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Exogenous hormone use, reproductive factors, and risk of intracranial meningioma in females

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Abstract

Object—The 2-fold higher incidence of meningioma in women compared with men has long suggested a role for hormonally mediated risk factors, but specific mechanisms remain elusive.

Methods—The study included data obtained in 1127 women 29–79 years of age with intracranial meningioma diagnosed among residents of Connecticut, Massachusetts, North Carolina, the San Francisco Bay Area, and 8 Texas counties between May 1, 2006, and October 6, 2011, and data obtained in 1092 control individuals who were frequency matched for age group and geography with meningioma patients.

Results—No association was observed for age at menarche, age at menopause, or parity and meningioma risk. Women who reported breastfeeding for at least 6 months were at reduced risk of meningioma (OR 0.78, 95% CI 0.63–0.96). A significant positive association existed between meningioma risk and increased body mass index ($p < 0.01$) while a significant negative association existed between meningioma risk and current smoking ($p < 0.01$). Among premenopausal women, current use of oral contraceptives was associated with an increased risk of meningiomas (OR 1.8, 95% CI 1.1–2.9), while current use of hormone replacement therapy among postmenopausal women was not associated with a significant elevation in risk (OR 1.1, 95% CI 0.74–1.67). There was no association between use of fertility medications and meningioma risk.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. 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.

Author contributions to the study and manuscript preparation include the following. Conception and design: Claus, Wrensch. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Claus. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Claus. Statistical analysis: Claus. Administrative/technical/material support: Claus, Calvocoressi, Schildkraut. Study supervision: all authors.

Conclusions—The authors' study confirms associations for body mass index, breastfeeding, and cigarette smoking but provides little evidence for associations of reproductive and menstrual factors with meningioma risk. The relationship between current use of exogenous hormones and meningioma remains unclear, limited by the small numbers of patients currently on oral hormone medications and a lack of hormone receptor data for meningioma tumors.

Keywords

meningioma; epidemiology; hormones; oral contraceptives; hormone replacement therapy; reproductive variables; body mass index; smoking; breastfeeding; oncology

From 2004 to 2007, over 60,000 adult females were diagnosed with meningioma in the US,6 the most frequently reported primary brain tumor in adults living in the US. Given the number of women affected, researchers have begun to examine risk factors potentially associated with the development of this tumor, including a suggestive but poorly defined role for hormonal factors. Evidence of an association between hormones and meningioma risk includes the higher incidence in women than men, most notably so in women before menopause;6 the presence of hormone receptors on some meningiomas;8 positive associations with uterine fibroids,7,18 endometriosis,7 and possibly breast cancer;7,11 indications that meningioma size varies during the luteal phase of the menstrual cycle and pregnancy;28 a potential association with current HRT/OC use;10 a decreased risk for women who report ever smoking;9,18 and in vitro proliferation of meningioma cell lines in culture after exposure to estrogens. In an effort to further clarify the nature of the relationship between endogenous and exogenous hormonal exposures and meningioma risk, this report compares the reproductive and hormonal histories of 1127 female case subjects to those of 1092 female control subjects in the largest case-control study of meningioma to date. The findings are evaluated in light of the growing literature on the topic and examined for possible clinical application given the large number of affected women.

Methods

Study Design

Eligible case patients included all persons diagnosed from May 1, 2006, to October 6, 2011, with a histologically confirmed intracranial meningioma among residents of the states of Connecticut, Massachusetts, and North Carolina as well as the California counties of Alameda, San Francisco, Contra Costa, Marin, San Mateo, and Santa Clara and the Texas counties of Brazoria, Fort Bend, Harris, Montgomery, Chambers, Galveston, Liberty, and Waller counties of Texas. Patients 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. Control individuals 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 patients with a history of meningioma and/or a brain lesion of unknown pathology were excluded. Individuals were English- or Spanish-language speaking. The study, consent forms, and questionnaire were approved by the institutional review boards at Yale University School of Medicine, Brigham and Women's Hospital, University of California at San Francisco, M D Anderson Cancer Center, and 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 Massachusetts Tumor Registry.

Data Collection

The physicians of each eligible patient were contacted to request permission to approach the individual. Patients approved for contact by their physicians, and control individuals identified by Kreider Research were sent an introductory letter. Approximately 1–2 weeks later, a trained interviewer contacted the potential study participant by telephone to administer the interview. Interviews took an average of 52 minutes. Proxies provided information for 9 patients and no controls. The questionnaire included detailed questions on demographics, family history of cancer, pregnancy and menstrual history, exogenous hormone history, and medical history. Women were considered perimenopausal if they reported no regular menses for up to 12 months and postmenopausal if they reported no regular menses for at least 12 months or had undergone a bilateral oophorectomy. Women who had missing or incomplete information on menstruation, who reported a hysterectomy, or who indicated use of exogenous hormones/intrauterine device while still menstruating were considered postmenopausal if they were 55 years of age or older, perimenopausal if they were between 46 and 55 years, or premenopausal if they were less than 46 years at interview. Individuals who had smoked a total of 100 cigarettes or more in their lifetime were defined as “ever” smokers. Those 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. Risk factor and screening information were truncated at the date of diagnosis for patients and the date of interview for controls (hereafter referred to as the reference date).

To date, 2404 eligible patients and 2958 eligible controls have been identified. Ninety-eight percent of eligible patients had a consenting physician. Among those patients, 65% participated in the interview portion of the study, while 52% of eligible controls participated in the interview. Six hundred ninety-six patients were ineligible due to out-of-state residency (n = 48), language (n = 74), recurrent meningioma (n = 84), incarceration (n = 3), age (n = 50), spinal meningioma (n = 148), pathology unavailable for review (n = 75), mental or medical (for example, deafness) illness (n = 110), death (cause of death other than meningioma) (n = 79), another pathology (for example, lung metastasis) (n = 16), or other reason (n = 9). One hundred ten control individuals were ineligible due to out-of-state residency (n = 6), language (n = 8), a history of brain tumor of unknown pathology (n = 8), age group (n = 1), mental or medical illness (n = 70), death (n = 3), or other reaon (n = 14). Interviewed and noninterviewed patients 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 being older than noninterviewed controls. The sample used in this analysis includes the 1127 female case and 1092 female control individuals.

Statistical Analysis

The initial portion of the statistical analysis included descriptive statistics. We used t-tests, chi-square tests, and Fisher exact tests 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 odds ratios (adjusted for age, alcohol use [yes/no], race [white versus nonwhite], education [(≤16 years versus > 16 years of age) in addition to the endogenous and exogenous hormone variables with 95% confidence intervals using the statistical package PC-SAS version 9.2 (SAS Institute). (Because the variables of income and education were co-linear, only education was included, as the data were more complete.) Linear trends were assessed across ordered categories.

Results

Descriptive statistics for the study sample are provided in Table 1. The mean age was 57.2 years for patients versus 57.4 years for controls ($p = 0.58$). The majority of study subjects identified themselves as white. Patients and controls did not differ by age or geographic location by design. Controls were more likely to be white, to have 16 or more years of schooling, and to have an annual salary greater than $75,000.

Results from the multivariate analysis are presented in Table 2. Patients and controls did not differ by age at menarche, age at menopause, or number of full-term pregnancies, although the mean age at first live birth was higher in controls than patients (27.7 vs 25.9 years, respectively; $p < 0.01$). Breastfeeding was associated with a reduced risk of meningioma, significantly so if a woman had breastfed for 6 months or longer (OR = 0.75, 95% CI 0.60–0.94). Patients were more likely to report having undergone a bilateral oophorectomy, even after adjustment for a history of surgery for ovarian or endometrial cancer or fibroid tumors. Patients had a significantly higher BMI than did controls (28.0 vs 27.1, respectively, $p < 0.01$). Women in the second, third and fourth quartile had 1.06 (95% CI 0.83–1.35), 1.13 (95% CI 0.89–1.45), and 1.29 (95% CI 1.01–1.65) times the risk of women in the first quartile ($p = 0.04$, test for trend). As we have reported previously, current smoking status was associated with a significantly reduced risk of meningioma in females.9 Interestingly, the use of alcohol was also associated with a reduced risk of meningioma.

With respect to the use of exogenous hormones, overall there was no increase in risk associated with use (ever/ never) of OCs. When all women, regardless of menopausal status, were included in the analysis, an elevated risk was not seen for women currently using OCs (OR 1.45, 95% CI 0.94–2.24). When the analysis was restricted to include only premenopausal women, a significant increase in risk was appreciable for current OC users (OR 1.8, 95% CI 1.1–2.9), although the number of exposed women was low (only 87 patients and 71 controls were defined as current OC users). Although a similar pattern of risks was appreciated between HRT and meningioma risk, no statistically significant increase in risk was seen for “ever,” past, or current users relative to “never” users, with less than 10% of the sample reporting current HRT use. No association was present between the reported use of fertility medications and meningioma risk.

Discussion

This is the largest and most recent case-control study to examine the relationship between hormonal or reproductive factors and meningioma risk. Unlike many previous studies, in the present one we were able to control for a number of confounding factors such as race, education, and cigarette smoking. We found that high BMI, current use of OCs in premenopausal women, and not smoking were significantly associated with meningioma risk. There was limited evidence of an association between reproductive variables and meningioma risk with younger age at first live birth and a history of breastfeeding associated with decreased risk. No significant association was seen between use of either fertility medication or HRT and risk.

A number of studies have examined the association between meningioma risk and OC use[3,5,12,15,17,18,22,23,31] (Table 3) as well as HRT[2,4,5,12,15,17–20,22,23,31] (Table 4). Little evidence is seen for an increased risk associated with “ever” use of OC, although several studies (primarily cohort) and ours suggest an increase in risk with current OC use. The EPIC investigators[23] noted a higher risk for current versus “never” OC users (OR 3.61, 95% CI 1.75–7.46), whereas the Nurses Health Study[17] reported an elevated but not statistically increased risk (OR 1.34,95% CI 0.18–9.96) for current users. (The Million Women Study[3]

did not report current use risk.) Few investigators have been able to examine the relationship between sex hormone receptor expression and OC use. The two case-control studies that did so reported conflicting results, the interpretation of which is complicated by differing definitions of receptor positivity across studies.[12,19]

Hormone Replacement Therapy

There is little evidence of an association between HRT use and risk of meningioma in any of the case-control studies (including ours), but three[2,17,23] of the four[18] prospective cohort studies (as well as two[4,19] of the three[5] retrospective cohorts) reported significantly elevated risks either for current[2,17,23] or "ever"[19] use of HRT (Table 4). In a case-control analysis within the Nurses Health Study,[17] the relative risk of meningioma associated with current HRT for pre- and postmenopausal women was 2.48 (95% CI 1.29–4.77) and 1.86 (95% CI 1.07–3.24), respectively when compared with postmenopausal women who had never used hormones.[17] Results from the Million Women Study[2] (RR 1.34, 95% CI 1.03–1.75) and EPIC[23] cohorts (HR1.79, 95% CI 1.18–2.71) concur. The reason for such conflicting results by study design (for example, casecontrol vs cohort) is unclear but may point to common difficulties associated with case-control studies including recall bias or the inclusion of controls with significantly higher socioeconomic status than cases. Three studies examined risk by HRT preparation: one case-control[12] study found no association, but two cohort studies[2,19] reported increased risk with estrogen-only preparations of note given the generally low rates of estrogen and high rates of progesterone receptor expression in meningioma tumors.[8] Two case-control studies[12,20] examined risk by hormone receptor status with no evidence of an association. If current but not past use of oral hormones is associated with meningioma risk, this may suggest a promoter rather than initiator role of these medications; however, further analyses by preparation type and tumor hormone receptor are needed. To date, no study has examined risk concurrently by both preparation and hormone receptor status.

Reproductive Factors

With the exception of the Nurses Health Study,[17] no association has been documented[12,18,22,23,26,30] between age at menarche and meningioma risk, which is consistent with our findings. The Nurses Health Study[17] investigators observed relative risks of 1.29 (95% CI 0.86 – 1.92) and 1.97 (95% CI 1.06, 3.66) for menarche at ages 12–14 and 14 or older, respectively, compared with menarche before age 12. In general, age at menopause,[18,23,30] age at first birth,[3,12,18,21,23,30] and parity[3,10,18,21,23,30] have not been associated with meningioma risk. One case-control study[22] with 219 cases found a protective effect for pregnancy, which increased with number of pregnancies and age at first pregnancy. Data on breastfeeding and risk are limited[12,15,23,30] but mostly[12,15,30] similar to our findings of an inverse association with risk. An unexpected but previously reported finding is the positive association between bilateral oophorectomy and risk.[18,23] The explanation for this finding is unclear but may relate to the fact that all but 5 of these patients also underwent a hysterectomy and were more likely to receive estrogen-only HRT than were women not undergoing such a procedure.

Smoking

As previously detailed,[9] a history of ever smoking significantly decreased the risk of meningioma in women. Similar findings were noted for current and past smokers. The effects were similar in both pre- and postmenopausal women. The finding of a protective effect of smoking among women is intriguing (and consistent across studies)[3,23] in light of the suggestive but poorly defined role for hormonal factors for meningioma. Cigarette smoking is hypothesized to be anti-estrogenic by enhancing the metabolism of estradiol to

inactive cathechol estrogens, increasing the binding of estrogen by serum sex hormone–binding globulin, and decreasing adipose-derived estrogen[1]

Body Mass Index

Our findings of a positive association between increased BMI and meningioma risk are consistent with all[3,12,17,18] but one[22] previous study, most of which were not able to reach statistical significance given small sample size. Mechanisms by which obesity may be related to risk include decreased insulin sensitivity or increased inflammatory response (of interest given our previous findings in these data for immune-related factors and risk).[27,29]

Limitations of the Study

Limitations include the fact that exogenous hormone use was not validated but was determined through a telephone interview. We created a picture booklet of OCs and HRT to use as a memory aid. Despite this, approximately 25% of women could not recall the name of at least one preparation that they had used over their lifetime, a percentage that appears to correlate with data from other studies of OC use.[24] In addition, despite being the largest study to date of meningioma, the data are limited by small numbers of current OC users (as meningioma is generally diagnosed in postmenopausal women) and of current postmenopausal HRT users (likely due to the sharp reduction in use of HRT in the US over the past decade.[16] Differential recall by case-control status is possible, although widespread knowledge of any association between meningioma and hormonal therapies 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 individuals. Patients and controls did not differ by race, age, or geographical site but did differ with respect to education and income, with controls reporting higher income and education levels than patients, 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 exogenous hormone use, may lead to bias in risk estimation. In addition, we obtained information on a range of covariables that could impact the association between HRT and meningioma. Our ability to control for these variables enabled us to minimize potential overestimation of risk. Histological confirmation was obtained for all patients, suggesting that these results may only be applicable to lesions that are deemed in need of surgery rather than conservative management.

Conclusions

The examination of variants drawn from genes in hormones[13,14,25] and meningioma risk remains unexplored, with few genes examined in only small samples. The extent to which risk for meningioma associated with exposure to exogenous hormones is modified by genotype is unknown. Overall, our data suggest but do not confirm a role for hormone-related factors but are limited by the small numbers of patients currently on oral hormone medications and a lack of hormone receptor data, and this is an important area for future study.

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Abbreviations used in this paper

BMI	body mass index
EPIC	European Prospective Investigation into Cancer and Nutrition
HRT	hormone replacement therapy
OC	oral contraceptive

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TABLE 1

Demographic characteristics of the study sample

	No. of Individuals (%)		
Characteristic	**Patient**	**Controls**	**p Value**
no. of cases	1127	1092	
age in yrs			0.58
20–29	15(1.3)	8(0.7)	
30–39	66 (5.9)	71 (6.5)	
40–49	228(20.3)	212 (19.5)	
50–59	341 (30.3)	342(31.5)	
60–69	329 (29.3)	280 (25.8)	
70–79	146 (13.0)	174(16.0)	
mean ± SD	57.2 ±11.4	57.4 ±11.7	
race			<0.01
White	921 (81.9)	946 (86.6)	
Black	100(8.9)	55 (5.0)	
Other	104(9.2)	93 (8.4)	
residence			0.49
Connecticut	116(10.3)	121 (11.1)	
California	226 (20.1)	212 (19.4)	
North Carolina	342 (30.4)	362 (33.2)	
Massachusetts	292 (25.9)	270 (24.7)	
Texas	127 (13.3)	127(11.6)	
education			<0.01
≤16 yrs	296 (26.4)	204 (18.7)	
>16 yrs	827 (73.6)	887(81.3)	
income			<0.01
≤$75,000	589 (59.7)	486 (50.5)	
>$75,000	397 (40.3)	477 (49.5)	

TABLE 2

Multivariate-adjusted odds ratios for meningiomas according to the level of risk factor*

Characteristic	No. of Individuals (%)		OR (95% CI)/ p Value
	Patients	Controls	
no. of cases	1127	1092	
menopause status			
premenopausal	265 (23.6)	259 (23.7)	1.0
perimenopausal	149 (13.2)	131 (12.0)	1.16(0.84–1.60)
nonop menopause	580(51.6)	615(56.3)	0.98(0.70–1.36)
bilat oophorectomy	131 (11.6)	87 (8.0)	1.56(1.03–2.35)
age at menopause†			
≤45	231 (32.5)	207 (29.5)	1.0
45–49	171 (24.1)	171 (24.3)	1.04(0.77–1.40)
50–54	232 (32.6)	252 (35.9)	1.00(0.75–1.33)
≥55	77 (10.8)	72 (10.3)	1.22(0.82–1.81)
trend			p = 0.80
mean age at menopause	46.6 (7.7)	47.0 (7.5)	p = 0.26
age at menarche			
≤11	237(21.0)	223 (20.4)	1.0
12	282 (25.0)	306 (28.0)	0.89(0.69–1.14)
13	294(26.1)	300 (27.5)	0.98(0.76–1.26)
≥14	299 (26.5)	259 (23.7)	1.16(0.89–1.50)
trend			p = 0.16
mean age at menarche†	12.7	12.6	p = 0.07
no. of F TPs			
none	149 (13.2)	146 (13.4)	1.08(0.84–1.40)
≥1	977 (86.8)	941 (86.6)	1.0
mean no. of F TPs	2.5	2.6	p = 0.5
age at FLB‡			
<20	108(9.1)	62 (5.7)	1.0
20–30	574(66.2)	442 (57.4)	1.12(0.79–1.58)
>30	185(21.3)	256 (33.2)	0.69(0.46–1.02)
trend			
mean age at FLB	25.9	27.7	p<0.01
ever use 0C§			
never	315(27.9)	265 (24.3)	1.0
past	725 (63.3)	756 (69.2)	1.05(0.83–1.32)
current	87(7.7)	71 (6.5)	1.45(0.94–2.24)
ever use HRT†			
never	316(46.3)	320 (46.0)	1.0
past	299 (43.8)	315(45.3)	0.97(0.76–1.24)

Characteristic	No. of Individuals (%)		OR (95% CI)/ p Value
	Patients	Controls	
current	67 (9.8)	61 (8.7)	1.12(0.74–1.67)
ever use fertility meds			
no	1046(93.7)	1005(92.3)	1.0
yes	70 (6.3)	84 (7.7)	0.80(0.57–1.13)
smoking			
never	630 (56.2)	569 (52.2)	1.0
ever	491 (43.8)	521 (47.8)	0.89(0.74–1.15)
current	109 (14.8)	122 (17.7)	0.73 (0.54–0.98)
alcohol use			
never	712 (63.6)	592 (54.4)	1.0
ever	407 (36.4)	496 (45.6)	0.77 (0.64–0.93)
BMI			
<23.4	303 (26.8)	340 (28.5)	1.0
23.4–26.6	237(21.2)	255 (23.4)	1.06(0.83–1.35)
26.6–30.9	269 (24.1)	249 (22.9)	1.13(0.89–1.45)
>30.9	308 (27.6)	245 (22.5)	1.29(1.01–1.65)
trend			p = 0.04
mean BMI	28.0	27.1	p<0.01
breastfeeding			
never	629 (55.8)	569 (52.1)	1.0
ever	498 (44.2)	523 (47.9)	0.92(0.76–1.11)
≥6 mos	260 (23.1)	313 (28.7)	0.78 (0.63–0.96)

[*] Adjusted for age, race, education, and the other variables in the table.

Mean data are presented ± SD. Abbreviations: FLB = first live birth; FTP = full-term pregnancy.

[†] Among postmenopausal women.

[‡] Among parous women.

[§] Regardless of menopausal status.

TABLE 3

Studies examining the association between meningioma risk and oral contraceptive use

Authors & Year	No. of Cases	Study Design	Comparison*	OR (95% CI)
OC use & risk of intracranial meningioma				
Custer et al., 2006	143	case-control, population-based	past†	1.5(0.8–2.7)
			Current	2.5 (0.5–12.6)
			Ever	
			0%–25%PR+	3.2(1.3–8.0)
			25%–75%PR+	1.1 (0.6–1.9)
Lee et al., 2006	219	case-control, hospital-based	past‡	0.5 (0.3–0.8)
			current‡	0.1 (0.0–0.5)
Wigertz et al., 2006	178	case-control, population-based	ever§	1.0(0.6–1.6)
Hatch et al., 2005	151	case-control, hospital-based	ever¶	1.02(0.63–1.66)
			current¶	1.33(0.43–4.12)
Korhonen et al., 2010	264	case-control, population-based	Ever	1.33(0.94–1.89)
			estrogen receptor positive	1.31 (0.79–2.17)
			progesterone receptor positive	1.39(0.92–2.10)
Jhawar et al., 2003	125	Nurses Health Study cohort	past**	0.76(0.51–1.14)
			current**	1.34(0.18–9.96)
Benson et al., 2008	375	Million Women Study cohort	<5 yrs††	1.06(0.81–1.38)
			≥5 yrs	1.10(0.86–1.40)
Michaud et al., 2010	194	EPIC cohort	past‡‡	1.20(0.86–1.68)
			Current	3.61 (1.75–7.46)
Johnson et al., 2011	125	Iowa Women's Health Study cohort	ever§§	0.82(0.50–1.33)
other (nonoral) hormonal contraceptive use & risk of meningioma				
Wigertz et al., 2006	178	population-based & case/control	ever§	1.5(0.9–2.6)
			≥10 yrs of use§	1.7(0.9–7.5)
hormones given for gynecological problems¶¶& risk of meningioma				
Wigertz et al., 2006	178	population-based case/control	ever§	1.5(0.9–2.6)
			≥10 yrs of use§	1.7(0.9–7.5)

*Baseline category includes women who have never used OC.

†Adjusted for age and education.

‡Adjusted for age, race, hospital, menarche, parity, menopausal status, smoking history, thyroid disorders, and radiation treatment.

§Adjusted for age, residential area, education, and parity.

¶Adjusted for matching factors, marital status, and education.

** Adjusted for age, BMI, menopausal status, and medical history.

†† Relative risk and adjusted for height, BMI, exercise, socioeconomic status, smoking, alcohol, parity, age at first birth, and region.

‡‡ Hazard ratio and adjusted for smoking, education, BMI, and menopausal status.

§§ Adjusted for age.

¶¶ Includes bleeding and irregular menstruation.

TABLE 4

Studies examining HRT and risk of meningioma

Authors & Year	No. of Cases	Study Design	Comparison*	OR (95% CI)
Custer et al., 2006	143	case-control, population-based	past†	0.7(0.4–1.3)
			current†	1.0(0.4–2.2)
			ever†	
			estrogen only	0.9(0.5–1.6)
			estrogen-progesterone	1.3(0.6–2.8)
			0%–25%PR+	0.8(0.4–1.6)
			25%–75%PR+	0.9(0.5–01.6)
Lee et al., 2006	219	case-control, hospital-based	ever	0.7(0.4–1.2)
Wigertz et al., 2006	178	case-control, population-based	ever‡	1.7(1.0–2.8)
Hatch et al., 2005	151	case-control, hospital-based	ever§	0.84(0.50–1.39)
			current	0.88(0.49–1.58)
Korhonen et al., 2010	264	case-control, population-based	ever	0.90(0.63,1.27)
			ER+	0.79(0.48–1.31)
			PR+	0.97(0.65–1.46)
Jhawar et al, 2003	125	NHS cohort	current premenopausal¶	2.48(1.29–4.77)
			current postmenopausal¶	1.86(1.07–3.24)
			past postmenopausal¶	1.01 (0.49–2.1)
Blitshteyn et al., 2008	1410	cohort (retrospective)	ever**	2.2(1.9–2.6)
Benson et al., 2010	311	Million Women Study cohort	current (n = 112)††	1.34(1.03–1.75)
			current estrogen only (n =4 8)††	1.44(1.03–2.02)
			current estrogen-progesterone (n = 45)††	1.10(0.77–1.56)
			past††	1.29(0.96–1.72)
Johnson et al., 2011	125	Iowa Women's Health cohort	ever**	1.17(0.81–1.68)
Michaud et al., 2010	194	EPIC cohort	past‡‡	1.40(0.78–2.49)
			current	1.79(1.18–2.71)
Korhonen et al., 2012	483	Finland cohort	ever estradiol only	1.29 (1.15–1.44)§§
			ever estradiol/progesterone	0.93 (0.80–1.06)§§

*Baseline category includes women who are postmenopausal and have never used HRT.

†Adjusted for age and education.

‡Adjusted for age, residential area, education, and parity.

§Adjusted for matching factors, marital status, and education.

¶Relative risk and adjusted for age and BMI.

**Adjusted for age.

††Relative risk and adjusted for age, SES, residence, height, and BMI.

[##] Hazard ratio and adjusted for smoking, education, menopausal status, oral contraceptive use, and BMI.

[§§] Standardized incidence ratio.