0.764, Egger, P = 0.610 for maternal smoking before pregnancy; Begg, P = 0.368, Egger, P = 0.189 for paternal smoking before pregnancy).

**Discussion**

In this systematic review of epidemiological studies, no clear relationship was found between parental smoking and the risk of CBT. Similar results were obtained in dose-response analysis and stratified analysis. Although some of the summary RRs (maternal smoking before pregnancy and paternal smoking before pregnancy) were borderline significant, the magnitudes of these associations were quite modest and within the range in which various sources of bias could explain them. Our findings were based on a total of 17 studies (including over 5,000 cancer cases) without obvious heterogeneity and publication bias. However, limited data were available for certain subgroups (e.g., cohort studies, studies conducted in Asia). Therefore, these results should be interpreted with caution.

Low to moderate between-study heterogeneity was observed for several pooled RRs and subgroup results. For example, low between-study heterogeneity was observed (I² = 28.2%, 95% CI 1.6%-60.7%) for maternal smoking during pregnancy, which was not surprising given the differences in study design, characteristics of populations, histological subtypes, and adjustment for confounding factors. Influence analysis suggested that after omitting some specific studies, the pooled RRs of remaining studies became significant, which indicated that some combined RRs of this meta-analysis were not very steady. For example, the omission of the study conducted by Brooks et al [12] led to a significant inverse association between maternal smoking during pregnancy and CBT risk. This may be because Brooks et al’s study is a prospective cohort study, which included large samples (1,441,942 Swedish births) and reported a significant positive association between maternal smoking during pregnancy and CBT risk [12].

Currently, a variety of genetic syndromes, including NF1, NF2, TSC1, TSC2, and VHL, have been causally linked to CBT [38]. However, the environmental risk factors of brain tumors have not been fully established. The only recognized factor is exposure to ionizing radiation, which has been widely reported as significantly increasing the risk of CBT [39,40]. Other environmental factors, such as cured meats, certain viruses (e.g., JC virus, SV40, etc.), parental heat exposure before pregnancy and fertility treatment, have shown inconsistent associations with CBT [40-42]. Although the relationship between parental smoking and CBT risk is biologically plausible, the epidemiological data are complex. Meta-analysis is a useful tool for revealing trends that might not be apparent in individual studies. Using this method, our study doesn’t support that parental smoking is an environmental risk factor of CBT.

The largest number of available studies on a specific type of parental smoking was for maternal smoking during pregnancy (n = 16). Consistent with a previous meta-analysis published in...
| First author          | Year   | Design | Region        | Exposure assessment          | Outcome ascertainment     | Diagnosis criteria | Age   | Matched factors                        | Types of CBT | Cases  | Controls or cohort |          |
|----------------------|--------|--------|---------------|-----------------------------|---------------------------|--------------------|-------|---------------------------------------|--------------|--------|-------------------|----------|
| Barrington-Trimis et al | 2013   | PCC    | USA           | In-person interview         | SEER registries           | ICD-O-1            | ≤10   | Age, sex, center                      | Astroglial   | 97     | 285                |          |
| Milne et al          | 2013   | PCC    | Australia     | Mailed questionnaire       | Pediatric oncology center | NR                 | ≤15   | Age, sex, state                       | Gliomas      | 170    | 941                |          |
| Stavrou et al        | 2009   | Cohort | Australia     | Midwives Data Collection   | Central Cancer Registry   | ICD-O-3            | ≤12   | -                                     | Total CBT    | 143    | 1,045,966         |          |
| Plichart et al       | 2008   | PCC    | France        | Telephone interview        | French National Registry  | ICD-O-3            | ≤15   | Age, sex                             | Embryonal tumors | 100    | 1,681              |          |
| Brooks et al         | 2004   | Cohort | Sweden        | Swedish Birth Register     | Swedish Cancer Register   | ICD7               | NR    | -                                     | Ependymoma   | 51     | 1,441,942         |          |
| Pang et al           | 2003   | PCC    | UK            | Interview                  | Pediatric oncology units | ICD-O-2            | ≤15   | Age, sex, residence area             | Total CBT    | 635    | 6,987              |          |
| Filippini et al      | 2002   | PCC    | Multicenter   | Interviewed in person      | Cancer registries         | ICD-O-2            | ≤19   | Age, sex                             | Astroglial tumor | 623    | 2,223              |          |
| Schuz et al          | 2001   | PCC    | Germany       | Questionnaire, telephone interview | Childhood Cancer Registry | NR                 | ≤15   | Age, sex                             | Astrocytoma   | 119    | 2,458              |          |
| Filippini et al      | 2000   | PCC    | Italy         | Telephone interview        | Hospital records          | ICD-9              | ≤15   | Age, sex, residence area             | Astroglial tumours | 115    | 502                |          |
| Hu et al             | 2000   | HCC    | China         | Interview                  | Six major hospitals       | NR                 | ≤18   | Age, sex, residence area             | Astrocytoma   | 21     | 246                |          |
| First author | Year | Design | Region | Exposure assessment | Outcome ascertainment | Diagnosis criteria | Age | Matched factors | Types of CBT | Cases | Controls or cohort |
|-------------|------|--------|--------|---------------------|----------------------|-------------------|-----|----------------|-------------|-------|-------------------|
| Ji et al    | 1997 | PCC    | China  | Direct interview    | Cancer Registry      | ICD-9             | ≤ 15| Age, sex       | Medullopithelioma | 13    |                   |
|             |      |        |        |                     |                      |                   |     |                | Craniopharyngioma | 11    |                   |
|             |      |        |        |                     |                      |                   |     |                | Others       | 38    |                   |
| Bunin et al| 1994 | PCC    | USA and Canada | Telephone interview | Children’s Cancer Group | NR             | ≤ 6 | Age, race, residence area | Astrocytoma | 155    | 321               |
|             |      |        |        |                     |                      |                   |     |                | PNET         | 166    |                   |
| Gold et al | 1993 | PCC    | USA    | Structured interview | SEER program registries | NR             | ≤ 18| Age, sex, mother’s race | Astrocytoma | 152    | 1,083             |
|             |      |        |        |                     |                      |                   |     |                | Medulloblastoma | 60    |                   |
|             |      |        |        |                     |                      |                   |     |                | Others       | 126    |                   |
| John et al | 1991 | PCC    | USA    | Structured interviews | Cancer Registry      | NR             | ≤ 14| Age, sex, residence area | Total CBT   | 48     | 196               |
| Kuitjen et al | 1990 | PCC    | USA    | Telephone interview | Tumor registries      | NR             | ≤ 15| Age, race, residence area | Astrocytoma | 163    | 163               |
| Howe et al | 1989 | PCC    | Canada | In-person interview | Hospital records      | NR             | ≤ 18| Age, sex       | Astrocytoma | 21     | 138               |
|             |      |        |        |                     |                      |                   |     |                | Medulloblastoma | 24     |                   |
|             |      |        |        |                     |                      |                   |     |                | Ependymoma   | 10     |                   |
|             |      |        |        |                     |                      |                   |     |                | Others       | 19     |                   |

PCC: population based case-control, HCC: hospital based case-control, NR: not reported.

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2002 [43], our meta-analysis also found no association between maternal smoking during pregnancy and the risk of CBT. Previous studies have reported that maternal smoking during pregnancy is a possible risk factor for stillbirth [44], child overweight [45] and childhood NHL [46] but not for childhood HL [46], leukemia [47] or testicular cancer [48]. Therefore, maternal smoking may have different effects on offspring through multiple mechanisms, specific and non-specific.

Table 2. Results of subgroup analyses of the association between maternal smoking during pregnancy and the risk of childhood brain tumors.

| Variables                  | Study          | RR (95% CI) | $p^2$ (%) | Q | $I^2$ (95%CI) (%) |
|----------------------------|----------------|-------------|-----------|---|-------------------|
| Total                      | 16 (12–14,24–30,32–37) | 0.96 (0.86–1.07) | 20.88 | 28.2 (1.6–60.7) |
| Study design               |                |             |           |   |                   |
| Cohort                     | 2 (12,26)      | 1.07 (0.72–1.58) | 2.44 | 59.0 (-)         |
| Case–control              | 14 (13,14,24,25,27–30,32–37) | 0.92 (0.84–1.00) | 13.41 | 3.1 (0.0–56.4) |
| Geographical region        |                |             |           |   |                   |
| North America              | 6 (25,32–36)   | 0.92 (0.76–1.11) | 4.41 | 0.0 (0.0–74.62) |
| Europe                     | 6 (12–14,27,29,37) | 1.03 (0.84–1.27) | 14.35 | 65.2 (16.3–85.5) |
| Australia                  | 2 (24,26)      | 0.86 (0.64–1.16) | 0.07 | 0.0 (-)          |
| China                      | 1 (30)         | 1.20 (0.45–3.23) | - | -                |
| Histological subtype       |                |             |           |   |                   |
| PNET                       | 8 (12–14,27–29,32,33) | 0.89 (0.74–1.06) | 6.58 | 0.0 (0.0–67.6) |
| Astrocytomas               | 9 (12–14,27–29,32,33,35) | 1.05 (0.93–1.18) | 7.69 | 0.0 (0.0–64.8) |
| Ependymomas                | 4 (12,14,27,29) | 1.09 (0.72–1.66) | 4.22 | 28.9 (0.0–73.8) |
| No of cases                |                |             |           |   |                   |
| $≤300$                     | 9 (13,25–27,30,34–37) | 1.02 (0.83–1.25) | 9.53 | 16.1 (0.0–58.1) |
| $>300$                     | 7 (12,14,24,28,29,32,33) | 0.94 (0.83–1.06) | 10.38 | 42.2 (0.0–75.7) |
| Publication year           |                |             |           |   |                   |
| $≤2000$                    | 8 (13,30,32–37) | 1.05 (0.88–1.24) | 5.41 | 0.0 (0.0–67.6) |
| $>2000$                    | 8 (12,14,24–29) | 0.92 (0.80–1.06) | 14.04 | 50.1 (0.0–77.7) |

* P for heterogeneity of the stratum-specific summary RRs. 

Figure 2. Forest plot of maternal smoking during pregnancy and the risk of CBT. 

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Our meta-analysis also explored the relationship between paternal smoking before and during pregnancy and the risk of CBT. A relationship between paternal smoking and CBT risk is biologically plausible. Linschooten et al reported that paternal smoking could affect the chance of heritable mutations in unstable repetitive DNA sequences [49]. The study of Laubenthal et al also supported that cigarette smoke was a human germ cell mutagen [50]. Additionally, paternal smoking may play a role through the mother’s passive exposure to secondhand smoke during pregnancy. Previous studies found that certain compounds in environ-

| Variables                      | Number | RR (95% CI) | \( P^* \) | Q | \( I^2 \) (95%CI) (%) |
|--------------------------------|--------|-------------|----------|---|---------------------|
| Total                          | 9 (24,25,27,29,30,32–34,36) | 1.09 (0.97–1.22) | 2.35 | 0.0 (0.0–64.8) |
| Geographical region            |        |             |          |   |                     |
| North America                  | 5 (25,32–34,36) | 1.03 (0.85–1.25) | 1.45 | 0.0 (0.0–79.2) |
| Europe                         | 2 (27,29) | 1.13 (0.96–1.34) | 0.23 | 0.0 (-)         |
| Australia                      | 1 (24)  | 1.04 (0.74–1.46) | -     | -               |
| China                          | 1 (30)  | 1.17 (0.67–2.04) | -     | -               |
| Histological subtype           |        |             |          |   |                     |
| PNET                           | 4 (27,29,32,33) | 1.10 (0.88–1.37) | 0.50 | 0.0 (0.0–84.7) |
| Astrocytomas                   | 4 (27,29,32,33) | 1.13 (0.79–1.61) | 6.27 | 52.1 (0.0–84.2) |
| Ependymomas                    | 2 (27,29) | 1.48 (0.99–2.20) | 0.07 | 0.0 (-)         |
| No of cases                    |        |             |          |   |                     |
| \( \leq 300 \)                  | 5 (25,27,30,34,36) | 1.18 (0.96–1.45) | 0.86 | 0.0 (0.0–79.2) |
| \( >300 \)                     | 4 (24,29,32,33) | 1.04 (0.91–1.20) | 0.56 | 0.0 (0.0–84.7) |
| Publication year               |        |             |          |   |                     |
| \( \leq 2000 \)                 | 5 (30,32–34,36) | 1.05 (0.86–1.28) | 1.63 | 0.0 (0.0–79.2) |
| \( >2000 \)                    | 4 (24,25,27,29) | 1.11 (0.96–1.28) | 0.51 | 0.0 (0.0–84.7) |

* \( P \) for heterogeneity of the stratum-specific summary RRs.

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Table 4. Results of subgroup analyses of the association between maternal smoking before pregnancy and the risk of childhood brain tumors.

| Variables                      | Study | RR (95% CI) | \( P^* \) | Q | \( I^2 \) (95%CI) (%) |
|--------------------------------|-------|-------------|----------|---|---------------------|
| Total                          | 7 (13,14,24,28,30,33,34) | 0.93 (0.85–1.00) | 3.23 | 0.0 (0.0–70.8) |
| Geographical region            |        |             |          |   |                     |
| North America                  | 2 (33,34) | 0.89 (0.69–1.15) | 0.00 | 0.0 (-)         |
| Europe                         | 2 (13,14) | 1.02 (0.79–1.31) | 2.07 | 51.6 (-)         |
| Australia                      | 1 (24)  | 0.99 (0.70–1.40) | -     | -               |
| China                          | 1 (30)  | 0.62 (0.10–3.80) | -     | -               |
| Histological subtype           |        |             |          |   |                     |
| PNET                           | 3 (14,28,33) | 0.87 (0.69–1.09) | 0.59 | 0.0 (0.0–89.6) |
| Astrocytomas                   | 3 (14,28,33) | 0.91 (0.80–1.03) | 0.04 | 0.0 (0.0–89.6) |
| Ependymomas                    | 1 (14)  | 0.73 (0.40–1.35) | -     | -               |
| No of cases                    |        |             |          |   |                     |
| \( \leq 300 \)                  | 3 (13,30,34) | 1.14 (0.85–1.53) | 0.84 | 0.0 (0.0–89.6) |
| \( >300 \)                     | 4 (14,24,28,33) | 0.91 (0.83–0.99) | 0.31 | 0.0 (0.0–84.7) |
| Publication year               |        |             |          |   |                     |
| \( \leq 2000 \)                 | 4 (13,30,33,34) | 0.99 (0.82–1.21) | 2.32 | 0.0 (0.0–84.7) |
| \( >2000 \)                    | 3 (14,24,28) | 0.91 (0.83–1.00) | 0.28 | 0.0 (0.0–89.6) |

* \( P \) for heterogeneity of the stratum-specific summary RRs.

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mental tobacco smoke may pass through the placental barrier and interact with fetal DNA, resulting in DNA damage and mutation [51,52]. However, the epidemiological evidence on this topic is very controversial. Our meta-analysis, including all the published studies, doesn’t support a link between paternal smoking before and during pregnancy and the risk of CBT.

Overall, our meta-analysis did not support the relationship between parental smoking and the risk of CBT, regardless of the source of parental exposure. These similar results between maternal and paternal smoking before and during pregnancy were consistent with the findings of Milne et al, Hu et al, and Gold et al [24,30,33], who also investigated all four types of parental smoking. Clearly identifying and classifying the source of smoke exposure may help conduct unbiased assessments of parental smoking, which will help strengthen the conclusion and provide a comprehensive evaluation.

Our study has several strengths. Our meta-analysis of 17 studies involving a large number of cases and participants enhanced the statistical power to detect potential associations and provided more reliable estimates. A dose-response relationship between parental smoking and the risk of CBT was investigated, which further strengthened the conclusion. Half of the included studies considered several subtypes of CBT, allowing us to conduct separate analyses for these cancer subtypes. The absence of important heterogeneity and publication bias supported the robustness of the study findings.

Table 5 Results of subgroup analyses of the association between paternal smoking before pregnancy and the risk of childhood brain tumors.

| Variables                  | Number                  | RR (95% CI)      | P*  | Q  | I² (95% CI) (%) |
|----------------------------|-------------------------|------------------|-----|----|-----------------|
| Total                      | 7 (13,14,24,28,30,31,33) | 1.09 (1.00–1.20) | 3.29| 0  | (0.0–70.8)      |
| Geographical region        |                         |                  |     | 0.605 |                |
| North America              | 1 (33)                  | 1.08 (0.83–1.41) | -   | -  |                |
| Europe                     | 2 (13,14)               | 1.08 (0.93–1.25) | 0.53| 0  | (0.0)           |
| Australia                  | 1 (24)                  | 0.99 (0.71–1.38) | -   | -  |                |
| China                      | 2 (30,31)               | 1.42 (0.90–2.24) | 1.07| 6.3| (0.0–70.8)      |
| Histological subtype       |                         |                  |     |     |                 |
| PNET                       | 3 (14,28,33)            | 0.94 (0.77–1.16) | 1.50| 0  | (0.0–89.6)      |
| Astrocytomas               | 3 (14,28,33)            | 1.11 (0.95–1.28) | 1.37| 0  | (0.0–89.6)      |
| Ependymomas                | 1 (14)                  | 1.03 (0.59–1.78) | -   | -  |                |
| No of cases                |                         |                  | 0.130|    |                 |
| ≤ 300                      | 3 (13,30,31)            | 1.27 (0.98–1.64) | 1.42| 0  | (0.0–89.6)      |
| >300                       | 4 (14,24,28,33)         | 1.07 (0.97–1.18) | 0.41| 0  | (0.0–84.7)      |
| Publication year           |                         |                  | 0.151|    |                 |
| ≤ 2000                     | 4 (13,30,31,33)         | 1.17 (0.98–1.41) | 2.15| 0  | (0.0–84.7)      |
| >2000                      | 3 (14,24,28)            | 1.07 (0.96–1.19) | 0.40| 0  | (0.0–89.6)      |

* P for heterogeneity of the stratum-specific summary RRs.

![Figure 3. Dose-response analysis of maternal smoking during pregnancy and the risk of CBT.](image)

![Figure 4. Funnel plot of maternal smoking during pregnancy and the risk of CBT.](image)
However, several limitations of our meta-analysis should also be acknowledged. First, in this meta-analysis, the vast majority of the included studies were case-control studies. As mentioned previously, recall bias and selection bias might cause a decrease in quality of smoking exposure data. Mothers of children with CBT may be more harmful to report harmful events during pregnancy than mothers of healthy children [53]. Therefore, this misclassification may lead to biased or spurious results. In recent years, several studies reported that cotinine measured in the dried blood spots was a reliable and accurate marker of maternal smoking close to the time of delivery [54–56]. Therefore, this low-cost and objective method could be adapted in future relevant etiologic studies to overcome a moderate amount of exposure measurement error. Second, a meta-analysis is unable to solve problems with confounding factors that could be inherent in the included studies. Inadequate control of all known confounders can produce bias in either direction, toward exaggeration or underestimation of risk estimates [57]. Although we included the data from the most fully adjusted models, residual confounding cannot be completely excluded as a potential interpretation of the observed findings. Third, the results of this study were mainly based on information from western populations, while only two studies [30,31] from other populations. Different races may have different genetic backgrounds that may affect CBT risk. Thus to generalize the findings, further study in other populations is warranted.

In conclusion, the results from this meta-analysis suggest that, based on available information, parental smoking is not associated with the risk of CBT. Because our meta-analysis has several limitations and the influence analysis suggests that some of the combined results are not very steady, future large well-designed prospective cohort studies with better exposure assessment are warranted to confirm the findings from our study and provide a higher level of evidence.

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**Supporting Information**

**Checklist S1** PRISMA checklist.

**Figure S1** Forest plot of paternal smoking during pregnancy (A), maternal smoking before pregnancy (B), paternal smoking before pregnancy (C), and the risk of CBT.

**Figure S2** Dose-response analysis of paternal smoking during pregnancy (A), maternal smoking before pregnancy (B), paternal smoking before pregnancy (C), and the risk of CBT. The solid line represents point estimates of association between parental smoking and CBT risk; dashed lines are 95% CIs. Circles are the dose-specific RR estimates. The relative size of each circle is proportional to the inverse variance of the RR.

**Figure S3** Influence analysis of maternal smoking during pregnancy (A), paternal smoking during pregnancy (B), maternal smoking before pregnancy (C), paternal smoking before pregnancy (D), and the risk of CBT.

**Author Contributions**

Conceived and designed the experiments: YH. Performed the experiments: YH JH CH. Analyzed the data: YH HL GZ. Contributed reagents/materials/analysis tools: YH HL GZ CH. Contributed to the writing of the manuscript: YH JH.
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