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ORIGINAL RESEARCH

Cigarette smoking and risk of adult glioma: a meta-analysis of 24 observational studies involving more than 2.3 million individuals

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Background: Cigarette smoking has been shown to be a risk factor for adult glioma by some but not all studies. We conducted a meta-analysis to systematically assess the potential association.

Methods: PubMed and EMBASE were searched from the date of their inception to October 1, 2015, to identify relevant articles. Reference lists from these articles were reviewed to identify additional studies. Both cohort and case–control studies were included. Fixed-effects models were used to calculate the overall relative risk (RR) with corresponding 95% confidence intervals (CIs).

Results: The final analysis included 24 studies (seven cohort and 17 case–control studies), involving more than 2.3 million individuals. The combined RR was 1.04 (95% CI: 1.00, 1.09; P=0.073) for ever-smokers, 0.97 (95% CI: 0.88, 1.07; P=0.574) for current-smokers, and 1.07 (95% CI: 0.98, 1.16; P=0.130) for past smokers, with little evidence of heterogeneity. Omission of any single study from the analysis had little effect on the result. No evidence of publication bias was found. A small but statistically significant increase was found in past smokers in females (RR: 1.13, 95% CI: 1.00, 1.28; P=0.046) but not in males.

Conclusion: In general, there was no association between cigarette smoking and adult glioma. The small but statistically significant association in females requires further investigation.

Keywords: cigarette smoking, glioma, meta-analysis, risk

Introduction

Glioma accounts for >70% of all brain tumors in adults, with an estimated incidence of 6.0/100,000 per year.[1,2] The development of glioma is clearly associated with ionizing radiation.[3,4] Putative association with other factors, including pesticide exposure,[5] alcohol consumption,[6] smoking,[7] obesity,[8] and sex hormones,[9] has also been noted. Cigarette smoking is the most important modifiable cause of many types of human cancers, including the respiratory, digestive, hematologic, and urinary systems.[10]

Association between adult glioma and cigarette smoking has been reported both in females[11,12] and in males.[13] However, increased risk of glioma in smokers has not been replicated in many other studies, including case–control studies[11,14–16] and cohort studies.[17–21] A meta-analysis of 17 studies in 2009 failed to show significant association, but a small and significant increased risk was noted in a cohort study.[7] Recently, a series of cohort studies and case–control studies have been published,[21–25] again, with conflicting results. In particular, a recent large population-based case–control study involving >13,000 individuals in the People's Republic of China supported a positive association between cigarette smoking and gliomas.[25] As a result, a reanalysis is appropriate.

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Materials and methods

Literature search

Two investigators (HXL and XXP) independently conducted a systematic search of the PubMed and EMBASE databases to identify relevant publications from the inception of the databases to October 1, 2015. The search terms were (glioma OR brain neoplasm OR brain cancer OR brain tumor) AND (smoke OR smoking OR cigarette OR tobacco OR smoker). The references of the retrieved articles were checked to identify additional studies.

Inclusion and exclusion criteria

The criteria for data inclusion were: 1) studies investigating the association between cigarette smoking and risk of adult glioma; 2) the study design being cohort or case–control study; 3) odds ratio (OR), relative risk (RR), or hazard ratio (HR), with corresponding 95% confidence intervals (CIs), being provided or calculated from raw data; and 4) at least one of the following smoking exposure variables being provided: ever- versus never-smokers, current versus never-smokers, past versus never-smokers, duration, intensity, or cumulative smoking (pack-year). In the cases of multiple publications, only the one with the most complete information was used. Case report, meta-analysis, reviews, comments, and editorials were not included.

Data extraction

Two investigators (HXL and XXP) independently extracted the following data: first author's name, year of publication, study design, study country/period, data source (cohort study), follow-up years (cohort study), sample size, age of subjects, diagnostic criteria of glioma, sex strata, research instrument, control source (case–control study), smoking variables and adjustment factors, and risk estimate (RR, OR, HR, and 95% CI). Disagreements were resolved through discussion.

Statistical analysis

The meta-analysis was conducted using STATA 12.0 (StataCorp LP, College Station, TX, USA). Since glioma is a rare disease, OR and HR are practically equivalent to RR.[26] RR was used throughout this study. Heterogeneity was evaluated with Cochran's Q statistic[27] and I^2 statistic,[28] and defined as low ($I^2 \leq 25\%$), moderate ($I^2 = 25\%–50\%$), or high ($I^2 > 50\%$). RR was calculated using a fixed-effects model when $I^2 < 50\%$, and using a random-effects model otherwise. Sensitivity analysis was carried out to evaluate the potential effects of the individual study to the overall results, as described previously.[29] Publication bias was assessed using Begg's funnel plots and Egger's regression test.[30,31] Sensitivity analysis and publication bias were assessed for ever- versus never-smokers only. All analyses were two sided, with $P \leq 0.05$ indicating statistical significance.

Ever-, current-, and past smokers were defined as in the original publications. To probe into potential heterogeneity, several subgroup analyses were performed according to study design (cohort versus case–control study), control source (population-based versus hospital-based), research instrument (questionnaire versus interview for case–control study; mailed versus self-administered questionnaire for cohort studies), sex, geographical area, age at which smoking was started (≤20 versus >20 years), smoking intensity (≤20 versus >20 cigarettes per day), duration (≤20 versus >20 years), cumulative smoking (≤15 versus >15 pack-years), and year of study publication (before 1990 versus 1990–2000 versus 2000–2010 versus 2010–now).

Results

Search results and characteristics of studies

The initial screening identified a total of 873 articles (n=417 from PubMed and n=456 from EMBASE). After reading the titles and abstracts, 32 papers were selected for further processing. Reviewing the full text, eleven articles were eliminated for the following reasons: six for irrelevant articles;[32–37] two articles did not provide the data "never-smokers", "ever-smokers", or "current-smoker";[38,39] and two articles did not have sufficient data for the variable "ever-, current-, or past smokers", but were included the subgroup analysis based on smoking "intensity".[40,41] Two articles were from the same study,[11,42] and so only the one with most complete information was included.[11] One article included three case–control studies.[22] The final analysis in this study included a total of 24 studies from 22 articles.[11–25,43–49] The selection process is shown in Figure 1.

The characteristics of the included studies are listed in Table 1. Of the 24 studies included, seven were cohort studies[12,17–21,43] and the remaining 17 were case–control studies.[11,13–16,22–25,44–49] All together, these studies involved >2.3 million individuals. Among these studies, 13 were conducted in the USA,[12–15,17,19–22,44,46] four in Europe,[17,24,47,48] three in Canada,[23,43,45] two in Australia,[11,16] and two in the People's Republic of China.[25,49] Seven studies did not present the results using "ever- versus never-smokers" results; we synthesized the data by pooling the variables, from current- and past smokers,[13,15] or from males and females.[17,18,21,44,48] Of the 17 case–control studies, eight

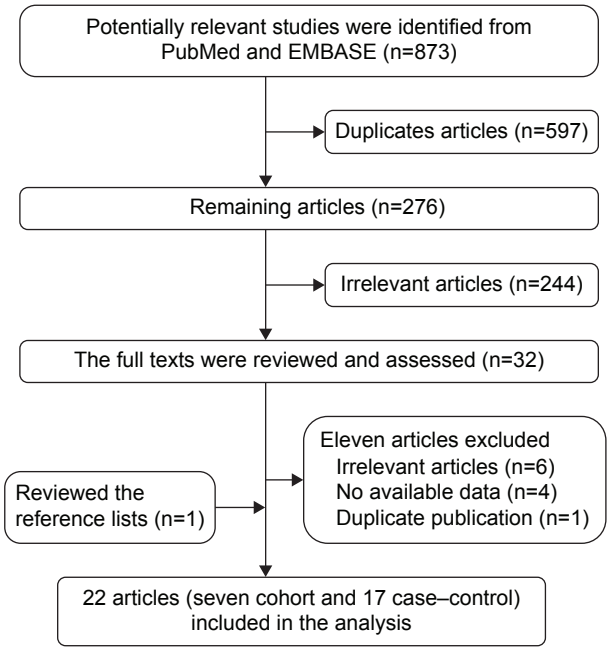

Figure 1 Flowchart of studies included in the meta-analysis.

studies were hospital based,[22–24,44,45,47] and the remaining nine were population based.[11,13–16,23,25,46,48] In the 17 case–control studies, smoking was evaluated using interview in eleven studies,[13,14,16,22–25,45,48,49] questionnaire in three studies,[11,15,22] medical records in two studies,[44,46] and a mixture of questionnaire and interview in one study.[47] Among the seven cohort studies, smoking was assessed using questionnaire via mail in four studies,[17–20] and self-administered questionnaire in three studies.[12,21,43] Among these studies, two reported increased risk in females but not in males,[11,12] and one reported an increase in males only.[13] No association was found in the two studies exclusively on females.[17,43] The two case–control studies conducted in males only did not find increased risk.[14,44] The latest case–control study involving 13,000 individuals found increased risk regardless of sex.[46] However, several studies that included both sexes failed to find an association between smoking and glioma risk in either males or females.[15,16,18,21]

Main analysis

Ever-smokers

All 24 studies estimated the risk in ever-smokers. The analysis of never-smokers included >920,912 participants, with >4,812 glioma cases, while the analysis of ever-smokers included >1,851,038 participants, with >4,121 glioma cases. The pooled RR for ever-smokers (n>1,855,159) versus never-smokers (n>925,724) was 1.04 (95% CI: 1.00, 1.09; P=0.072). No significant heterogeneity was found (I^2=28.6%, P=0.096; Figure 2).

Current-smokers

Risk estimates for current-smokers were reported in ten studies.[12,15–19,21,43,44,48] The analysis of current-smokers included >1,222,544 participants, with >368 glioma cases. The pooled RR for current-smokers (n>1,222,912) versus never-smokers (n>925,724) was 0.97 (95% CI: 0.88, 1.07; P=0.574), with low heterogeneity (P=0.225, I^2=23.7%; Figure 3).

Past-smokers

Ten studies evaluated the risk in past-smokers.[12,15–19,21,40,43,44] The analysis of current-smokers included >623,095 participants, with >839 glioma cases. The pooled RR for past-smokers (n>623,934) versus never-smokers (n>925,724) was 1.07 (95% CI: 0.98, 1.16; P=0.130), with low heterogeneity (P=0.353, I^2=9.7%; Figure 4).

Stratified analysis

To examine the potential heterogeneity, several subgroup analyses were performed. The results of "ever smoker versus never smoker" are listed in Table 2.

In the stratified analysis by study design, more than 2,756,887 participants and 1,956 glioma cases were included in cohort studies, and more than 6,977 participants and 15,063 glioma cases were included in case–control studies. The pooled RR for ever-smokers (n>1,329,577) versus never-smokers (n>913,450) was 1.05 (95% CI: 0.97, 1.13; P=0.200) in cohort studies, and the RR for ever-smokers (n>9,999) versus never-smokers (n>12,283) was 1.04 (95% CI: 0.98, 1.10; P=0.201) in case–control studies. Within the case–control studies, the RR for ever-smokers was 0.98 (95% CI: 0.87, 1.11) in hospital-based studies and 1.06 (95% CI: 0.99, 1.13) in population-based studies.

In the cohort studies, the RR for ever-smokers was 1.08 (95% CI: 0.98, 1.19) in studies using mailed questionnaire and 1.14 (95% CI: 0.84, 1.54) in studies using self-administered questionnaire. In the case–control studies, the RR for ever-smokers was 1.05 (95% CI: 0.98, 1.12) among studies using interview and 1.00 (95% CI: 0.84, 1.19) among studies using questionnaire. Homogeneity was detected (I^2=67.9%) among studies using questionnaire.

In the stratified analysis by sex, a total of 12 studies were included. Among these studies, ten studies[11–13,15,17,18,21,23,25,43] were included to evaluate the association between ever-smokers and the risk of glioma in females, and the pooled RR for ever-smokers (n>1,458,747) versus never-smokers (n>1,457,322) was 1.12 (95% CI: 1.03, 1.22; P=0.007). Ten studies[11–15,18,21,23,25,44] were included to evaluate the association

Table 1 Study characteristics of published cohort and case–control studies on cigarette smoking and the risk of adult glioma

References	Country/period	Data source	Follow-up (years)	No of case/ participants (overall)	No of case/ participants (N)	No of case/ participants (E)	No of case/ participants (P)
Cohort studies							
Braganza et al[21]	USA/1995–1996	NIH-AARP	10.5 (mean)	704/477,095	265/174,244	439/837,848	374/243,407
Benson et al[17]	UK/May 1996–April 2001	National Health Service (UK)	6.2 (mean)	681/1,177,087	322/599,949	296/577,138	189/332,775
Holick et al[18]	USA/1976–NR	HPFS; NHS; NHS II	14–27	365/257,918	165/72,838	200/429,326	145/46,051
Silvera et al[43]	Canada/1980–1985	CNBSS	16.5 (mean)	117/89,709	59/NR	58/NR	38/NR
Efird et al[12]	USA/1977–1985	KPMCP-NC	13.3 (mean)	130/133,811	51/65,544	79/NR	45/NR
McLaughlin et al[19]	USA/1953–1980	US veterans	26	468/177,903	NR	NR	NR
Mills et al[20]	USA/1976–1982	CSDA	6	18/34,000	13/NR	18/NR	NR

References	Country/period	No of case/ control (overall)	No of case/ control (N)	No of case/ control (E)	Sex strata/ age (years)
Case–control studies					
Hou et al[25]	People's Republic of China/1989–1991	4,556/9,112	2,676/5,542	1,880/3,570	MF/≥30
Vida et al[23]	Canada/2002–2004	166/648	78/311	88/337	MF/30–59
Cabaniols et al[24]	France/January 2005–December 2005	116/116	54/50	62/66	MF/≥18
Lachance et al[22]	USA/1997–2008	855/1,160	429/539	426/621	MF/≥20

No of case/ participants (C)	Sex strata/age (years)	Diagnostic criteria	Research instrument	Smoking variables assessed and adjustment	Risk estimate: ever-, current-, or past- vs never-smokers, RR (95% CI)
65/594,441	MF/50–71	First primary malignant glioma and histopathologically	Self-administered questionnaire	Past; current; intensity; cigar/pipe smoking; time since quitting; adjustment (sex, education, marital status, and race/ethnicity)	C: 0.83 (0.63, 1.09); P: 0.95 (0.81, 1.12)
107/244,363	F/50–65	Registers of National Health Service (UK)	Mailed questionnaire	Never, past, current smoking; adjustment (height, BMI, socioeconomic status, alcohol intake, strenuous exercise, age at first birth, parity, and oral contraceptive use)	C: 0.91 (0.73, 1.15); P: 1.09 (0.91, 1.31)
55/383,275	MF/25–75	Medical records	Mailed questionnaire	Current, past, intensity, duration, pack-years, age at start; adjustment (age, total meat intake, alcohol, and coffee consumption)	C: 1.06 (0.76, 1.47); P: 1.21 (0.98, 1.49)
20/NR	F/40–59	Canadian cancer database	Self-administered questionnaire	Ever, current, past, intensity, duration, pack-years, age at start; adjustment (age, education, BMI, parity, age at first live birth, age at menarche, menopausal status, center)	E: 1.30 (0.88, 1.93); C: 1.05 (0.62, 1.78); P: 1.51 (0.97, 2.34)
34/NR	MF/≥25	Tumor registry; biopsied and histologically; radiographic and clinical history	Self-administered questionnaire	Ever, current, past, intensity; adjustment (cigars, pipes, sex, race, education, alcohol, and coffee consumption)	E: 1.40 (1.00, 2.10); C: 1.60 (1.00, 2.50); P: 1.30 (0.90, 2.00)
NR	MF/31–84	Death certificates	Mailed questionnaire	Ever, current, past; adjustment (attained age and calendar year time period)	E: 1.10 (0.90, 1.30); C: 1.10 (0.90, 1.30); P: 1.10 (0.90, 1.40)
NR	MF/≥25	Histopathologically confirmed	Mailed questionnaire	Ever; adjustment (age and sex)	E: 0.82 (0.28, 2.39)

Diagnostic criteria	Control source	Research instrument	Smoking variables assessed and adjustment	Risk estimate: ever-, current-, or past- vs never-smokers, RR (95% CI)
Autopsy, histological test, surgical operation, imaging or laboratory tests, clinical assessment, deduction after death	PCC	Interviews	Current, sex, urban or rural residence, years of smoking, cigarettes smoked daily; adjustment (age, urban, or rural residence)	E: 1.11 (1.03, 1.21)
Histologically confirmed or based on unequivocal diagnostic imaging	PCC	Interviews	Ever, pack-years, duration, sex, by education level; adjustment (age, sex, education level, region)	E: 0.96 (0.67, 1.38)
All new cases of malignant primitive brain tumors	HCC	Interviews	Ever; adjustment (age, sex)	E: 0.86 (0.50, 1.48)
Histologically confirmed	HCC	Interviews and questionnaire	Ever	E: 1.02 (0.67, 1.57)[a]; 1.05 (0.79, 1.38)[b]; 0.74 (0.55, 1.00)[c]

(*Continued*)

Table 1 (*Continued*)

References	Country/period	No of case/control (overall)	No of case/control (N)	No of case/control (E)	Sex strata/age (years)
Zheng et al[15,d]	USA/NR	375/2,434	190/1,107	185/1,327	MF/40–85
Hu et al[49]	People's Republic of China/September 1989–May 1995	218/436	113/235	105/201	M, 39.2/F, 40.3
Lee et al[13]	USA/August 1991–March 1994	434/430	192/189	242/241	MF/≥20
Hurley et al[11]	Australia/July 1987–December 1991	416/422	174/190	242/232	MF/20–70
Ryan et al[16]	Australia/February 1997–April 1990	110/417	NR	NR	MF/25–74
Brownson et al[44]	USA/January 1984–December 1988	312/1,248	NR	NR	M/54.6 (mean)
Schlehofer et al[48]	Germany/1987–1988	115/418	NR	NR	MF/NR
Preston-Martin et al[14]	USA/1980–1984	202/202	NR	NR	M/25–69
Burch et al[45]	Canada/1979–1982	215/215	NR	NR	MF/25–80
Carpenter et al[46]	USA/1943–1979	41/04	16/47	25/57	MF/NR
Musicco et al[47]	Italy/January 1979–March 1980	42/201	24/127	18/74	MF/≥20

Notes: [a]Data were collected from Mayo Clinic, Rochester, MN, USA; [b]Data were collected from University of California, San Francisco (UCSF), CA, USA; [c]Data were collected from Duke University Medical Center, Raleigh, NC, USA; and University of Illinois, Chicago (Duke-UIC), IL, USA; [d]Only this study provides the number of cases in group current-smokers and past-smokers.

Abbreviations: N, never-smokers; E, ever-smokers; C, current-smokers; P, past-smokers; M, males; F, Females; MF, males and females; BMI, body mass index; NIH-AARP, American Association of Retired Persons; HPFS, The Health Professionals Follow-up Study; NHS, The Nurses' Health Study I; NHS II, The Nurses' Health Study II; CNBSS, Canadian National Breast Screening Study; KPMCP-NC, Kaiser Permanente Medical Care Program of Northern California; CSDA, California Seventh-Day Adventists; PCC, population-based case–control; HCC, hospital-based case–control; NR, not reported, if information is part of the scope of the study, but not reported, CI, confidence interval, RR, risk ratio.

between ever-smokers and the risk of glioma in males, and the pooled RR for ever-smokers (n>229,901) versus never-smokers (n>111,759) was 1.03 (95% CI: 0.96, 1.10) (*P*=0.408). In addition, after stratified analysis by current and past in females smokers, the summary RR for current-smokers (n>629,003) versus never-smokers (n>1,457,322) was 1.06 (95% CI: 0.95, 1.18; *P*=0.275), including six studies,[15,17,18,21,25,43] and for past smokers (n>827,870) versus never-smokers (n>1,457,322) was 1.13 (95% CI: 1.00, 1.28; *P*=0.046), involving five studies.[15,17,18,21,25] These results suggested that females who reported being past smokers were at increased risk of glioma compared with never-smokers, while current-smokers did not appear to be at an increased risk.

Upon a stratified analysis based on geographical area, no significant association was observed, and the combined RR was 0.99 (95% CI: 0.92, 1.06) for the USA, 1.17 (95% CI: 0.93, 1.48) for Canada, 0.97 (95% CI: 0.86, 1.10) for Europe, 1.26 (95% CI: 0.97, 1.64) for Australia, and 1.11 (95% CI: 1.03, 1.20) for the People's Republic of China.

There are six studies providing the sufficient data for the smoking duration subgroup.[11,15,18,23,25,43] The summary RR was 0.97 (95% CI: 0.76, 1.24) for short-term (≤20 years), and 1.06 (95% CI: 0.90, 1.26) for long-term (>20 years).

Eight studies provided the information for smoking intensity.[12,15,18,20,25,40,41,43] The pooled RR was 1.02 (95% CI: 0.96, 1.09) for light (≤20 cigarettes per day), and 1.11 (95% CI: 0.91, 1.35) for heavy (>20 cigarettes per day) smokers.

There were no significant differences between publication times. The summary RR for ever-smokers were 0.91 (95% CI: 0.78, 01.07), 1.14 (95% CI: 1.00, 1.30), 1.09

Diagnostic criteria	Control source	Research instrument	Smoking variables assessed and adjustment	Risk estimate: ever-, current-, or past- vs never-smokers, RR (95% CI)
Histologically confirmed	PCC	Questionnaire	Ever, past, current, duration, intensity, pack-years, by sex; adjustment (age, body mass index, education, exercise, duration living in area served by chlorinated surface water, first-degree relative with brain cancer)	E: 0.84 (0.66, 1.08); C: 0.87 (0.63, 1.19); P: 0.87 (0.66, 1.19)
Histologically confirmed	HCC	Interviews	Ever	E: 1.13 (0.80, 1.58)
Histopathologically confirmed	PCC	Interviews	Ever, filtered, unfiltered, both; pack-years, by sex; adjustment (age, education, income)	E: 1.03 (0.66, 1.59)
Histopathologically confirmed	PCC	Questionnaire	ever, pack-years, duration, age at start, by sex; adjustment (age, sex, reference date)	E: 1.29 (0.95,1.75)
Newly diagnosed primary gliomas	PCC	Interviews	Ever, current, past, pack-years; adjustment (age, sex)	E: 1.19 (0.73, 1.95); C: 1.11 (0.62, 1.99); P: 1.39 (0.74, 2.63)
Histopathologically confirmed	Other cancers	Cancer registry	Current, past	C: 0.90 (0.70, 1.30); P: 1.00 (0.70, 1.50)
Histopathologically confirmed	PCC	Interviews	Current, past; adjustment (age, sex)	C: 0.70 (0.50,1.10); P: 0.90 (0.60, 1.50)
Diagnosis of primary glioma	Neighborhood	Interviews	Ever	E: 0.70 (0.40, 1.00)
Histopathologically confirmed	HCC	Interview	Ever, plain, filter, dose–response	E: 1.44 (0.89, 2.34)
Death certificates	Employees from nuclear facilities	Medical records	Ever	E: 1.10 (0.50, 2.70)
Histologically; radiologic and arteriography	HCC	Questionnaire and Interview	Ever, heavy-smokers; adjustment (sex, age, residence)	E: 1.80 (0.55, 5.90)

(95% CI: 0.93, 1.26), and 1.04 (95% CI: 0.97, 1.10) according to studies published in before 1990, 1991–2000, 2001–2010, and 2011–now, respectively.

Little evidence of heterogeneity was observed in most analyses of our study except in subgroups of self-administered questionnaire (heterogeneity: I^2=67.9%, P=0.045), short-term smoking duration (heterogeneity: I^2=50.3%, P=0.09), long-term smoking duration (heterogeneity: I^2=58.1%, P=0.036), heavy intensity smoking (heterogeneity: I^2=65.4%, P=0.008), and year of study publication (2000–2010; heterogeneity: I^2=50.7%, P=0.088).

Sensitivity analysis and publication bias

Removing one study at a time did not significantly alter the results, resulting in the pooled RR having a narrow variation range from 1.01 (95% CI: 0.81, 1.26) to 1.06 (95% CI: 0.88, 1.28; Figure 5). No evidence of publication bias was detected for Begg's (P=0.862) and Egger's test (P=0.630; Figure 6).

Discussion

To the best of our knowledge, this meta-analysis is the most comprehensive analysis of a putative association between cigarette smoking and adult glioma risk up to date. The analysis included seven cohort studies and 17 case–control studies involving >2.3 million subjects. The overall analysis did not find significant association between cigarette smoking and glioma, regardless of smoking definition (ever-, current-, or past smokers). Subgroup analysis also failed to find an association regardless of the stratification factors, with an

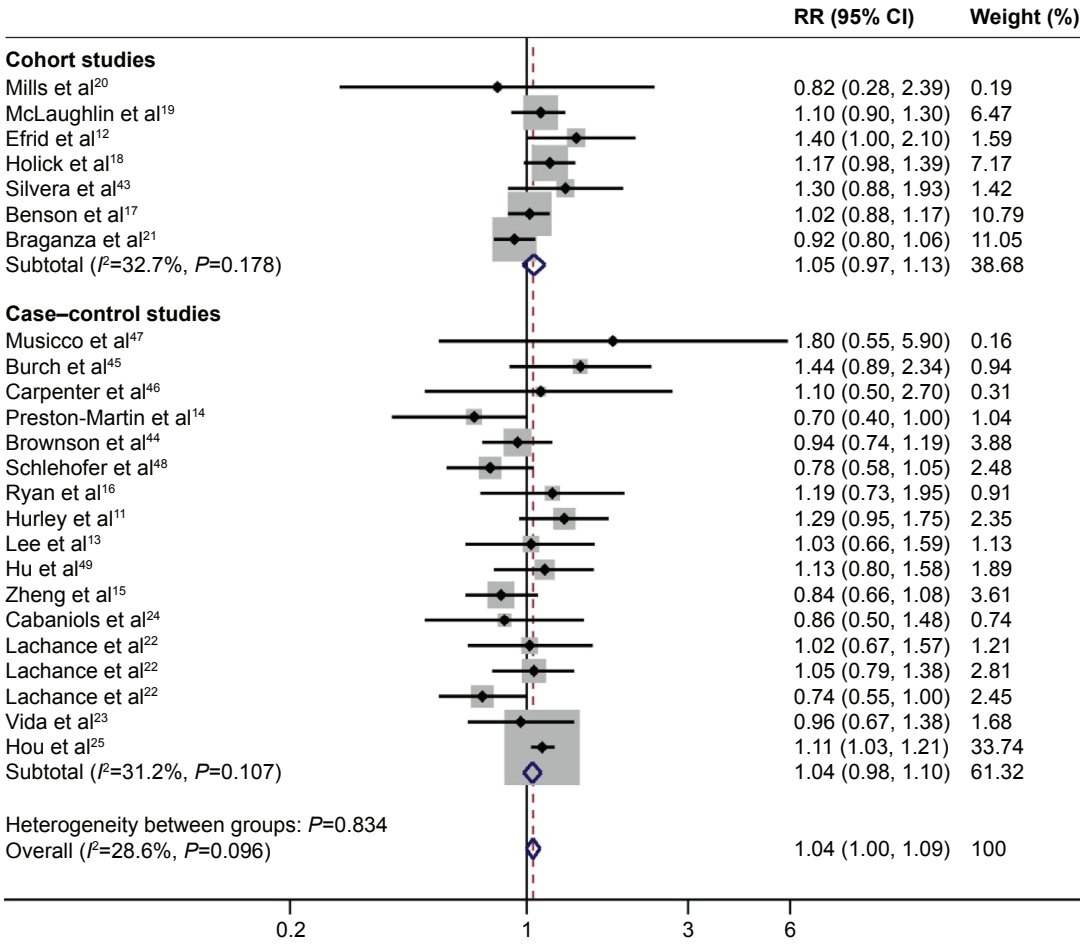

Figure 2 Forest plot of cigarette smoking and the risk of glioma (ever-smokers versus never-smokers).
Notes: The pooled RR for current-smokers versus never-smokers was 0.97 (95% CI: 0.88, 1.07), with low heterogeneity (P=0.225, I^2=23.7%).
Abbreviations: RR, relative risk; CI, confidence interval.

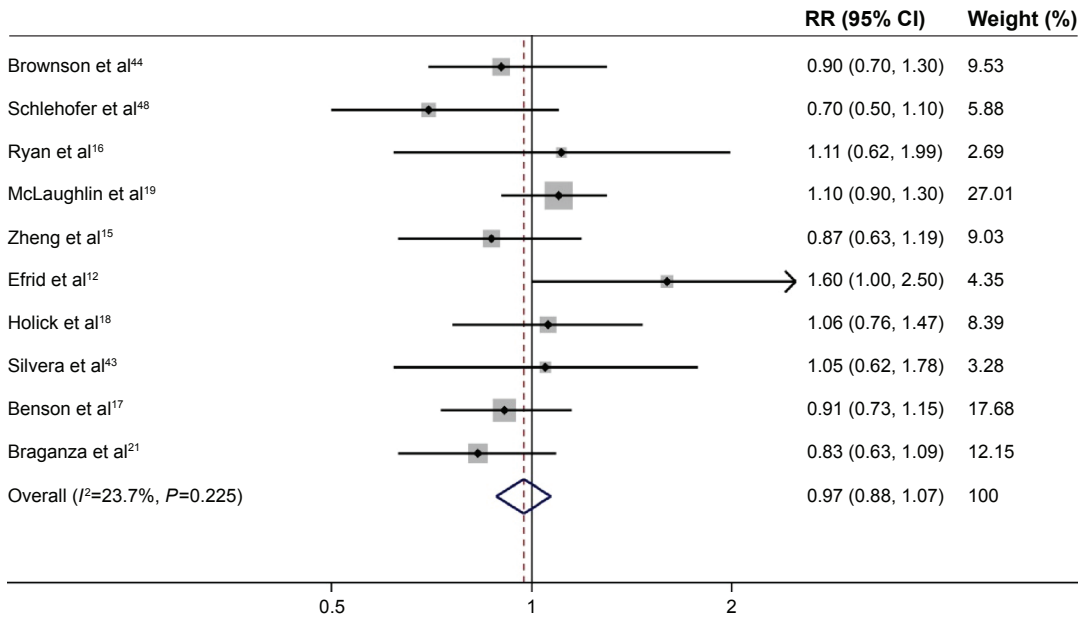

Figure 3 Forest plot of the risk of developing adult glioma in current-smokers.
Note: The pooled RR for current-smokers versus never-smokers was 0.97 (95% CI: 0.88, 1.07), with low heterogeneity (P=0.225, I^2=23.7%).
Abbreviations: RR, relative risk; CI, confidence interval.

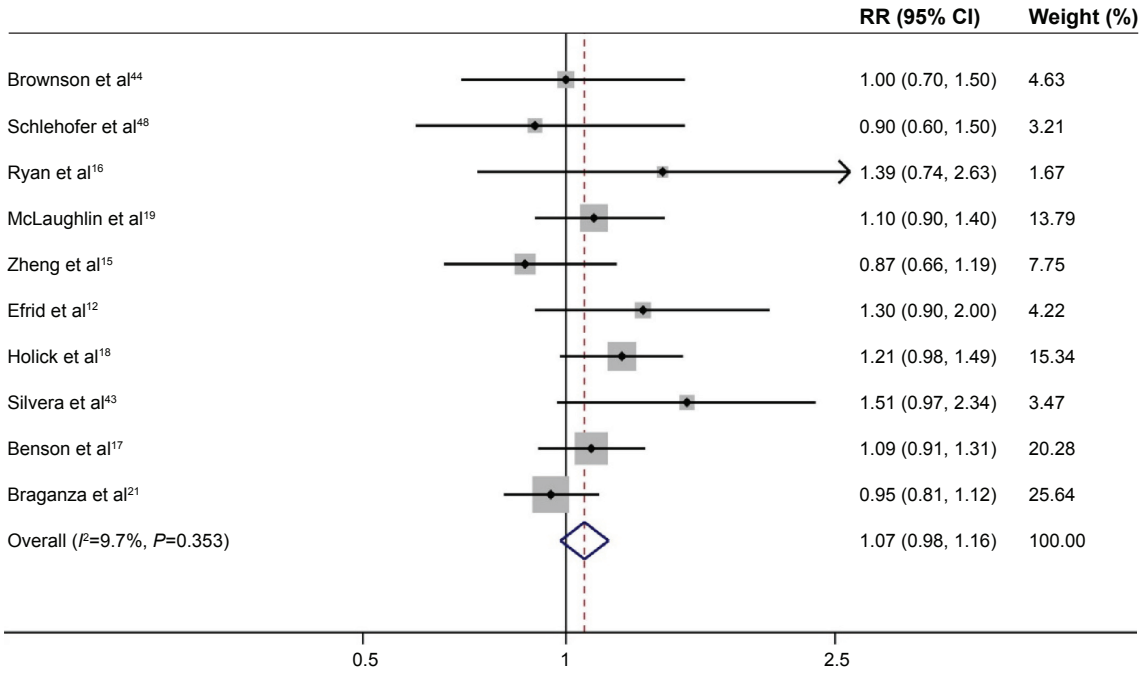

Figure 4 Forest plot of the risk of developing adult glioma in past-smokers.
Note: The pooled RR for past-smokers versus never-smokers was 1.07 (95% CI: 0.98, 1.16), with low heterogeneity (P=0.353, I^2=9.7%).
Abbreviations: RR, relative risk; CI, confidence interval.

exception of a small but statistically significant increase in females for past smokers (RR: 1.13, 95% CI: 1.00, 1.28; P=0.046).

Subgroup analysis in this study identified a small but statistically significant association between smoking and glioma among females but not males. The association was in accordance with results from two studies,[20,43] but not others.[11,13,15,17,18,21,23,25] Efird et al[12] reported on a cohort of 133,811 subjects to the Kaiser Permanente Medical Care Program of Northern California, with follow-up of up to 21 years; 130 cases were diagnosed with glioma, and compared with never-smokers, an increased risk of gliomas was seen among female smokers smoking <1 pack (RR=1.7, 95% CI=0.9, 3.1), 1–2 packs (RR=1.8, 95% CI=0.8, 4.1), and >2 packs (RR=3.0, 95% CI=0.9, 10.6) per day, respectively; but no association was observed in males.

Our result stratified analysis by past and current smokers in females showed that past females smokers had increased risk of glioma, but not current smokers. The result was consistent with Silvera et al's study,[43] but our result could have been due to chance. Silvera et al[43] reported that pastsmokers were at increased risk of glioma compared with never-smokers in females, but upon stratifying past smokers by years since having quit smoking, they found an inverse association between past-smokers who stopped smoking >10 years prior to baseline compared with those who stopped smoking within the 10 years prior to baseline (HR =0.39, 95% CI: 0.19, 0.82), indicating that the association between past smokers and glioma may have been driven by females who recently stopped smoking.[43]

The mechanism underlying the association between cigarette smoking and adult glioma in females but not in males is unknown. However, some causal relationships are conceivable. First, several animal studies showed that smoking increases the levels of certain sex hormones and sex hormones promote tumor progression,[50,51] including glioma.[9] Second, the risk of smoking-related cancers (such as in the esophagus, lungs, and oral cavity) has been observed to be higher in females compared to males in some studies,[52–54] and these phenomena may also appear in brain cancer. Third, females may be more susceptible to carcinogens in cigarette smoke than males in terms of a greater frequency for specific mutations in the *p53*[55] and *K-RAS*[56] genes, which increased the concentration of carcinogen adducts in smoking-affected tissue,[57] elevated the expression of certain enzymes in the cytochrome p450 family,[58] reduced capacity for DNA repair,[59] and may also induce glioma. Furthermore, cigarette smoking affects both the innate and adoptive immune arms, and leads to a series of immunological disorders (such as atopic diseases and asthma),[60] and females are more susceptible to the immunological disorders.[61] It may be considered that smoking affects immunological function, and immunological factors induce brain cancer.[62–64]

Little evidence of heterogeneity was observed in the current analysis. High between-study heterogeneity was only observed from subgroup results: the group self-administered

Table 2 Results of meta-analysis for cigarette smoking and risk of glioma

Group	No of studies	RR (95% CI)	*P*-value	I^2 (%)	*P*-heterogeneity	Analysis model
Total	24	1.04 (1.00, 1.09)	0.072	28.6	0.096	Fixed-effects model
Study design						
Cohort	7	1.05 (0.97, 1.13)	0.200	32.7	0.178	Fixed-effects model
Case–control	17	1.04 (0.98, 1.10)	0.201	31.2	0.107	Fixed-effects model
Hospital-based	8	0.98 (0.87, 1.11)	0.773	0.0	0.423	Fixed-effects model
Population-based	9	1.06 (0.99, 1.13)	0.106	43.1	0.080	Fixed-effects model
Research instrument (cohort)						
Mailed questionnaire	4	1.08 (0.98, 1.19)	0.105	0.0	0.633	Fixed-effects model
Self-admin questionnaire	3	1.14 (0.84, 1.54)	0.403	67.9	0.045	Random-effects model
Research instrument (case–control)						
Interview	11	1.05 (0.98, 1.12)	0.142	36.3	0.118	Fixed-effects model
Questionnaires	3	1.00 (0.84, 1.19)	0.972	35.1	0.201	Fixed-effects model
Sex						
Male	10	1.03 (0.96, 1.10)	0.408	49.2	0.038	Fixed-effects model
Female	10	1.12 (1.03, 1.22)	0.007	24.7	0.216	Fixed-effects model
Geographic area						
USA	13	0.99 (0.92, 1.06)	0.782	29.2	0.168	Fixed-effects model
Europe	4	0.97 (0.86, 1.10)	0.637	20.7	0.286	Fixed-effects model
Canada	3	1.17 (0.93, 1.48)	0.178	6.4	0.344	Fixed-effects model
Australia	2	1.26 (0.97, 1.64)	0.079	0.0	0.785	Fixed-effects model
People's Republic of China	2	1.11 (1.03, 1.20)	0.008	0.0	0.920	Fixed-effects model
Age at start smoking (years)						
Younger (≤20)	3	1.15 (0.95, 1.39)	0.145	42.1	0.178	Fixed-effects model
Older (>20)	3	1.25 (1.02, 1.52)	0.029	0.0	0.553	Fixed-effects model
Duration (years)						
Short-term (≤20)	5	0.97 (0.76, 1.24)	0.799	50.3	0.090	Random-effects model
Long-term (>20)	6	1.06 (0.90, 1.26)	0.473	58.1	0.036	Random-effects model
Intensity (years)						
Light (≤20)	7	1.02 (0.96, 1.09)	0.547	41.9	0.112	Fixed-effects model
Heavy (>20)	7	1.11(0.91, 1.35)	0.309	65.4	0.008	Random-effects model
Pack-years						
Light (≤15)	4	1.16 (0.96, 1.42)	0.132	0.0	0.821	Fixed-effects model
Heavy (>15)	7	0.91 (0.80, 1.06)	0.218	28.4	0.211	Fixed-effects model
Year of study publication						
Before 1990	7	0.91 (0.78, 1.07)	0.261	18.1	0.292	Fixed-effects model
1990–2000	5	1.14 (1.00, 1.30)	0.055	0.0	0.908	Fixed-effects model
2000–2010	5	1.09 (0.93, 1.26)	0.284	50.7	0.088	Random-effects model
2010–now	5	1.04 (0.97, 1.10)	0.293	49.2	0.096	Fixed-effects model

Abbreviations: CI, confidence interval; RR, relative risk.

questionnaire, duration (short-term, long-term), intensity (heavy), and year of study publication (2000–2010). It is not surprising given the differences in study designs, characteristics of populations, definition of cigarette smoking, geographic area, and adjustment for confounding factors. As a result, a random-effects model, a conservative method to estimate the pooled effect, was used in these subgroup analyses.

As a crucial barrier that maintains brain homeostasis, the blood–brain barrier (BBB) selectively excludes many endogenous and xenobiotic substances, including some carcinogens, from entering the brain.[65,66] Whether *N*-nitroso compounds, the major carcinogens in cigarette smoke from cigarette smoking, could cross the BBB in adults remains uncertain. A previous study in rats showed that, upon intravenous administration, *N*-nitroso compounds could induce glioma formation.[67] Nicotine could also stimulate the malignant behavior of glioma cells.[68] There are some in vivo evidences that showed that nicotine could increase the permeability of the BBB, by allowing carcinogens (eg, nitrosamines) to reach the brain.[69] However, another study failed to show that *N*-nitrosamines could cause cancer in the brain.[70] Therefore, future studies should explore the biological mechanisms between cigarette smoking and glioma risk.

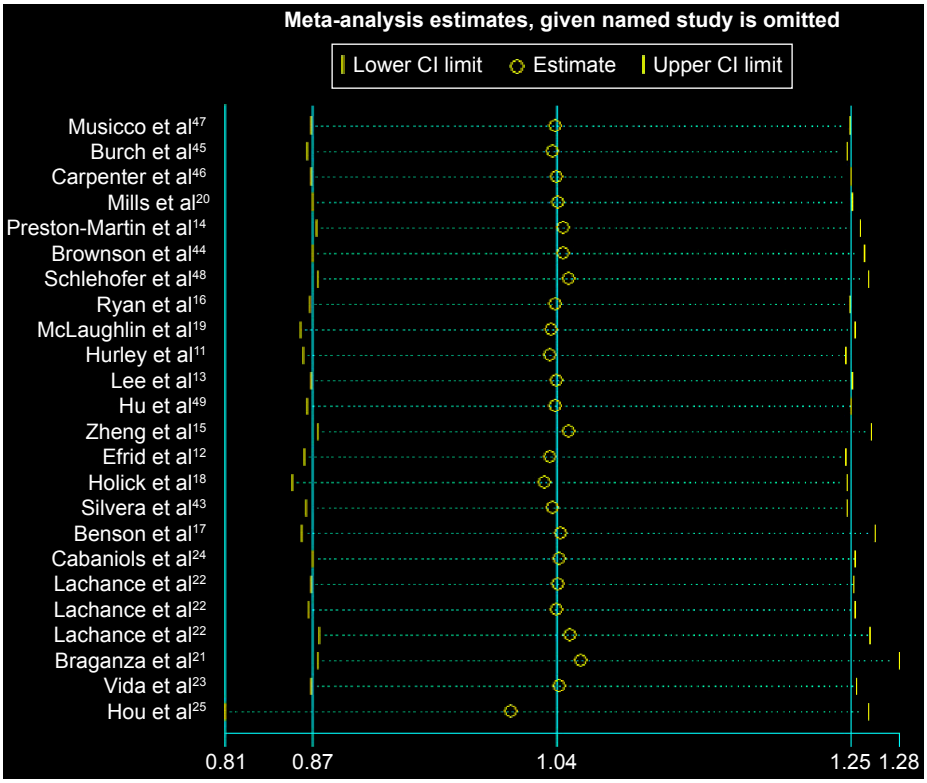

Figure 5 Sensitivity analysis for the association between ever-smoking and glioma.
Notes: The two ends of the lines represent the 95% CI.
Abbreviation: CI, confidence interval.

Several important strengths should be mentioned in our analysis. First, the major strength of this meta-analysis is the large number of participants and diversity of studied populations. Compared with the former meta-analysis in 2009,[7] our study included 17 case–control and seven cohort studies involving more than 2.3 million individuals. Second, a number of subgroup analyses were conducted in our study. No publication bias was found in this study, which further supported the robustness of the study results.

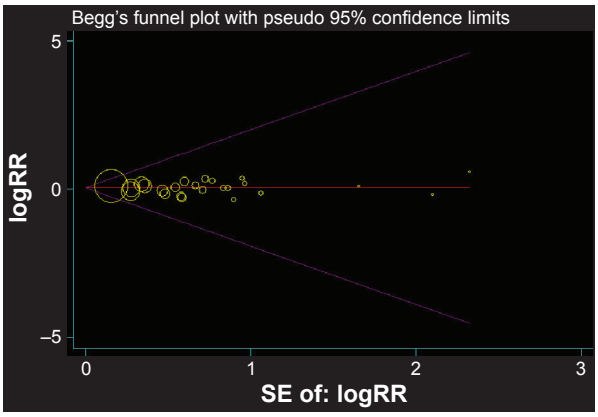

Figure 6 Begg's funnel plot of all 24 studies for the associations between ever-smoking and glioma.
Note: Each point represents separate study for the indicated association.
Abbreviations: RR, relative risk; SE, standard error.

There are some potential limitations in this study. First, only English language publications were included, which may omit other languages studies. Second, both cohort and case–control studies were included, and so methodological differences and confounding factors were unavoidable. However, we conducted a separate analysis for the two types of studies, with consistent results. Third, moderate-to-high heterogeneity was observed in some subgroups, which could not be avoided because of the confounding factors from original studies.

Conclusion

Cigarette smoking is not significantly associated with adult glioma in the overall population. However, there is a small but statistically increased association in females smokers.

Disclosure

The authors report no conflicts of interest in this work.

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