

Smoking and Glioma Risk

Evidence From a Meta-Analysis of 25 Observational Studies

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Abstract: To systematically assess the relationship between smoking and glioma risk.

A dose–response meta-analysis of case–control and cohort studies was performed. Pertinent studies were identified by searching database and reference lists. Random-effects model was employed to pool the estimates of the relative risks (RRs) with corresponding 95% confidence intervals (CIs).

A total of 19 case–control and 6 cohort studies were included. Overall, compared with those who never smoked, the pooled RR and 95% CI was 0.98 (0.92–1.05) for ever smoker. The subgroups were not significantly different regarding risk of glioma except the group of age at start smoking (RR = 1.17, 95% CI: 0.93–1.48 for age < 20; RR = 1.25, 95% CI: 1.02–1.52 for age ≥ 20). Dose–response analysis also suggested no significant association between smoking and the risk of glioma, although some evidence for a linear relationship between smoking and glioma risk was observed.

In conclusion, this meta-analysis provides little support for a causal relationship between smoking and risk of glioma.

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Abbreviations: CIs = confidence intervals, RR = relative risk, UK = United Kingdom, WHO = World Health Organization.

INTRODUCTION

Gliomas are the most frequently type of primary brain tumors with high invasiveness and poor prognosis, which are categorized into 4 groups (Grade I to IV) according to World Health Organization (WHO) guideline.^{1,2} Generally, gliomas are more often with increasing age, male gender, white race, and non-Hispanic ethnicity.^{3,4} Currently, besides the genetic syndromes (neurofibromatosis type I, Li Fraumeni syndrome), knowledge concerning glioma etiology remains limited to high dose therapeutic ionizing radiation, which was considered to be only well-documented environmental risk factor for gliomas.^{5,6}

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Tobacco products provide a major source of exogenous *N*-nitroso compounds and its neurocarcinogens effect has been shown to induce glioma in animal experiment.^{7–9} Therefore, cigarette smoking is a plausible and important behavior exposure that might influence the development of glioma and confirming the causal relationship between glioma risk and smoking can provide more effective strategies for the prevention of cancer. Previous epidemiological studies reported conflicting results regarding to smoking and glioma/total brain tumors.^{10–49} Thus, we systematically reviewed the available literature and performed a meta-analysis of case–control and cohort studies to provide a quantitative assessment of the relationship between smoking and glioma risk.

METHODS

Literature Search

Pertinent studies were identified through a literature search of PubMed and Embase databases. The search used a combination of the following keywords: smoking, smoke, cigarette, tobacco, glioma, brain cancer, brain tumors, and brain neoplasm. No restriction on language was set. Reference lists of eligible studies were also scrutinized to identify other publications of interest that were missed in our literature search. Ethical approval was not required, as our study is a meta-analysis of published studies.

Inclusion Criteria

Case–control or cohort studies of the relationship between smoking and glioma published before June 2015 were considered in this study. To be included in further analyses, estimates of the relative risk (RR) (such as odds ratio, hazard ratio, or risk ratio) with corresponding 95% confidence intervals (CIs) or standard errors (SEs), or raw data should be presented in original studies. When several publications from the same subjects were published, we selected the most informative one. We excluded those studies involving total brain tumors in their subjects, as total brain tumors included both benign tumors and malignant tumors.

Data Extraction

We extracted the following information: first author's last name, year of publication, country where study was undertaken, type of study design, study period for case–control/cohort studies and years of follow-up for cohorts, number of cases and controls/size of cohort, exposure-specific RR estimates with 95% CIs (when more than 1 RR and 95% CI were reported in 1 study, we included the RR that reflected the greatest degree of control for potential confounders), and variables matched between cases and controls/adjusted. Data were extracted and cross-checked independently by 2 reviewers and any disagreements were resolved by discussion.

Data Synthesis and Analysis

In current meta-analysis, odds ratio, hazard ratio, and risk ratio were deemed equivalent to RRs. This combining step is based on the assumption that the prevalence of glioma was rare.⁵⁰ We estimated the pooled RR with corresponding 95% CI using the random-effects model that accounts for heterogeneity between studies.⁵¹ When studies provided results for females and males separately, the risk estimates for females and males were considered to be 2 separate reports.⁵² When multiple exposure categories in a study fell in the exposure level representing ever smoking, we combined the corresponding estimates with the method proposed by Hamling et al⁵³; otherwise we used random-effects models. Statistical heterogeneity among studies was measured by Cochran Q (significance level at $P < 0.10$) and I^2 tests (values of the I^2 test ranges from 0% to 100%).^{54,55} We performed a sensitivity analysis in which 1 study at a time was omitted and the rest of studies were analyzed to assess whether the results could have been influenced significantly by a single study. An estimation of potential publication bias was performed through funnel plots and Egger test.^{56,57}

We first performed a comparison of ever versus never smoking. Subset analyses were performed according to study design (Retrospective study vs. Prospective study), geographic region (North America vs. Europe vs. Asia/Australia), gender (Male vs. Female), specific-type of tobacco product (Plain vs. Filtered vs. Un-Filtered vs. Pipes vs. Cigars), age at start smoking (<20 vs. ≥ 20). In further analysis, a dose–response analysis of smoking duration, smoking intensity, and pack-years of smoking was undertaken using the method described by Greenland and Longnecker⁵⁸ and Orsini et al.⁵⁹ We assessed a potential curve linear association between smoking and glioma using restricted cubic splines with 3 knots at percentiles 25%, 50%, and 75% of the distribution.⁶⁰ A P -value for linearity or nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0.⁶¹ This analysis requires that the distributions of cases and person-years or controls for at least 3 quantitative categories are presented. Also, the RRs with 95% CIs for each category have to be available in original studies. The median or mean smoking duration, smoking intensity, and pack-years of smoking in each category was used as the corresponding dose of consumption. When studies reported the ranges of smoking duration, smoking intensity, and pack-years of smoking, the value assigned to each category was the midpoint for closed categories. If the highest category was open ended, the corresponding category was set at 1.2 times the lower boundary.

All statistical analyses were performed with STATA 12.0 software (StataCorp, College Station, TX).

RESULTS

Literature Search

Our search flow is presented in Figure 1. The search terms initially yielded a total of 723 records from PubMed and Embase databases. The duplicates were omitted first, and then records were further excluded after screening the title and abstract. Thus, 38 records were chosen for full-text assessment. Reasons for exclusion were that studies were meta-analyses or conference abstracts,^{35–39} investigated the same population,^{40,41} used reference group improperly,^{42,43} and involved the total brain tumors.^{44–49} Three studies of interest were found in reference lists. Ultimately, there are altogether 25 studies included for our statistical analyses.^{10–34}

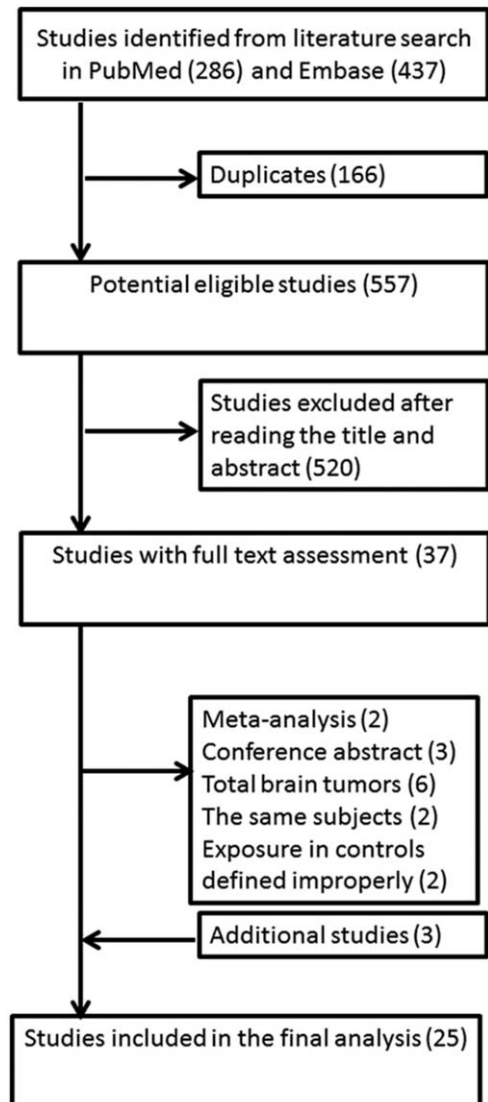


FIGURE 1. Flow diagram of studies selection for inclusion.

Study Characteristics

The main characteristics of included studies are shown in Table 1 and Table S1 (Supplemental Digital Content 1, <http://links.lww.com/MD/A596>). The study publish period spanned from 1970 to 2015. All studies were in English. Studies were carried out in different countries, including USA, Italy, Sweden, Canada, Germany, Australia, China, the UK, and France. Nineteen of the included studies were retrospective case–control studies. Correspondingly, the rest of studies were prospective cohort studies. An overwhelming majority of the cases were histologically confirmed, but some cases were radiographic methods, clinical history, or cancer registries. In case–control studies, the controls were recruited from general population, hospitals, neighborhood, and friends. Data for smoking habits were collected by phone interview, face to face interview, or self-reported questionnaire, or reviewing medical records.

TABLE 1. Characteristics of the Studies Included in This Meta-Analysis of Smoking and Glioma

Study	Country	Study Design	Study Period/Year of Follow-Up	No. of Cases and Sex	No. of Controls/Size of Cohort	RR and 95% CI (Ever vs. Never)	Adjustment/Matching
Choi et al ¹⁰	USA	RS	1963–1964	55 M + F	55 M + F	0.64 (0.27–1.47)	1–4,14
Musico et al ¹¹	Italy	RS	1979–1980	42 M + F	201 M + F	1.8 (0.55–5.9)	1,2,4
Ahlbom et al ¹²	Sweden	RS	1980–1981	72 M + F	367 M + F	1.4 (0.6–3.9)	1,2,4
Burch et al ¹³	Canada	RS	1979–1982	215 M + F	215 M + F	1.44 (0.89–2.34)	1,2,4,9,20
Carpenter et al ¹⁴	USA	RS	1943–1979	41 M + F	104 M + F	1.1 (0.5–2.7)	1–3,21
Mills et al ¹⁵	USA	PS	1976–1982/6	21 M + F	34,000 M + F	0.82 (0.28–2.39)	1,2
Preston-Martin et al ¹⁶	USA	RS	1980–1984	202 M	202 M	0.7 (0.4–1.0)	1,3,4
Hochberg et al ¹⁷	USA	RS	1977–1981	160 M + F	128 M + F	1.0 (0.62–1.61)	1,2,4,10
Schlehofer et al ¹⁸	Germany	RS	1987–1988	115 M + F	418 M + F	0.71 (0.46–1.09)	1,2
Ryan et al ¹⁹	Australia	RS	1987–1990	110 M + F	417 M + F	1.19 (0.73–1.95)	1,2
Bondy et al ²⁰	USA	RS	1994–1995	45 M + F	117 M + F	0.78 (0.39–1.57)	1–3
Hurley et al ²¹	Australia	RS	1987–1991	250 M + 166 F	252 M + 170 F	1.29 (0.95,1.75)	1,2,20
Blowers et al ²²	USA	RS	1986–1988	94 F	94 F	1.3 (0.5–3.1)	1–4
Lee et al ²³	USA	RS	1991–1994	237 M + 197 F	229 M + 201 F	M:0.9 (0.5–1.5); F: 1.3 (0.6–2.6)	1,2,5,9
Hu et al ²⁴	China	RS	1989–1995	218 M + F	436 M + F	1.13 (0.80–1.58)	1,2,4
Zheng et al ²⁵	USA	RS	NR	201 M + 174 F	1601 M + 833 F	M:0.9 (0.6–1.2); F: 0.8 (0.6–1.2)	1,2,4,5,11,13,22
Efrid et al ²⁶	USA	PS	1977–1985/mean 13.2	130 M + F	133,811 M + F	1.4 (1.0–2.1)	2,3,5,7,8,
Silvera et al ²⁷	Canada	PS	1980–1985/mean 16.5	117 F	89,709 F	1.30 (0.88–1.93)	1,5,6,13,18
Holick et al ²⁸	USA	PS	1976–2003/14–27	110 M + 255 F	46,327 M + 115,087 F	M:1.15 (0.78–1.70); F:1.15 (0.90–1.48)	1,7,8,12
Benson et al ²⁹	UK	PS	1996–2001/mean 6.2	646 F	1177, 087 F	1.01 (0.86–1.19)	1,7,10,11,13,17,18,19,25
Cabaniols et al ³⁰	France	RS	2005.01–2005.12	122 M + F	122 M + F	0.86 (0.50–1.48)	1,2
Lachance et al ³¹	USA	RS	1997–2008	855 M + F	1160 M + F	MC:1.02 (0.67–1.57) UCSF:1.05 (0.79–1.38) DUIC:0.74 (0.55–1.00)	1,2
Braganza et al ³²	USA	PS	1995–1996/mean 10.5	492 M + 212 F	283,979 M + 193,116 F	0.93 (0.79–1.09)	2,3,5,9
Vida et al ³³	Canada	RS	2002–2004	105 M + 61 F	317 M + 331 F	0.96 (0.67–1.38)	1,2,4,5
Seliger et al ³⁴	The UK	RS	1995–2012	1106 M + 899 F	11,060 M + 8990 F	0.90 (0.81–0.99)	1,2,4,20,26, 27

Matching or adjustments were: (1) age, (2) sex, (3) race, (4) area of residence/study center, (5) education, (6) menopausal status, (7) alcohol/beer/spirit consumption, (8) coffee, (9) income/marital status, (10) socioeconomic status, (11) physical exercise, (12) meat intake, (13) body mass index, (14) hospital of admission, (15) occupational exposure, (16) consumption of vegetables and fruit, (17) parity, (18) age at first birth, (19) oral contraception, (20) interview year for control/date of diagnosis for cases, (21) year of hire, (22) having a first-degree relative with brain cancer, (23) cigars/pipes, (24) age at menarche, (25) height, (26) general practice, and (27) years of active history in the CPRD before the index date.
CI = confidence interval; DUIC = Duke University Medical Center-University of Illinois, Chicago; F = female; M = male; MC = Mayo Clinic; NR = not report; PS = prospective study; RR = relative risk; RS = retrospective study; UCSF = University of California, San Francisco; UK = United Kingdom.

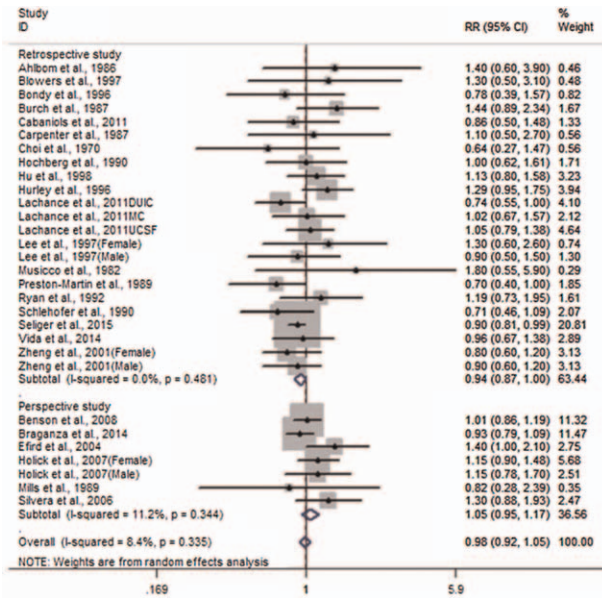


FIGURE 2. Forest plot for smoking and glioma.

Overall Association of Smoking and Risk of Glioma

Risk estimates for ever versus never smoking were reported in 25 studies and range from 0.64 to 1.8.^{10–34} Figure 2 shows the forest plots of glioma with smoking. The pooled RR with 95% CI was 0.98 (0.92–1.05).

Subset Analyses

Study Type

Associations of glioma with smoking were assessed in 19 retrospective studies and 6 prospective studies. On the basis of prospective studies,^{15,26–29,32} the pooled RR with 95% CI was 1.05 (0.97–1.15). Correspondingly, the pooled RR with 95% CI was 0.94 (0.87–1.00) for retrospective studies.^{10–14,16–25,30,31,33,34}

Geographic Area

Of the 25 studies, 16 originated from North America,^{10,13–17,20,22,23,25,28,31–33} 6 from Europe,^{11,12,18,29,30,34} and 3 from Asia/Australia.^{19,21,24} The pooled RRs with 95% CIs were 0.92 (0.85–1.00), 0.99 (0.91–1.07), and 1.21 (0.99–1.49) for Europe, North America, and Asia/Australia, respectively.

Sex

Twelve studies provided information for females and males separately.^{16,19,21–23,25–29,32,33} The pooled RR with 95% CI was 1.01 (0.84–1.22) for males, whereas for females group, the pooled RR with 95% CI was 1.10 (0.97–1.24).

Type of Tobacco Product Smoking

The correlation between risk of glioma and specific-types of tobacco product smoking was addressed in 5 studies.^{13,22,23,26,32} The pooled RRs with 95% CIs were 1.33 (0.96–1.84) for plain, 1.07 (0.82–1.42) for filtered, 1.36 (0.92–2.00) for un-filtered, 0.98 (0.47–2.02) for pipes, and 1.23 (0.79–1.92) for cigars.

Age at Start Smoking

Three studies investigated the relationship between glioma risk and age at start smoking.^{21,27,28} The pooled RR with 95% CI was 1.17 (0.93–1.48) for smokers who were younger than age 20 at start smoking, while in smokers who were older than 20, the pooled RR with 95% CI was 1.25 (1.02–1.52).

Test Heterogeneity

Evaluation of heterogeneity suggested there was no significant heterogeneity observed (Table 2) except in subgroups of pipes ($I^2 = 59.6\%$, $P = 0.084$).

Sensitivity Analysis and Publication Bias

The results were robust to the exclusion of any individual study (Figure 3). No significant publication bias was detected by Egger test (P for Egger test = 0.157) and Begg funnel plot (Figure 4).

Dose–Response

Duration of Smoking

Five studies were eligible for the dose–response analysis of duration of smoking with glioma risk.^{21,25,27,28,33} Some evidence of a linear relationship between smoking and glioma risk was observed ($P = 0.236$), but the results were not statistically significant and the risk did not increase sharply (Figure 5).

Smoking Intensity

There are 4 studies providing the sufficient data required for dose effect of smoking intensity.^{17,25–27} The linear dose–response trend ($P = 0.568$) showed a nonstatistically significant increased risk of glioma with increasing number of cigarettes per day (Figure 5).

Number of Pack-Years

Five studies investigated a dose–risk relationship between number of pack-years smoking and glioma.^{21,25,27,28,33} Similarly, no evidence of statistically significant departure from linearity ($P = 0.201$). As shown in Figure 5, a linear trend of nonstatistically significant decreased risk of glioma risk with larger pack-years of smoking.

DISCUSSION

A significant number of case–control and cohort studies investigated the relationship between smoking and risk of glioma, but inconsistent results were shown. To settle disputes, a meta-analysis of 17 case–control and cohort studies which covered the studies published up to the end of 2008 was performed, and Mandelzweig et al³⁶ concluded that smoking was not associated with risk of glioma. Since then, several studies with large simple size were published. Therefore, an updated meta-analysis was conducted to better understand the association between smoking exposure and glioma. Compared with previous meta-analysis, in our study, we excluded the studies of total brain tumors associated with smoking,^{44–49} included studies published to date; group-analyzed by study design (Retrospective study vs. Prospective study), geographic region (North America vs. Europe vs. Asia), gender (Male vs. Female), and specific-type of tobacco product (Plain vs. Filtered vs. Un-Filtered vs. Pipes vs. Cigars), age at start smoking (<20 vs. ≥20), and investigated the possible dose–response analysis of duration of smoking, smoking intensity, and number of pack-

TABLE 2. Summary RRs for Smoking and Glioma

Group	No. of Studies	Summary Effect		Heterogeneity	
		RR (95% CI)	P-Value	I ² (%)	P-Value
All studies	25	0.98 (0.92–1.05)	0.634	8.4	0.335
Study design					
Retrospective study	19	0.94 (0.87–1.00)	0.062	0.0	0.481
Prospective study	6	1.05 (0.97–1.15)	0.327	11.2	0.344
Geographic area					
Europe	6	0.92 (0.85–1.00)	0.061	0.0	0.430
North America	16	0.99 (0.91–1.07)	0.780	2.4	0.428
Asia/Australia	3	1.21 (0.99–1.49)	0.069	0.0	0.849
Gender					
Male	9	1.01 (0.84–1.22)	0.895	36.2	0.129
Female	11	1.10 (0.97–1.24)	0.230	22.5	0.230
Specific-type of tobacco product					
Plain	2	1.33 (0.96–1.84)	0.083	0.0	0.240
Filtered	3	1.07 (0.82–1.42)	0.609	38.3	0.182
Un-filtered	3	1.36 (0.92–2.00)	0.124	0.0	0.749
Pipes	3	0.98 (0.47–2.02)	0.949	59.6	0.084
Cigars	3	1.23 (0.79–1.92)	0.358	25.3	0.262
Age at start smoking					
<20 years	3	1.17 (0.93–1.48)	0.187	32.9	0.215
≥20 years	3	1.24 (1.02–1.52)	0.034	0.0	0.443

CI = confidence interval; RR = relative risk.

years smoking with glioma risk. Our meta-analysis included 19 case–control and 6 cohort studies with more than 7000 patients. Finding from current meta-analysis shows that when compared with people who have never smoked, ever smoking was not significantly associated with glioma risk. These results were consistent between retrospective studies and prospective studies. In subgroup analysis by geographic area, an increased risk of borderline significance was observed for Asia/Australia, but a decreased risk of marginal significance for Europe. The significance of these findings is unclear, and thus this is a field of ongoing investigation. Besides the issue of geographic area, several other points disclosed in our study were also worth of paying attention.

Involvement of the neuroprotective effect of estrogens in the development of glioma has been shown in experimental and animal studies.⁶² In observational studies, glioma occurs 1.5 to 2 times more frequently in men than in women.⁶² Among the included studies, 12 studies provided data for females and males separately.^{16,19,21–23,25–29,32,33} However, the issue of risk modification by gender was not addressed previous meta-analyses.^{35,36} In present study, further stratification by sex revealed no sex-based differences were observed between smoking and glioma risk.

Changes in cigarette design and composition have gradually occurred since 1950.^{63,64} The changes included lower tar and nicotine and increasing use of tobacco additives, some of

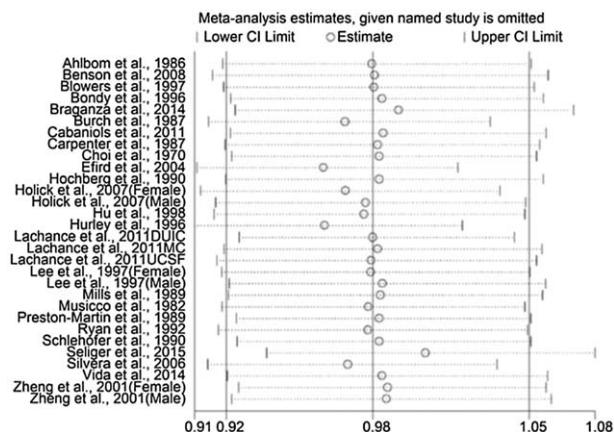


FIGURE 3. Sensitivity analyses for smoking and glioma.

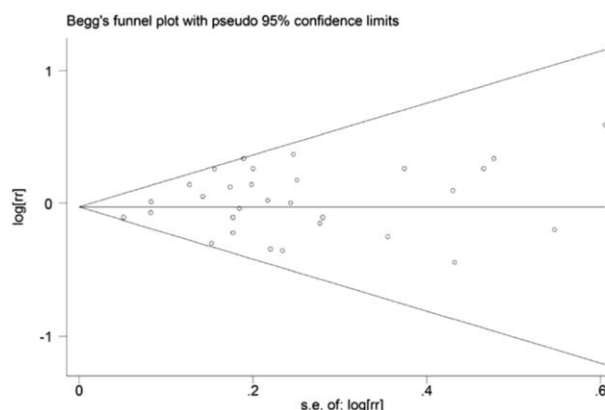


FIGURE 4. Begg funnel plot for smoking and glioma.

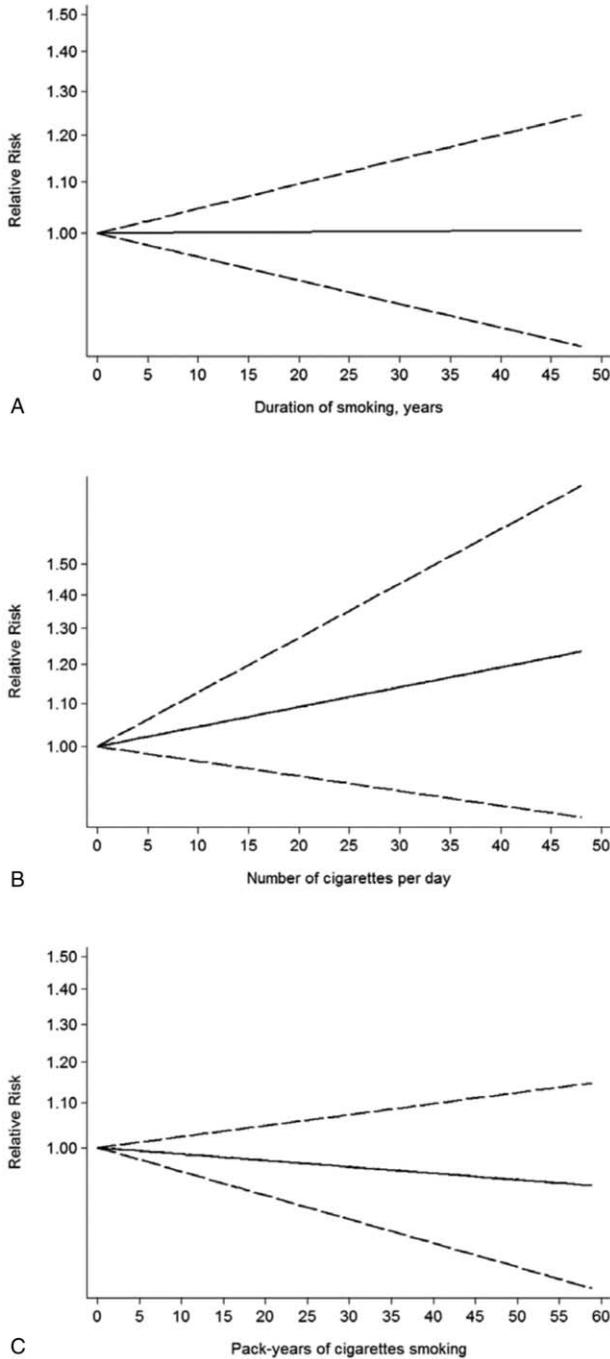


FIGURE 5. Dose–response relationship between glioma risk and smoking duration (A), smoking intensity (B), and pack-years of smoking (C). Solid line represents the estimated relative risk and the dashed lines represent the 95% confidence intervals.

which were thought to be carcinogens or lead to an increase of carcinogenic substances during combustion. These changes were mainly achieved through the introduction of filter tips, selection of tobacco types and varieties, use of highly porous cigarette paper. Hence, having a good understand of the type of tobacco smoking on tumor risk is important. Specific-type of tobacco smoking (filtered, unfiltered, regular (85 mm), king-

sized (100 mm), long, mentholated, plain, pipes, and cigars) with glioma risk was assessed in 5 studies.^{13,22,23,26,32} Overall, no significant association between specific-type of tobacco smoking and the risk of glioma, with one exception of 133,811 subjects, which showed a small and positive risk of marginal significance associated with filtered, regular (85 mm), and plain.²⁶ Our study revealed that there was no difference in the risk of glioma by type of tobacco smoking.

Mixed results have been reported between age at start smoking and the risk of glioma.^{21,22,27,28} The observation of a 67% increase in glioma risk among smokers who started smoking before the age of 20 was observed in a prospective cohort study of 89,709 Canadian women.²⁷ However, the opposite was reported only for men aged ≥ 20 when the subjects started smoking (RR = 2.72; 95% CI: 1.48–5.02).²¹ Two other investigation reported no significant association between age at start smoking and glioma risk.^{22,28} Since the age groups matched perfectly in previous studies, we performed a subset analyses of age at smoking initiation (<20 vs. ≥ 20). The pooled results showed that a significant increased risk of glioma was found in smokers who were older than 20 years, but not in smokers who were younger than age 20 at start smoking. Early age at the start of smoking usually implies a longer period of tobacco exposure and thus those smokers may bear a larger risk of glioma. Thus, interpretation of this finding should be with caution.

Estimation of dose–response association in observational studies provides more evidence for establishing a causal association between lifelong exposure and disease. We performed a dose–response analysis of smoking duration, smoking intensity, and pack-years of smoking using the method described by Greenland and Longnecker and Orsini and colleagues. These analyses showed a linear trend between smoking and glioma risk, although all results were not statistically significant. Interestingly, a linear trend of decreased risk of glioma risk with larger pack-years of smoking was observed, whereas a linear relationship of increased risk of glioma with increasing number of cigarettes per day. Considering few studies were included in dose–response analysis, the finding, of 2 opposite trends, is a chance finding. Therefore, the issue of how glioma risk changed with the dose effect of smoking duration, smoking intensity, and pack-years of smoking deserves open discussion.

Two problematic smoking exposure of interest were “current smoking” and “past smoking,” which were evaluated in 9 studies.^{11,18,19,25–29,32} Mandelzweig et al³⁶ found that current smoking was not significantly associated with glioma risk, while past smokers seemed to have an increased risk of glioma (RR = 1.10, 95% CI: 0.99–1.22). In subset analyses by study design, this trend was much stronger in case–control studies (RR = 1.16, 95% CI: 1.04–1.29) and disappeared in cohort studies (RR = 0.90, 95% CI: 0.73–1.11). It is important to note that different exposure time before reference date in retrospective versus prospective studies was taken into account between current and past smoking. Therefore, a uniform definition of current and past smoking was not established in original studies and thus a subgroup analysis by smoking status associated with glioma risk was not performed in our study. Moreover, 4 studies raised the question whether there was a threshold after quitting smoking when glioma risk decreased.^{17,22,27,32} No significant association (inverse or positive) between time since smoking cessation and glioma risk was shown in 2 case–control and one cohort studies.^{17,22,32} However, an inverse association between past smokers who stopped >10 years before baseline in comparison to those who

stopped within the 10 years before baseline (RR = 0.39, 95% CI: 0.19–0.82) in a prospective cohort study with a mean of 16.4 years of follow-up, which included 89,709 Canadian women aged 40 to 59 years.²⁷

The relationship between smoking and other brain tumors have been investigated by a multitude of case–control or cohort studies, with conflicted finding reported. Two meta-analyses of the association between smoking and meningioma had been published.^{65,66} A meta-analysis of 6 studies found that females who had ever smoking were at significantly decreased risk of meningioma relative to never smokers (OR = 0.82, 95% CI: 0.68–0.98).⁶⁵ However, for males, ever smokers were associated with a significantly increased risk of meningioma, compared with never smokers (OR = 1.39, 95% CI: 1.08–1.79).⁶⁵ In another meta-analysis of 7 case–control and 2 cohort studies by Fan et al,⁶⁶ no association between ever smoking and the risk of meningioma was observed and no significant differences in subgroup results of study design, type of exposure assessment, and gender. For pituitary tumors and acoustic neuroma, 4 studies investigated the relationship with smoking.^{67–70} Schoemaker et al⁶⁷ first performed a population-based case–control study of 563 acoustic neuroma cases and 2703 controls in the UK and Nordic countries. Acoustic neuroma tumor risk was significantly reduced in subjects who had ever regularly smoked cigarettes (OR = 0.7, 95% CI: 0.6–0.9), but the reduction did not apply to ex-smokers (OR = 1.0, 95% CI: 0.8–1.3).⁶⁷ Evidence from a case–control study of 299 cases and 630 controls aged 18 to 59 years shows no association was found between smoking and incidence of pituitary tumor.⁶⁸ In a prospective study of 1.2 million middle-aged women in the United Kingdom with an average of 8.2 follow-up years, Benson et al⁶⁹ confirmed that current smokers were at a decreased risk of acoustic neuroma (RR = 0.41, 95% CI: 0.24–0.70) and past smokers did not have significantly different risk of acoustic neuroma than never smokers (RR = 0.87, 95% CI: 0.62–1.22). Similarly, females smokers were not at a significantly reduced risk of pituitary tumors relative to never smokers (RR in current vs. never smokers = 0.9, 95% CI: 0.60–1.40)⁶⁹ and the risk of acoustic neuroma was reduced in current smokers (OR = 0.54, 95% CI: 0.36–0.81).⁷⁰

Three major limitations involved in our study should be raised. First, because of the observational design of the included studies, the effect of potential confounding is a well-known problem of concern. A close relationship between smoking and alcohol, education, income, and social class is usually to be considered. Thus, residual confounding or even interaction between these variables should be clarified in future. Moreover, various biases (ie, select bias, recall bias, information bias) in observational studies may also result in an overestimation or underestimation of the true association. For example, 2 opposite trends were observed between case–control studies and cohort studies, although the results did not reach significance (Table 2). Second, since our analysis was based on the published studies, potential publication bias could have reduced the reliability of our finding. Third, we could not perform a comprehensive analysis according to different grades of glioma defined by WHO guideline to investigate the true relationship, as almost all of include studies did not report results separately for subtype of gliomas. Gliomas include astrocytomas, oligodendrogliomas, ependymomas, glioblastoma, and other tumors arising from glial cells, which show different biological behaviors, such as invasion and prognosis. Thus, they may share little in the field of etiology, which would likely reflect different responses to neurocarcinogens from smoking. Further assessment of the

relationship between smoking and gliomas should pay more attention to the subtype of tumors.

In conclusion, this updated dose–response meta-analysis suggests smoking is not significantly associated with risk of glioma. Further large sample size, prospective design, and long follow-up studies with particular attention to the effect of gender, type of tobacco product smoking, smoking status, dosage, duration, intensity, age at smoking initiation, and years since quitting on glioma risk are warranted to confirmed these findings.

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