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Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study

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Abstract

Background—The aetiologies of glioma and meningioma tumors are largely unknown. Although reproductive hormones are thought to influence the risk of these tumors, epidemiologic data are not supportive of this hypothesis; however, few cohort studies have published on this topic. We examined the relation between reproductive factors and risk of glioma and meningioma among women in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Methods—After a mean of 8.4 years of follow-up, 193 glioma and 194 meningioma were identified among 276,212 women. Information on reproductive factors and hormone use was collected at baseline. Cox proportional hazard regression was used to determine hazard ratios (HR) and 95% confidence intervals (CI).

Results—No associations were observed between glioma or meningioma risk and reproductive factors, including age at menarche, parity, age at first birth, menopausal status, and age at menopause. A higher risk of meningioma was observed among postmenopausal women who were current users of hormone replacement therapy (HR = 1.62, 95% CI = 1.04-2.54) compared with never users. Similarly, current users of oral contraceptives were at higher risk of meningioma than never users (HR = 3.61, 95% CI = 1.75-7.46).

Conclusion—Our results do not support a role for estrogens and glioma risk. Use of exogenous hormones, especially current use, appears to increase meningioma risk. However, these findings could be due to diagnostic bias and require confirmation.

Impact—Elucidating the role of hormones in brain tumor development has important implications and needs to be further examined using biological measurements.

Keywords

Brain tumors; glioma; meningioma; reproductive factors; exogenous hormone use; oral contraceptive use; hormone replacement therapy; cohort studies

Introduction

The aetiologies of meningiomas and gliomas, the two most common types of brain tumors, remain largely unknown as established risk factors for many cancers, such as smoking, alcohol, and occupational exposures, do not appear to play a role in these tumors. Established risk factors, including ionising radiation, family history, certain rare genetic conditions, and a few chromosomal regions (1-2), can only explain a small portion of total brain tumor cases, leaving the majority of cases with unknown causes. Sex differences in glioma and meningioma incidences suggest that hormones could influence the development of these tumors; the incidence of meningiomas is about 2 times greater in women than in men, whereas the incidence of gliomas is around 1.5 times greater in men than in women (3). Increased growth rates of meningiomas have been observed during pregnancy (4), and a

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strong association exists between breast cancer and meningioma (5). Taken together, these observations support a role for female hormones in the aetiology of meningiomas.

Reproductive factors, including age at menarche, age at first birth, number of pregnancies, and menopausal status, have been examined in relation to meningioma and/or glioma in several case-control studies (6-16) and in three cohort studies (17-20). The majority of findings from these studies are null or inconsistent with respect to direction of association. For meningioma, four studies reported elevated risks with hormone replacement therapy (HRT) use (7, 19, 21-22). Findings in relation to oral contraceptive use have been mostly null for both glioma and meningioma risk (7, 9-11, 14, 18, 20).

Given that most previous studies on hormonal factors and brain tumors have been case-control studies, and findings are inconsistent, we examined reproductive and exogenous hormone use in relation to risk of glioma and meningioma in a large multi-centred prospective cohort study.

Materials and methods

Study cohort

The EPIC prospective cohort study was initiated in the early 1990s when 23 centres in 10 European countries collaboratively recruited more than half a million individuals. Additional details on the EPIC study design are reported elsewhere (23).

Loss to follow-up (defined as unknown vital status at the last follow-up time) was lower than 6% across centres. Approval for the study was obtained from the ethical review boards of the participating institutions and from the International Agency for Research on Cancer.

Case ascertainment

Incident cancer cases (including benign brain tumors) were identified through linkage to population cancer registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden, and the UK, or with a combination of methods including linkage to health insurance records, cancer and pathology registries, and active follow-up of study participants or their next of kin in France, Germany, and Greece. We removed France from this analysis due to missing histology on cancer cases. We included all primary incident cases diagnosed with glioma (coded using International Classification of Diseases-Oncology [ICD-O] 2nd edition: 9380-9460, 9505) or meningioma (ICD-O-2 codes 9530-9537) through the end of follow-up (from January 2003 to November 2006 depending on centre). Among all women, a total of 193 glioma and 194 meningioma cases were available for analyses on reproductive factors and oral contraceptive use, and 159 glioma and 150 meningioma cases were available for the HRT analyses among peri- and postmenopausal women.

Assessment of HRT, oral contraceptives, and reproductive factors

Information on HRT use, oral contraceptive use, and reproductive factors were collected on the baseline questionnaires. Participants were asked about ever and current use of HRT, age at start and total duration of use, route of administration and brand name of current HRT use. Analyses were performed for ever, current, and former use of HRT, and duration of ever HRT use. Because few cases at baseline were current HRT users (50 meningioma and 34 glioma) we had insufficient power to examine type of HRT. Information on ever use of oral contraceptives, duration of use, and ages at starting and stopping use was collected. Age at menarche and menopause, number of full-term pregnancies (live and still births), age at the first full-term pregnancy and the reason for menopause (natural vs. surgical) were self-

reported at recruitment. Information on breastfeeding and its cumulative duration was collected for the first three full-term pregnancies and the last one.

Statistical analysis

We excluded prevalent cancers and benign brain tumors at recruitment (except for non-melanoma skin cancer) and individuals with incomplete follow-up for this analysis (n=27,082). Only women were included in this analysis. After excluding data from France (missing histological data on cancer cases), 276,451 women were available for the main analysis.

Menopausal status was defined according to information on menstruation status, ovariectomy and hysterectomy (for details please refer to Allen *et al.* (24)). Women were considered peri-menopausal if they reported no regular menses over the past 12 months (< 9 cycles). Women with missing or incomplete information on the cycle of menses, who reported a hysterectomy, or who indicated use of exogenous hormones while still menstruating were considered post-menopausal if they were ≥ 55 years old, peri-menopausal if they were between 46 and 55 years, or pre-menopausal if they were < 46 years old at recruitment. For the HRT analyses, we combined perimenopausal women with postmenopausal women because the risk of brain tumors was similar for perimenopausal and postmenopausal women (compared to premenopausal women).

Hazard ratios (HR) and their 95% confidence intervals (95% CIs) for brain tumors were estimated using Cox proportional hazards models with age at enrolment as the time scale. Person-time was calculated from date of recruitment until date of incident brain tumor diagnosis, death, date of last contact, or end of follow-up period, whichever came first. All models were stratified by EPIC-participating center, to account for center effects related to different recruitment and follow-up procedures, and by age at recruitment in 1-year categories. The proportionality of hazards was verified based on the slope of the Schoenfeld residuals over time, which is equivalent to testing that the log hazard ratio function is constant over time. All models were adjusted (using categorical variables) for smoking status (never, former, current), education (none/primary, technical/professional, secondary, university), and BMI (<25, ≥25-<30, ≥30 kg/m^2); although these covariates did not appreciably alter the associations, we kept them in the model as these have been previously associated with the risk of brain tumors in one or more studies. Other covariates often adjusted for in cancer analyses were not included in the multivariate models as they are not known or suspected risk factors for brain tumors. Country-specific analyses were also performed. All p-values were two-sided. All analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

After an average of 8.4 years of follow-up, 194 cases of meningioma and 193 cases of glioma were diagnosed among women from nine countries in the EPIC cohort. The average age at recruitment was 50.4 (10.5 SD) years. The average age at diagnosis was 53.9 (8.0 SD) years for meningioma and 54.1 (8.9 SD) years for glioma.

Table 1 shows the distribution of exogenous hormone use by country. Oral contraceptive (OC) use was highest in Germany (80.8%) and The Netherlands (72.7%) and lowest in Greece (9.6%). Among post- and peri-menopausal women, hormone therapy (HRT) use was highest in Germany (55.4%) and lowest in Greece (6.8%).

We examined the relation between potential risk factors (i.e., age, BMI, education and smoking) and HRT use (Table 2). Women who were current users of HRT at recruitment

were younger, slightly leaner, more educated and more likely to be current smokers than women who were past or never HRT users. In addition, women on HRT were also more likely to have been ever users of OCs (65% of current HRT users vs. 41% of never HRT users).

There was a suggestive increase risk of glioma among post- and peri-menopausal women, compared to premenopausal women, but these associations were not statistically significant (Table 3); the association remained statistically insignificant when peri and postmenopausal women were combined (HR = 1.68, 95% CI = 0.82-3.41). In contrast, menopausal status appeared to be inversely related to the risk of meningioma (Table 3; combining peri- and postmenopausal HR = 0.63, 95% CI = 0.34-1.17, compared to premenopausal women). Compared to premenopausal women, women who had a bilateral ovariectomy had a statistically significant elevated risk of glioma (HR= 3.51, 95% CI = 1.45-8.49), and possibly meningioma (as the association was not statistically significant, HR = 1.89, 95% CI = 0.84-4.26; Table 3); these associations did not change when controlling for OC or HRT use. Other reproductive factors, including age at menarche, age at menopause, parity and age at first birth, were not associated with risk of meningioma or glioma (Table 3). Being ever parous compared to nulliparous was not associated with risk of glioma (HR = 0.96, 95% CI = 0.88-1.04) or meningioma (HR = 1.00, 95% CI = 0.93-1.08). Women who had a hysterectomy (after excluding women who had a bilateral ovariectomy) were at slightly higher risk of meningioma (Table 3). Women with one ovary removed did not have a higher risk of glioma or meningioma (data not shown). Likewise, breastfeeding (ever or by duration) was not related to either type of brain tumors (data not shown).

Women who reported being current users of OCs at the time of recruitment into the cohort had a substantially higher risk of meningioma than women who never used OCs (HR = 3.61, 95% CI = 1.75-7.46), whereas former users did not have an elevated risk (Table 3). This association was very similar among premenopausal women (HR = 3.70, 95% CI = 0.88-15.6, total 40 cases, 3 cases current OC users) and postmenopausal women mutually adjusting for HRT use (HR = 3.54, 95% CI = 1.50-8.37, total 149 cases, 7 cases current OC users; note, current OC users were in the perimenopausal group). There was no clear dose-response with duration of ever OC use and meningioma risk overall (Table 3), but there was a dose-response among premenopausal women (compared to never, HR [95% CI]: 1.21 [0.36-4.06], 1.55 [0.53-4.56], 2.97 [1.08-8.15], 3.22 [1.04-10.0], 3.60 [1.00-13.0] for ≤1, >1 -<5, ≥5-<10, ≥10-≤15, >15 years of use, respectively, p-trend = 0.01; data not in tables). No association with OC use was observed in relation to glioma risk (Table 3).

Among post- and peri-menopausal women, current users of hormone replacement therapy (HRT) had a higher risk of meningioma (HR = 1.79, 95% CI = 1.19-2.71) compared to never users and the risk was also elevated (though not significantly so) among past HRT users (Table 4). There was no clear dose-response relationship between duration of HRT use and meningioma risk, and no association with HRT use and risk of glioma (Table 4).

Discussion

In this large European prospective cohort study, we observed elevated risks of meningioma among users of OCs or HRT at enrolment when compared with never users. No associations were found for reproductive factors and risk of meningioma. For glioma, we observed no associations with reproductive factors or exogenous hormone use. However, a significantly elevated risk of glioma was observed among women who had undergone a bilateral ovariectomy at baseline, and a statistically non-significant elevated risk was also noted for meningioma tumors; the positive associations were not explained by HRT use. While the findings for women with bilateral ovariectomy were unexpected and should be interpreted

with caution, more studies should examine these to determine if they are of potential significance.

Supporting evidence for a role of hormones in brain tumors comes for a number of case reports of women who experienced rapid changes in symptoms during pregnancy that were related to the presence of a meningioma (either resulting in a diagnosis or a recurrence of symptoms from an existing tumor)(25-27). Similarly, a study reported growth of a meningioma after estrogen-progestin therapy in a transsexual patient (28). Biological data support an association as well; in vitro studies have demonstrated proliferation of meningioma cells with exposure to estradiol or progesterone (29), and inhibition of glioma cell growth with estrogen (30-31).

To date, studies that have examined reproductive hormones and brain tumors have been largely based on case-control studies. Some of these had small case numbers or relied on proxy-interviews for a portion of the data collected for deceased cases (up to 83% of all cases)(12); moreover, given the low incidence rate of brain tumors, identifying the true source population and representative controls is challenging and consequently, in these studies, bias is difficult to rule out. Therefore, cohort studies can provide more reliable evidence.

Overall, positive associations between age at menarche and glioma risk have been observed in five studies (four case-control and one cohort)(9-10, 14, 16, 18), which suggests that delayed puberty may increase subsequent risk of glioma. In contrast, associations between age at menarche and meningioma have been largely null (6, 8, 10-11), with one exception where a positive association was reported in a cohort study (19). Other reproductive factors which could influence lifetime hormonal exposure, such as age at menopause and age at first birth, have not been associated with risk of glioma or meningioma.

Our observation for meningioma risk and HRT was consistent with two prospective cohort studies: the Nurse' Health Study (current vs. never users, RR =1.86, 95% CI = 1.07-3.24; 66 meningioma postmenopausal cases)(19) and the Million Women Study (current vs. never, RR = 1.34, 95% CI = 1.03-1.75)(22), and with two retrospective studies (comparing ever to never HRT use: OR=1.7, 95% CI = 1.0-2.8 (7) and OR = 2.2, 95% CI = 1.9-2.6 (21)). However, three other case-control studies found no associations with hormone replacement therapy and meningioma (6, 10-11). The association among former users was not as strong in our dataset (Table 4), suggesting that the effect, if causal, is likely to act late in the stages of carcinogenesis. However, it is unclear how hormones are involved in brain tumors from a mechanistic standpoint.

Results from earlier studies on oral contraceptive use and risk of meningiomas are less consistent with our findings, as most of the earlier studies reported null associations (7, 10, 19-20) and one association was inverse (6). However, few of the previous studies reported results for current use of OC; one case-control with data on current use observed a RR of 2.5 (95% CI = 0.5-12.6)(11), while two other reported small increased risk with large confidence intervals due to small case numbers for current OC use (RR=1.34, 95% CI=0.18-9.96(19); RR=1.33, 95% CI=0.43-4.12)(10). Therefore, it is possible that an association was missed in some studies if most users were past users and if the effect is only present among current users (as observed with HRT use). It is conceivable that the mechanism involves increased tumor growth rates during the exposure period (current use) and that the risk decreases with time after no longer being a current user. The statistically significant dose-response relationship for duration of OC use (among ever users) observed among premenopausal women (at baseline) supports this hypothesis; more research is needed to examine this finding.

Alternatively, the increase in risk of meningioma among active exogenous hormone users could be due to diagnostic bias; conceivably, women under prescription drugs who are under more rigorous or more frequent medical surveillance may be more likely to have a follow-up of symptoms that could lead to the diagnosis of benign meningioma. In this cohort, age-specific rates were comparable to those in the US (which are comparable to European rates (32)). In this cohort, the age-specific rates for glioma were 4.2 (per 100,000) for ages 35-44 and 11.5 for ages 65-74, and 2.9 and 11.5 for meningiomas in those same age groups, respectively. In the CBTRUS report (which separates benign and malignant tumors), the age specific rates range from 4.4 at ages 35-44 to 17.3 for ages 65-74 for glioma, and from 2.9 to 14.2 for the same age comparisons for meningioma. Therefore, case ascertainment appears to be as expected in this cohort for both subtypes of brain tumors.

The strengths of this cohort study include a prospective design, which removes potential error from selection bias or use of proxy interviews, detailed data on reproductive factors, exogenous hormone use, and other variables that could be potential confounders. The weaknesses of this study include having no followed data on HRT use; some women will change HRT, OC and/or menopausal status during follow-up, which will cause misclassification of exposure and potentially bias the results. However, as this would result in non-differential misclassification, it would most likely result in bias towards the null. Also we had insufficient brain tumor cases to examine duration of exogenous hormone use with sufficient power, or to explore analyses with different hormone combinations. Our findings need to be confirmed in other populations.

In this study, we observed elevated risk of meningioma among current users of hormone replacement therapy or oral contraceptive. In contrast, other reproductive factors were not associated with the risk of meningioma. Furthermore, no relation was observed for reproductive factors and the risk of glioma. Additional studies should carefully examine the relation with current use of exogenous hormones, both HRT and OC, and meningioma risk.

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Table 1

Use of oral contraceptive (OC) at recruitment among all women and menopausal hormone therapy (HRT) among peri- and post-menopausal women in the EPIC cohort by country

Characteristic	All (n=276,451)	Denmark (n=29,320)	Germany (n=28,481)	Italy (n=31,519)	Netherlands (n=27,168)	Norway (n=35,941)	Spain (n=25,356)	UK (n=56,357)	Greece (n=15,396)	Sweden (n=26,913)
Meningioma cases	194	28	15	18	16	43	16	23	4	31
Glioma cases	193	41	12	18	24	12	15	43	4	24
Among all women										
OC ever use %										
Yes	55.9	57.6	80.8	40.4	72.7	64.1	42.1	64.9	9.6	38.8
No	40.6	41.3	19.0	58.1	26.7	35.9	57.8	31.9	89.8	36.6
Unknown	3.5	1.1	0.2	1.5	0.6	0	0.1	3.2	0.6	24.7
Nulliparous (%)	12.8	8.8	11.2	10.2	19.8	8.5	9.6	27.6	6.8	7.4
Mean age at first pregnancy (SD) *	24.8 (4.4)	23.7 (4.2)	24.3 (4.4)	25.8 (4.3)	25.4 (4.2)	24.1 (4.5)	24.6 (3.9)	25.9 (4.7)	24.2 (4.7)	24.7 (4.5)
Mean age at menarche (SD)	13.1 (1.6)	13.6 (1.6)	13.2 (1.5)	12.5 (1.5)	13.3 (1.6)	13.3 (1.4)	12.9 (1.6)	12.9 (1.6)	13.2 (1.7)	13.5 (1.5)
Hysterectomy (%)	10.2	14.8	15.0	8.9	17.4	4.7	8.4	12.5	8.2	--
Among all post or peri-menopausal women	(n=174,134)	(n=27,209)	(n=15,267)	(n=19,135)	(n=18,157)	(n=23,311)	(n=11,772)	(n=28,977)	(n=9,736)	(n=20,570)
Mean age at menopause (SD) †	48.7 (4.8)	49.0 (4.9)	49.5 (3.3)	49.0 (4.3)	48.5 (5.1)	47.7 (4.0)	48.0 (4.7)	48.3 (5.5)	47.9 (5.2)	49.2 (4.6)
HT ever use, %										
Yes	34.2	46.7	55.4	23.9	26.1	45.3	18.7	38.3	6.8	22.5
No	58.3	51.4	36.3	74.3	72.6	54.7	80.1	56.9	92.7	33.9
Unknown	7.4	1.9	8.3	1.8	1.3	0	1.2	4.9	0.5	43.6
Among ever HT users	(n=62,092)	(n=12,709)	(n=8,455)	(n=4,583)	(n=4,739)	(n=10,562)	(n=2,195)	(n=11,087	(n=662)	(n=4,637)
Status of use										
Current	66.6	65.5	77.9	44.8	51.5	79.8	55.2	67.8	32.5	63.2
Past	29.1	34.4	22.1	54.4	44.6	8.0	43.8	30.6	67.4	18.5
Unknown	4.3	0.03	0	0.8	3.9	12.2	1.0	1.6	0.1	18.3

*Among parous women

†Among natural postmenopausal women

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Table 2

Distribution of baseline characteristics by menopausal hormone therapy use among peri- and post-menopausal women and by oral contraceptive use among all women in the EPIC cohort*

Characteristic	Menopausal hormone therapy use (HRT)			Oral contraceptive use (OC)		
	Never (n = 101,573)	Former (n = 17,362)	Current (n = 39,711)	Never (n=112,303)	Former (n=136,862)	Current (n=16.223)
Mean age at recruitment (SD), yrs	57.0 (7.4)	57.4 (5.8)	54.4 (5.3)	54.8 (9.9)	48.7 (8.8)	37.2 (9.2)
Smoking status, %						
Never	59.0	50.7	47.7	62.8	46.7	54.1
Former	21.7	26.4	28.0	18.8	27.8	23.1
Current	19.3	22.9	24.3	18.5	25.5	22.8
Mean body mass index (SD), kg/m^2	26.5 (4.8)	26.3 (4.4)	25.1 (3.9)	26.5 (4.8)	24.9 (4.3)	23.6 (3.8)
Ever use of OCs, %						
Yes	41.0	53.2	64.6			
No	58.2	46.1	34.6			
Unknown	0.8	0.7	0.8			
Education (%)						
None/Primary	48.8	43.0	33.0	52.7	27.4	12.7
Technical/professional	24.2	30.5	36.0	20.9	32.0	32.5
Secondary	14.4	13.1	14.7	13.6	18.0	23.0
University	12.6	13.4	16.3	12.8	22.6	31.8
Mean age at menarche (SD)	13.3 (1.6)	13.2 (1.6)	13.3 (1.6)	13.2 (1.6)	13.1 (1.5)	12.9 (1.5)
Nulliparous (%)	9.3	9.7	7.9	13.1	10.4	37.4
Mean age at first pregnancy (SD)†	25.0 (4.4)	24.5 (4.3)	24.2 (4.2)	25.0 (4.4)	24.7 (4.5)	24.8 (4.5)
Mean age at menopause (SD) ‡	48.7 (4.8)	48.2 (5.3)	47.5 (5.5)	48.5 (5.1)	48.4 (4.8)	44.8 (7.7)
Hysterectomy (%)	12.7	19.2	23.1	13.7	11.8	0

*χ^2 and one-way analysis of variance or Kruskal-Wallis test; all tests were $p<0.001$.

Abbreviations: SD, standard deviation; OCs, oral contraceptives

†Among parous women

‡Among natural postmenopausal women

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Table 3

Reproductive factors and risk of meningioma and glioma in the EPIC cohort

	No. subjects	Meningioma	Meningioma HR (95% CI)*	Glioma	Glioma HR (95% CI)*
MENOPAUSAL STATUS					
Premenopausal	102,232	44	1.0	34	1.0
Natural postmenopausal	118,587	99	0.69 (0.35-1.36)	108	1.62 (0.75-3.47)
Perimenopausal	47,170	38	0.57 (0.30-1.11)	37	1.69 (0.81-3.54)
Bilateral oopherectomy	8,029	13	1.89 (0.84-4.26)	14	3.51 (1.45-8.49)
HYSTERECTOMY †					
No	209,754	112	1.0	127	1.0
Yes	20,883	21	1.32 (0.81-2.17)	20	1.16 (0.71-1.91)
Missing	37,352	48		32	
AGE AT MENOPAUSE YRS) ‡					
<47	25,243	26	1.0	25	1.0
47-53	52,394	41	0.75 (0.45-1.24)	44	0.81 (0.49-1.33)
>53	17,888	13	0.75 (0.38-1.49)	20	1.08 (0.59-1.97)
Missing	70,232	57		56	
PARITY					
0	35,341	12	1.0	18	1.0
1	31,409	19	0.97 (0.47-2.02)	21	1.29 (0.67-2.48)
2	81,492	59	1.07 (0.57-2.04)	70	1.58 (0.91-2.76)
≥3	104,215	87	1.40 (0.75-2.59)	73	1.18 (0.68-2.06)
Missing	23,561	17		11	
AGE AT FIRST FULL-TERM PREGNANCY (YRS)					
Nulliparous	35,341	12	1.0	18	1.0
<25	115,707	96	1.28 (0.69-2.39)	94	1.49 (0.86-2.58)
≥25 - ≤30	79,538	57	1.18 (0.62-2.22)	54	1.16 (0.66-2.04)
>30	21,871	12	0.99 (0.44-2.23)	16	1.42 (0.71-2.84)

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	No. subjects	Meningioma	Meningioma HR (95% CI)*	Glioma	Glioma HR (95% CI)*
Missing	23,561	17		11	
AGE AT MENARCHE (YRS)					
<12	50,216	36	1.00	36	1.0
≥12 - ≤15	207,822	140	0.80 (0.54-1.17)	142	0.87 (0.60-1.28)
>15	17,980	18	1.01 (0.55-1.84)	15	0.88 (0.47-1.63)
OC USE					
Never	112,105	81	1.0	90	1.0
Former	136,672	92	1.20 (0.86-1.68)	84	0.84 (0.61-1.18)
Current	16,201	10	3.61 (1.75-7.46)	8	1.23 (0.53-2.83)
Missing	11,040	11		11	
DURATION OF EVER OC USE (YRS)					
Never	112,105	81	1.0	90	1.0
≤1	29,804	20	1.10 (0.66-1.83)	16	0.73 (0.42-1.28)
>1 - <5	34,657	23	1.19 (0.73-1.95)	17	0.76 (0.44-1.30)
≥5-<10	34,451	28	1.66 (1.05-2.65)	22	1.00 (0.61-1.65)
≥10-≤15	27,742	14	1.01 (0.55-1.87)	18	0.92 (0.53-1.59)
>15	21,277	15	1.54 (0.86-2.77)	13	0.79 (0.43-1.47)
Missing	15,982	13		17	

*Multivariate model includes smoking status, education, body mass index and menopausal status.

†Removing women with bilateral ovariectomy

‡Among postmenopausal women (missings are mostly perimenopausal)

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Table 4

Hormone replacement therapy (HRT) in relation to risk of meningioma and glioma among peri- and postmenopausal women in the EPIC cohort

	No. subjects	Meningioma	Meningioma MV HR (95% CI)*	Glioma	Glioma MV HR (95% CI)*
HRT USE					
Never	101,394	67	1.0	91	1.00
Former	17,324	15	1.40 (0.78-2.49)	18	0.93 (0.55-1.56)
Current	39,617	50	1.79 (1.18-2.71)	34	0.76 (0.49-1.19)
Missing	15,451	18		16	
DURATION OF EVER HRT USE (YRS)					
Never and ≤1	118,360	83	1.0	106	1.00
>1-≤3	12,918	11	1.18 (0.62-2.25)	12	0.91 (0.49-1.68)
>3-≤5	8,499	14	2.32 (1.28-4.20)	8	0.93 (0.44-1.94)
>5-≤10	9,678	8	1.09 (0.51-2.32)	5	0.36 (0.13-0.98)
>10	4,239	6	1.34 (0.55-3.30)	6	0.89 (0.37-2.14)
Missing	20,092	28		22	

*Adjusting for smoking status, education, surgical/natural/peri-menopause, oral contraceptive use and body mass index

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