Research Article

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Cigarette Smoking and Risk of Meningioma: The Effect of Gender

Elizabeth B. Claus[1,2], Kyle M. Walsh[5], Lisa Calvocoressi[1], Melissa L. Bondy[3], Joellen M. Schildkraut[4], Margaret Wrensch[5,6], and Joseph L. Wiemels[5]

Abstract

Background: A number of studies have reported on the association between smoking and meningioma risk, with inconsistent findings. We examined the effect of gender on the association between cigarette smoking and risk of intracranial meningioma in a large population-based, case–control study.

Methods: The data include 1,433 intracranial meningioma cases aged 29 to 79 years diagnosed among residents of the states of Connecticut, Massachusetts, North Carolina, the San Francisco Bay Area and eight Texas counties between May 1, 2006 and April 28, 2011 as well as 1,349 controls that were frequency matched on age, sex, and geography. The data are analyzed separately and in a meta-analysis with six previously reported studies.

Results: Female cases who reported having ever smoked were at significantly decreased risk of intracranial meningioma (OR, 0.8; 95% CI, 0.7–0.9) in contrast to male cases who were at increased risk (OR, 1.3; 95% CI, 1.0–1.7). Similar findings were noted for current and past smokers. Smoking-induced risk for females did not vary by menopausal status. For males, increased duration of use ($P = 0.04$) as well as increasing number of pack-years ($P = 0.02$) was associated with elevated risk. A meta-analysis including 2,614 cases and 1,179,686 controls resulted in an OR for ever smoking of 0.82 (95% CI, 0.68–0.98) for women and 1.39 (95% CI, 1.08–1.79) for men.

Conclusion: The association of cigarette smoking and meningioma case status varies significantly by gender with women at reduced risk and men at greater risk.

Impact: Whether the observed differences are associated with a hormonal etiology will require additional investigation. *Cancer Epidemiol Biomarkers Prev; 21(6); 943–50. ©2012 AACR.*

Introduction

In the most recent report from the Central Brain Tumor Registry of the United States (CBTRUS), intracranial meningiomas are identified as the most frequently reported primary brain tumor in adults within the United States (1). The increasing awareness of the import of these tumors has led to a desire to investigate possible risk factors with ionizing radiation (IR) the most consistently confirmed risk exposure (2–9). Few other factors have been identified (2) although a number of investigators have examined the role of cigarette smoking (10–21). The examination of this exposure is an intriguing one given both smoking's well-known association with a wide range of cancers as well as its potential antiestrogenic effects. Notably, an inverse association of cigarette smoking has been reported for tumors such as endometrial cancer (22) which like meningioma may have a hormonal etiology. Reports of an association between smoking and meningioma have been inconsistent when examined across gender (10–13). However, when stratified by gender, several projects have suggested a variable effect (14–21) with women at decreased and men at increased risk. Several reports have also suggested confounding of risk by menopausal status (20) as well as exposure to diagnostic (15) or therapeutic (16) IR although no confirmation of these results exist. With the exception of the Million Women Study Cohort (20), previous studies have been hampered by small sample size or an inability to control for potential confounding variables in the statistical analysis. This report compares self-reported smoking history in 1,433 persons with intracranial meningioma to those of 1,349 controls. The large sample size of this population-based study will provide a more precise estimate of any association by gender. Moreover, the multiple covariates included in the data collection allow for the first time the joint statistical control of potential confounding factors

Authors' Affiliations: [1]Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut; [2]Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts; [3]Department of Epidemiology, Baylor College of Medicine, Houston, Texas; [4]Department of Community and Family Medicine, Duke University School of Medicine, Durham, North Carolina; and Departments of [5]Epidemiology and Biostatistics and [6]Neurological Surgery, University of California at San Francisco School of Medicine, San Francisco, California

Corresponding Author: Elizabeth B. Claus, Department of Epidemiology and Public Health, Yale University School of Medicine, 60 College St., P.O. Box 208034, New Haven, CT 06520. Phone: 203-785-6415; Fax: 203-785-6912; E-mail: elizabeth.claus@yale.edu

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such as education, body mass index, and menopausal status.

Materials and Methods

Study design

Eligible case subjects include all persons diagnosed from May 1, 2006 to April 28, 2011 with a histologically confirmed intracranial meningioma among residents of the states of Connecticut, Massachusetts, and North Carolina as well as the Alameda, San Francisco, Contra Costa, Marin, San Mateo, and Santa Clara counties of California and the Brazoria, Fort Bend, Harris, Montgomery, Chambers, Galveston, Liberty, and Waller counties of Texas. Cases were identified through the Rapid Case Ascertainment systems and state cancer registries of the respective sites and were between the ages of 20 and 79 years at time of diagnosis. Controls were selected by random-digit-dialing by an outside consulting firm (Kreider Research) and were matched to cases by 5-year age interval, sex, and state of residence. Study subjects with a previous history of meningioma and/or a brain lesion of unknown pathology were excluded. Subjects were English or Spanish speaking. The study, consent forms, and questionnaire were approved by the Institutional Review Boards at the Yale University School of Medicine, Brigham and Women's Hospital, the University of California at San Francisco, the MD Anderson Cancer Center, and the Duke University School of Medicine. The study was also approved by the State of Connecticut Department of Public Health Human Investigation Committee with some data directly obtained from the Connecticut Tumor Registry in the Connecticut Department of Public Health as well as the MA Tumor Registry.

Data collection

The physicians of each eligible case were contacted to request permission to approach the case. Cases approved for contact by their physicians and controls identified by Kreider Research were sent an introductory letter. Approximately 1 or 2 weeks later, a trained interviewer contacted the potential study subject by telephone to administer the interview. Interviews took an average of 52 minutes. Proxies provided information for 9 cases and no controls. The questionnaire included detailed questions on demographics, family history of cancer, pregnancy and menstrual history, exogenous hormone history, and medical history. Subjects who had smoked a total of 100 cigarettes or more in their lifetime were defined as "ever smokers." Smokers were asked the age at which they started (and for past smokers the age at which they stopped) smoking cigarettes, the number of cigarettes smoked per day, and the total number of years of smoking. Subjects who answered "0" to the question "in a typical week over the past year, on how many days did you consume an alcoholic beverage of any type (beer, wine, hard liquor)?" were defined as nondrinkers. In defining exposure to therapeutic IR, subjects were asked whether they had ever undergone radiation treatment to the head, neck, face, or chest. For exposure to diagnostic radiation, subjects were questioned whether they had ever received a dental X-ray (bitewing, full mouth, or panorex) a cerebral angiogram or a computed tomograph (CT) of the head. Risk factor and screening information were truncated at the date of diagnosis for cases and the date of interview for controls (hereafter referred to as the reference date).

To date, 2,228 eligible cases and 2,604 eligible controls have been identified. Ninety-eight percent of eligible cases had a consenting physician. Among those cases, 65% participated in the interview portion of the study while 52% of eligible controls participated in the interview. Six hundred sixty-six cases were ineligible due to out-of-state residency (45), language (70), recurrent meningioma (83), incarcerated (3), age (50), spinal meningioma (144), pathology unavailable for review (56), mental or medical (i.e., deaf) illness (96), deceased (cause of death other than meningioma; 76), another pathology (i.e., lung metastasis; ref. 16), or other (27). Eighty-five controls were ineligible due to out-of-state residency (6), language (8), a history of previous brain tumor unknown pathology (8), age group (1), mental or medical illness (53), deceased (3), or other (9). Interviewed and noninterviewed cases were similar with respect to age, sex, and residence. Interviewed and noninterviewed controls did not differ by sex or residence but did differ by age with interviewed controls older than noninterviewed controls. The sample used in this analysis includes 1,433 case and 1,349 control subjects.

Statistical analysis

The initial portion of the statistical analysis included descriptive statistics. T-tests, χ^2, and Fisher exact tests were used to examine the association between meningioma risk and independent covariates. To assess the odds of meningioma associated with risk factors, conditional logistic regression was used to provide maximum likelihood estimates of the ORs [adjusted for age, alcohol use (yes/no), race (white vs. nonwhite), education ($\leq$16 vs. >16 years), and body mass index] with 95% CI using the statistical package PC-SAS version 9.2 (25). (As the variables income and education were colinear, only education was included as the data were more complete). Linear trend was assessed across ordered categories. As prior studies examined the association between cigarette smoking and meningioma risk by menopausal status (pre vs. post; ref. 19), receipt of a full-mouth dental X-ray (ever/never; ref. 15), and radiotherapy to the head (16), we also examined the effect of these variables in the final model.

An electronic search of the MEDLINE, ISI Web of Science, and EMBASE databases from 1970 to August 2011 identified 6 case–control (15–19,21) and 1 cohort (20) studies quantifying associations between cigarette smoking and meningioma by gender (Table 1). To be eligible for inclusion, publications had to include original data and to present gender-specific OR or relative risk quantifying the association between cigarette smoking

Table 1. Epidemiologic studies of ever smoking and meningioma by gender

	Females			Males		
Study	**Cases**	**Controls**	**OR (95% CI)**	**Cases**	**Controls**	**OR (95% CI)**
Case control						
Preston-Martin and colleagues[a]	185	185	1.4, $P = 0.15$			NA
Preston-Martin and colleagues[a]			NA	272	272	1.2 (0.6–2.7)[b]
Hu and colleagues[c]	22/113	25/226	0.5 (0.3–1.0)	48/70	98/140	1.1 (0.6–2.0)
Phillips and colleagues[d]	66/143	142/286	0.7 (0.5–1.1)	40/57	56/114	2.1 (1.1–4.2)
Lee and colleagues[e](stronger in premenopausal women)	101/217	146/248	0.6 (0.4–0.9)			NA
Flint-Richter and colleagues[e] (interaction with radiation in women)	50/171	68/196	0.8 (0.5–1.2)	53/71	46/84	2.1 (1.1–4.2)
Cohort						
Benson and colleagues[f]						
Past			0.9 (0.7–1.1)			NA
Current			0.9 (0.7–1.1)			NA

[a]Matched on age, race, and residence.
[b]Exact binomial CIs presented here differ from those presented on forest plot which are calculated by a normal approximation.
[c]Matched on gender, age, and residence.
[d]Estimate adjusted for age and education.
[e]Estimate adjusted for radiation.
[f]Estimate adjusted for height, body mass index, exercise, socioeconomic status, alcohol, parity, age at first birth, and oral contraceptive use.

(ever vs. never) and meningioma risk. Using the inverse variance mixed effects model of DerSimonian and Laird (23), separate meta-analyses were conducted for males and for females with the RevMan v5.1.2 software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Sweden). Study heterogeneity was assessed with the I^2 statistic (24). To assess the presence of reporting bias, funnel plots graphing estimates of study precision against the ORs were created and visually inspected.

Results

Meningioma Consortium data

Descriptive statistics for the study sample are provided in Table 2. The mean age was 57.5 years for cases versus 57.4 years for controls ($P = 0.74$). The majority of study subjects were female and White. Cases and controls did not differ by age, race, sex, and geographic location by design. Controls were more likely to have 16 or more years of schooling and to have a salary greater than $75,000.

Table 3 compares reported smoking histories for cases and controls. There was a significant interaction between ever having smoked and sex ($P = 0.01$) supporting the stratification of risk estimates by sex. Regardless of sex, cases and controls did not differ significantly by mean age at first use, last use, or mean duration. However, women smoked less than did men with an older age at first use, younger age at last use, and shorter duration than did men. Among cases, smokers were significantly older at age of diagnosis than were nonsmokers (60.4 vs. 56.0 years for males, $P < 0.01$ and 59.4 vs. 56.4 years for females, $P < 0.01$, respectively).

Women who reported ever having smoked cigarettes were at significantly decreased risk of meningioma (aOR, 0.8; 95% CI, 0.7–0.9) relative to women who had never smoked. Conversely, among men, ever smokers had an increased risk of meningioma (aOR, 1.3; 95% CI, 1.0–1.7) relative to never smokers. Risk for females did not vary by duration or amount of use while for men an elevated risk was seen with increased duration and increased number of pack-years; (OR, 1.6; 95% CI, 1.1–2.2) for men with a 13 or more pack-year history.

We attempted to examine previously reported effect modification by menopausal status as well as by history of diagnostic or therapeutic radiation. Among women, we tested for an interaction with smoking exposure by menopausal status however no significant differences were seen with ever ($P = 0.26$), current ($P = 0.28$), or past ($P = 0.41$) smoking status. When controlled for a history (ever/never) of bitewing, full mouth, or panorex dental films, a history of head CT, or a history of prior radiotherapy to the head, neck, face, or chest there is no evidence of effect modification.

Meta-analysis

In addition to our own data, the review identified 6 studies which merited inclusion in the meta-analyses [The 1980 study by Preston-Martin (18) was dropped for lack of numeric detail]. The meta-analysis of females included 2,015 cases and 1,178,932 controls. Females who reported

Table 2. Descriptive statistics of the study sample

	Case subjects ($n = 1,433$)		Control subjects ($n = 1,349$)		
	No.	%	No.	%	Cases versus controls
Age, y					
20–29	24	1.7	20	1.5	
30–39	89	6.2	87	6.5	
40–49	271	18.9	251	18.7	
50–59	405	28.3	410	30.5	
60–69	435	30.4	356	26.5	
70–79	208	14.4	220	16.3	
Mean (SD)	57.5 (11.7)		57.4 (12.0)		$P = 0.74$
Gender					
Male	384	26.8	392	29.0	
Female	1,049	73.2	957	71.0	$P = 0.18$
Race					
White	1,191	83.1	1,157	85.7	
Black	114	8.0	61	4.5	
Asian	51	3.6	50	3.8	
Other	67	5.3	81	6.0	$P = 0.11$
Residence					
Connecticut	147	10.3	167	12.4	
Massachusetts	314	21.9	320	23.8	
North Carolina	424	29.6	394	29.2	
California	366	25.4	317	23.5	
Texas	182	12.7	151	11.2	$P = 0.18$
Education					
≤16 y	386	27.1	238	17.7	$P < 0.01$
>16 y	1,041	72.9	1,108	82.3	
Income					
≤$75,000	720	57.2	590	48.6	$P < 0.01$
>$75,000	538	42.8	623	51.4	

ever smoking were at significantly decreased risk of meningioma relative to never smokers in the meta-analysis (OR, 0.82; 95% CI, 0.68–0.98; Fig. 1). Results of a sensitivity analysis, conducted by carrying out the cumulative meta-analysis with each study systematically omitted, one at a time with replacement, did not indicate that any one study was exerting undue influence on the summary measure. Moderate study heterogeneity was detected in the meta-analysis of females ($I^2 = 53\%$), but this heterogeneity is entirely due to a single study ($I^2 = 0\%$ when the study of Hu and colleagues is dropped from the analysis).

The meta-analysis of males included 599 cases and 754 controls. Ever smokers had a significantly increased risk of meningioma relative to never smokers (OR, 1.39; 95% CI, 1.08–1.79; Fig. 2). Sensitivity analyses did not indicate that any one study was exerting undue influence on the summary measure. Only minimal study heterogeneity was detected ($I^2 = 17\%$). Funnel plot results lessened concern for the presence of substantial publication bias for either sex (data not shown).

Discussion

This is the largest and the most recent case–control study to examine the relationship between cigarette smoking and meningioma risk. Unlike previous studies, we were able to both stratify by gender and control for a number of confounding factors such as education, alcohol use, and body mass index. In these data, active cigarette

Table 3. Smoking histories of meningioma cases and controls by gender

	Females			Males		
	Cases (n = 1,049)	Controls (n = 957)		Cases (n = 384)	Controls (n = 392)	
	%	%	OR (95% CI)[a]	%	%	OR (95% CI)
Smoking						
Never[b]	56.0	51.6	1.0	42.4	50.6	1.0
Ever[c]	44.0	48.4	0.8 (0.7–0.9)	57.3	49.4	1.3 (1.0–1.7)
Current	10.0	11.2	0.8 (0.6–1.0)	11.9	10.8	1.2 (0.7–1.9)
Past	34.0	37.2	0.8 (0.7–1.0)	45.4	38.6	1.3 (0.9–1.8)
Cigarettes per day						
≤20	38.7	42.9	0.8 (0.7–0.9)	42.4	38.5	1.3 (0.9–1.8)
>20	5.3	15.4	0.9 (0.6–1.3)	15	11.0	1.4 (0.9–2.3)
P_{trend}			0.07			0.07
Duration, y						
<20	24.7	28.6	0.8 (0.6–1.0)	28.2	27.2	1.2 (0.9–1.7)
≥20	19.3	19.8	0.8 (0.6–1.1)	29.2	22.3	1.5 (1.0–2.1)
			0.07			P = 0.04
Pack-years						
<13	24.5	29.2	0.8 (0.6–0.9)	22.0	23.4	1.1 (0.7–1.6)
≥13	19.3	18.7	0.9 (0.7–1.1)	35.2	25.8	1.6 (1.1–2.2)
P_{trend}			0.14			0.02
Mean age at first use	18.1	17.7	P = 0.18	16.7	17.3	P = 0.21
Mean age at last use	39.4	36.6	P = 0.06	40.2	38.6	P = 0.20
Mean duration, y	21.0	20.6	P = 0.62	24.2	22.5	P = 0.41

[a]Adjusted for age, race (white vs. nonwhite), body mass index, alcohol use, and education.
[b]Never is baseline category for all comparisons.
[c]One hundred or more cigarettes in lifetime.

smoking was associated with an increased risk in men but a decreased risk in females. A number of previous authors have examined the relationship between cigarette smoking and meningioma risk with inconsistent results when males and females are grouped together (10–13) but as formally examined by our meta-analysis, remarkably consistent results [with the exception of the early study by Preston-Martin (18) which included 185 females cases from the Los Angeles area] when stratified by gender.

The finding of a protective effect of smoking among women in our study is intriguing in light of the suggestive but poorly defined role for hormonal factors for meningioma (26). An association between hormones and

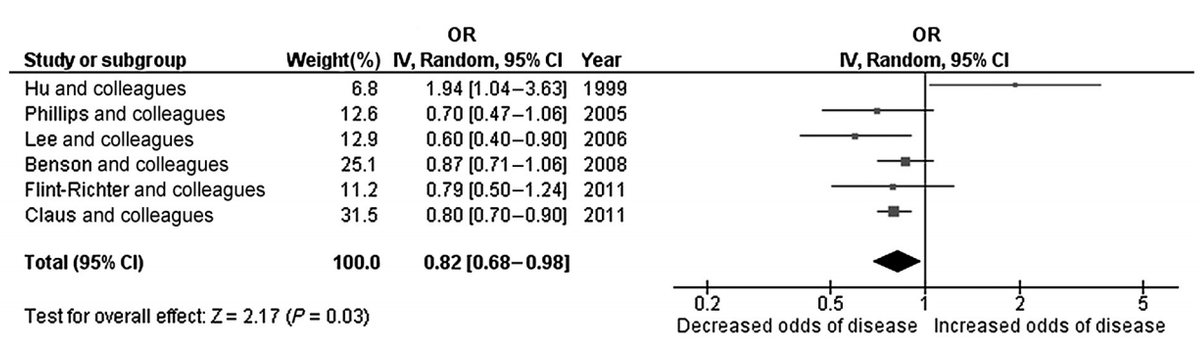

Figure 1. Forest plot of the association between meningioma and smoking status among females (ever smokers vs. never smokers). The area of study symbols is proportional to study weight.

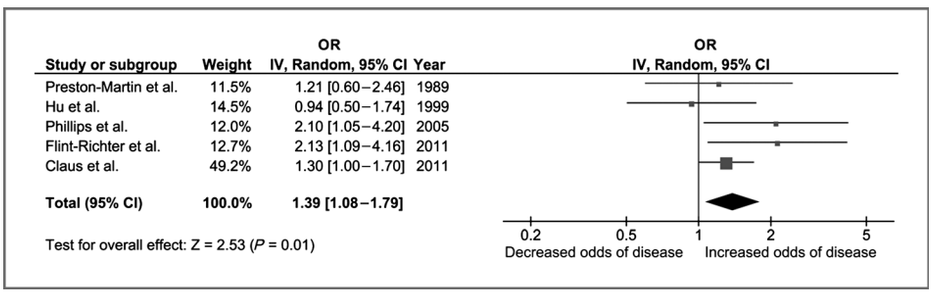

Figure 2. Forest plot of the association between meningioma and smoking status among males (ever smokers vs. never smokers). The area of study symbols is proportional to study weight.

meningioma risk has been suggested by the increased incidence of the disease in women versus men, the presence of hormone (particularly progesterone) receptors on some meningiomas, an association between breast cancer, uterine fibroids, endometriosis and meningioma risk (27), indications that meningiomas change in size during the luteal phase of the menstrual cycle and pregnancy, and *in vitro* proliferation of meningioma cell lines in culture after exposure to estrogens. In the one previous case–control study to examine risk by menopausal status a stronger effect was noted in premenopausal women (19) although we were not able to detect such an effect, potentially due to the smaller number of premenopausal women in our data. Cigarette smoking is hypothesized to be antiestrogenic by enhancing the metabolism of estradiol to inactive catechol estrogens, increasing the binding of estrogen by serum sex hormone–binding globulin, as well as decreasing adipose-derived estrogen (28). The effect of smoking has been examined in a number of hormone-associated cancers including breast for which results have been inconsistent and endometrial (9) for which smoking has been consistently associated with decreased risk. In addition to a hormonal difference, the observed variation in risk associated with cigarette smoking for women versus men may be due to other factors including differences in patterns of cigarette use by gender (28,29). Smoking may also serve as a marker for other variables associated with risk in men but not women including alcohol use, weight (and hence amount of adipose tissue), and socioeconomic variables, although these variables were controlled for in our analyses.

Strengths to the study include the population-based study design, large sample size, and relatively consistent magnitude and direction of risk estimates. Histologic confirmation was obtained for all case subjects suggesting that these results may only be applicable to lesions that are deemed in need of surgery rather than conservative management.

Limitations for this study include the possibility of misreporting of cigarette smoking by study participants. Self-reporting of cigarette smoking may also vary by gender although data that correlate thiocyanate and cotinine levels in male and female study subjects with self-reported cigarette use suggest that self-report is a reliable and cost efficient means to measure smoking behavior in both men and women (30, 31). Differential recall by case–control status is possible although a widespread knowledge of any association between meningioma and smoking among the general public is unlikely given the limited research on this topic. We noted lower than expected (although in line with other recent studies of brain tumors) response rates among control subjects. Cases and controls did not differ by race, age, sex, or geographic site but did differ with respect to education and income with controls reporting higher income and education than controls, suggesting a greater willingness among persons of higher socioeconomic status to participate in epidemiology research. Although these variables were adjusted for in all analyses, such differences in socioeconomic status, a factor likely related to cigarette smoking use, may lead to bias in risk estimation, although the opposite direction of risks identified here seems to argue against such a bias.

The extent to which risk for meningiomas associated with exposure to cigarette smoke is modified by genotype is unknown and this is an important area for future study. Genetic variants in genes involved in the control of aromatic hydrocarbons have been implicated in meningioma risk, but not confirmed (32–34).

Given the important role of IR in meningioma risk, several previous groups have attempted to control for IR exposure when assessing risk associated with smoking. In their population-based case–control study including 200 cases of meningioma, Phillips and colleagues (15) assessed risk with cigarette smoking that occurred 10 or more years before the meningioma surgery and reported gender-specific findings quite similar to ours. Although the actual estimates were not presented, when the authors controlled for subjects who reported ever having a full mouth dental X-ray series, findings for active smoking were strengthened. Flint-Richter and colleagues (16) assessed the role of smoking in presumed radiation- and nonradiation–related meningiomas using data from the Tineas Capitas Cohort (3). They reported an increased risk associated with smoking for men. For women, they observed a significant inverse association of meningioma with smoking (OR, 0.32; 95% CI, 0.14–0.77) with a dose–response association ($P < 0.01$) in nonirradiated (mean dose, 1.5 Gy) women and a nonsignificant increase risk of meningioma in irradiated women. These findings lead the authors to speculate on the existence of an interaction between IR and smoking in meningioma risk for women.

No effect modification by exposure to IR (either diagnostic or therapeutic) was appreciated in our analyses. Further study of the possible role of IR in the examination of smoking and meningioma risk is of interest. Studies such as this one allow for the collection of large numbers of persons with varying gene–environment combinations and hence comparison of the effect of exposures such as IR across genetic variant; our group plans to examine these interactions in future work.

Our results suggest a gender-specific relationship between smoking and intracranial meningioma risk. The large size of our data set (which includes information on important confounding variables) allows us to confirm a reduced risk for women who are active smokers and offers additional insight into what is likely a complex relationship between hormonal factors and meningioma risk.

Disclosure of Potential Conflicts of Interest

The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E.B. Claus, L. Calvocoressi, M.L. Bondy, J.M. Schildkraut, M.R. Wrensch, J.L. Wiemels
Development of methodology: E.B. Claus, K.M. Walsh, M.R. Wrensch, J.L. Wiemels
Acquisition of data: E.B. Claus, L. Calvocoressi, M.L. Bondy, J.M. Schildkraut, M.R. Wrensch, J.L. Wiemels
Analysis and interpretation of data: E.B. Claus, K.M. Walsh, L. Calvocoressi, M.L. Bondy, M.R. Wrensch, J.L. Wiemels
Writing, review, and/or revision of the manuscript: E.B. Claus, K.M. Walsh, L. Calvocoressi, M.L. Bondy, J.M. Schildkraut, M.R. Wrensch, J.L. Wiemels
Administrative, technical, or material support: E.B. Claus
Study supervision: E.B. Claus, L. Calvocoressi, M.L. Bondy, J.M. Schildkraut, M.R. Wrensch, J.L. Wiemels

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