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Body mass index, comorbidities, and hormonal factors in relation to meningioma in an ethnically diverse population: the Multiethnic Cohort

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Abstract

Background. Meningioma is the most common intracranial tumor in the US and its etiology remains poorly understood. Meningioma has been predominantly studied among white populations. The aim of this study was to evaluate the associations of anthropometric, comorbidity, and hormonal factors with meningioma in an ethnically diverse population.

Methods. A nested case-control analysis was performed within the Multiethnic Cohort (MEC). Meningioma cases were identified via linkage with Medicare and the California Office of Statewide Health Planning and Development Hospital Discharge data and were matched to up to 10 controls. Anthropometric, comorbidities, physical activity level, and hormonal factors at baseline based on questionnaires were evaluated for association with meningioma.

Results. A total of 894 cases and 8918 matched controls were included in this study. Increasing body mass index (BMI) (P-trend = 0.041) and weight increases since age 21 (P-trend = 0.0052) were positively associated with meningioma. Hormonal factors including oral contraceptive use (odds ratio [OR]: 1.24; 95% CI: 1.01–1.51) and estrogen hormonal therapy use (per 5 years, OR: 1.07; 95% CI: 1.01–1.15) were associated with meningioma risk. Hypertension was positively associated with meningioma (OR: 1.26; 95% CI: 1.09–1.47), with individuals who reported a history of both hypertension and diabetes showing a stronger association (OR: 1.54; 95% CI: 1.17–2.03). The tests for heterogeneity across race/ethnicity were not statistically significant (P heterogeneity ≥ 0.17); however, the association of BMI with meningioma was mainly observed in Japanese Americans (P-trend = 0.0036) and hypertension in Japanese Americans (OR: 1.63; 95% CI: 1.17–2.27) and Native Hawaiians (OR: 1.86; 95% CI: 1.02–3.40).

Conclusion. Obesity, hormonal factors, and hypertension were associated with meningioma in an ethnically diverse population.

Key Points

1. Hormonal factors, hypertension, and higher BMI were associated with increased meningioma risk.
2. The association between higher BMI and meningioma was particularly strong in Japanese Americans.

Importance of the Study

Meningioma remains the most common neurological malignancy and much remains unknown with regard to predisposing factors. Previous studies in predominantly white populations have shown that hormonal factors and higher BMI are associated with increased risk for meningioma. We conducted a comprehensive risk factor analysis for meningioma in a large and ethnically diverse prospective cohort. Our study, for the first time, showed that higher BMI, hypertension, and hormonal factors are associated with increased meningioma risk in ethnically diverse populations.

Meningiomas, predominantly low-grade brain tumors that originate from the meninges, are 36.8% of all brain tumors in the US.[1] Meningioma incidence shows a strong predominance in females, increases with age, and is slightly higher among African Americans compared with whites.[1,2] Meningiomas often result in severe morbidity and impaired quality of life.[3] Most meningiomas warrant treatment in the form of surgical resection and/or targeted radiation.

The epidemiology and etiology of meningiomas remain poorly understood, partially because meningiomas are relatively understudied due to their only recent inclusion in cancer registries in the US.[2] Patients with cancer predisposition syndromes neurofibromatosis type 2[4,5] or multiple endocrine neoplasia type 1[6] have a higher chance of developing meningiomas in comparison to the general population. Cranial radiation has been identified as an established risk factor for meningiomas.[7–9] Higher body mass index (BMI)[10–12] and oral contraceptive[13] and menopausal hormone use[14] have also been associated with higher risk of meningioma, but results are conflicting. Furthermore, most studies of meningioma have been conducted in mainly non-Latino white populations (hereafter called whites),[10–13] thus risk factors among ethnic/racial minority populations are largely unknown.

The current study aimed to evaluate risk factors for meningioma in African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in the Multiethnic Cohort (MEC). As such, it provides a unique insight into the epidemiology of meningioma across multiple racial/ethnic groups.

Study Population and Methods

Study Population

The MEC is a prospective cohort of more than 215000 men and women enrolled between 1993 and 1996 at age 45–75 years. The cohort comprises predominantly African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites. Specific details on study design and baseline characteristics of the MEC have been described previously.[15] The baseline mailed questionnaire assessed diet, lifestyle, medication use, anthropometrics, family and personal medical history, and, for women, menstrual and reproductive history and hormone use. The baseline questionnaire was administered in 1993–1996 and follow-up questionnaires were sent to participants approximately every 5 years. MEC participants older than 65 years were linked to Centers for Medicare Services claims (1999–2015),[16] and 89% of these participants have been linked. The California participants were also linked to the California Office of Statewide Health Planning and Development Hospital Discharge (OSHPD) data (1993–2015). The institutional review boards of the University of Southern California and the University of Hawaii approved this study.

For this study, we included participants from the 5 major ethnic groups in the MEC. Participants with a diagnosis of meningioma prior to cohort entry based on OSHPD were excluded (N = 34). Hawaii participants who were not Medicare fee-for-service members (N = 34643) were excluded, as we had no opportunity to discover a meningioma diagnosis in this group. A total of 167226 participants were eligible for the study.

Nested Case-Control Study

International Classification of Diseases (ICD) 9th Revision codes 192.1, 192.3, 225.2, 225.4, and 237.6 and 10th Revision codes C70.0, C70.1, D32.0, and D32.1 were used to ascertain meningioma cases from the Medicare hospitalization claim files (MedPAR) or from the OSHPD. Cases were also identified from Medicare outpatient and carrier files if there were 2 or more claims with the ICD codes as above and the claims were greater than 30 days apart. A total of 894 meningioma cases were identified between 1993 and 2015 after entry to the cohort. Potential controls were available from the eligible study participants without meningioma claims through 2015. For each case we selected up to 10 controls matched on sex, ethnicity, study area (Hawaii or California), and exact birth year.

Exposure Assessment

Demographics, weight, height, alcohol use, smoking history, physical activity, diabetes, hypertension, medication use, and other potential risk factors for meningioma were obtained from the baseline questionnaire (1993–1996). Data on age of menarche, exogenous hormone use, parity, and menopausal status were also collected for female participants at baseline. In this study, we selected exposures to analyze based on risk factors previously reported in whites for meningioma.

Statistical Analysis

BMI was calculated as weight in kilograms divided by height in square meters and categorized as <25, 25 to <30, and ≥30 kg/m^2. BMI was also evaluated as a continuous variable by 5-unit increase. Height and weight were categorized by sex-specific quartiles among controls. Height and weight were also evaluated as continuous variables by 10 cm and 5 kg increase, respectively. BMI change was evaluated by

percent change per year since age 21 as described previously.[17] Smoking status was categorized as never, past, or current, and alcohol use was categorized as none, <12, 12 to <24, and ≥24 ethanol grams per day. Sitting hours were categorized by quartiles (≤5.0, >5.0 to ≤7.5, >7.5 to ≤10.5, and >10.5 hours per day). Moderate activity was categorized ≤0.36 hours per day and then by tertiles (≤0.36, >0.36 to ≤0.71, >0.71 to ≤1.21, and >1.21 hours per day). Vigorous activity was categorized 0 and then by tertiles of hours per day (0, >0 to ≤0.11, >0.11 to ≤0.46, and >0.46 hours per day). Moderate and vigorous activity combined were categorized by quartiles of hours per day (≤0.36, >0.36 to ≤0.71, >0.71 to ≤1.32, and >1.32 hours per day). For women, age of menarche was categorized as ≤12, 13–14, and >14 years of age. Parity was assessed by nulliparity (no, yes) and by number of children. Age at first birth was categorized as 15–20, 21–30, and >30 years of age. Oral contraceptive use was categorized as ever use versus never use and number of usage years (none, <5 y, ≥5 y). Menopausal status was categorized as premenopausal, natural menopause, surgical menopause (oophorectomy with or without hysterectomy), other surgery that causes period cessation (hysterectomy, endometrial ablation), or unknown. Age at menopause (<50 y, ≥50 y) was categorized separately by type of menopause (natural, oophorectomy, other surgery), as well as evaluated separately by hormone therapy (HT) status. Menopausal estrogen and progesterone use was evaluated for number of years used and for different combinations of present and past usage. Finally, type of menopausal hormone use was evaluated per 5 years of use.

The association between risk factors and meningioma was quantified by odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable conditional logistic regression. All ORs were stratified by matched set and adjusted for education, BMI, alcohol use, hypertension, diabetes, and smoking status. Tests for trend were performed by entering the ordinal values representing categories of exposures as continuous variables in the models. Only participants with complete data on the above risk factors were included in the analyses. Sex- and ethnic-specific analyses were performed to assess differences by these parameters. Heterogeneity due to sex and ethnicity was evaluated by adding interaction terms between risk factor and sex or ethnicity in the logistic model. Statistical analyses were performed with SAS 9.4 software. All *P* values were two-sided.

Results

The baseline characteristics of meningioma cases and controls are shown in Table 1. As expected, more female than male cases were identified (76.0% female).[1] The mean

Table 1 Characteristics of meningioma cases and controls in MEC

	Men				Women				Overall			
	Cases		Controls		Cases		Controls		Cases		Controls	
	n = 215		*n* = 2150		*n* = 679		*n* = 6768		*n* = 894		*n* = 8918	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age at cohort entry												
Mean (range)	63.0 (45.0–76.0)		63.0 (45.0–77.0)		62.2 (45.0–77.0)		62.3 (45.0–78.0)		62.4 (45.0–77.0)		62.5 (45.0–78.0)	
Ethnicity												
White	52	24.2	520	24.2	140	20.6	1400	20.7	192	21.5	1920	21.5
African American	40	18.6	400	18.6	207	30.5	2065	30.5	247	27.6	2465	27.6
Native Hawaiian	14	6.5	140	6.5	42	6.2	405	6.0	56	6.3	545	6.1
Japanese American	55	25.6	550	25.6	123	18.1	1230	18.2	178	19.9	1780	20.0
Latino US born	28	13.0	280	13.0	91	13.4	908	13.4	119	13.3	1188	13.3
Latino Mex/SA born	26	12.1	260	12.1	76	11.2	760	11.2	102	11.4	1020	11.4
Area												
Hawaii	87	40.5	870	40.5	216	31.8	2146	31.7	303	33.9	3016	33.8
Los Angeles	128	59.5	1280	59.5	463	68.2	4622	68.3	591	66.1	5902	66.2
Education												
≤High school	83	38.6	929	43.2	338	49.8	3351	49.5	421	47.1	4280	48.0
Vocational/some college	68	31.6	635	29.5	193	28.4	1941	28.7	261	29.2	2576	28.9
College or higher	62	28.8	568	26.4	142	20.9	1387	20.5	204	22.8	1955	21.9

Meningioma ICD-9 codes 1921, 1923, 2252, 2254, 2376 and ICD-10 codes D320 and D321.
Medicare fee-for service cases selected using 1 inpatient claim or 2 or more outpatient/carrier claims greater than 30 days apart, 1999–2015.
CHDD cases selected using 1 hospitalization record, 1993–2015.
Case-control analysis (matched on area, sex, ethnicity, and birth year).
Average number of matched controls per case 10.0 (2.0–10.0).

age of cohort entry was 62.4 years (range 45.0–78.0). This analysis included 27.6% self-identified as African American, 20.0% as Japanese American, 24.7% as Latino, 6.1% as Native Hawaiian, and 21.5% as white. The majority of cases were from the Los Angeles area (66.1%).

The associations of anthropometric factors, diabetes, and hypertension with meningioma overall and by sex are presented in Table 2. A BMI of 25 to <30 kg/m^2 was positively associated with meningioma compared with a BMI <25 (OR: 1.21; 95% CI: 1.02–1.44), with BMI ≥30 showing a similar association (OR: 1.22; 95% CI: 0.99–1.50, P-trend = 0.04). Increased weight was also positively associated with meningioma overall (P-trend = 0.02). A positive BMI change since age 21 was associated with meningioma overall (overall P-trend = 0.005, P-trend in men = 0.02, P-trend in women = 0.33, *P* value for heterogeneity by sex = 0.29). Similarly, a positive average annual BMI change was associated with meningioma overall (overall P-trend = 0.04, P-trend in men = 0.03, P-trend in women = 0.16, *P* value for heterogeneity among sex = 0.3168). Increased weight was also associated with risk of meningioma (OR per 5 kg increase = 1.03; 95% CI: 1.00–1.06). Risk of meningioma was significantly higher among those who reported a history of hypertension overall (OR: 1.26; 95% CI: 1.09–1.47), in men (OR: 1.44; 95% CI: 1.07–1.94), and in women (OR: 1.21; 95% CI: 1.02–1.44), whereas the association between diabetes and meningioma was not significant overall (OR: 1.20; 95% CI: 0.96–1.50). Individuals with a history of both hypertension and diabetes showed an even higher risk (OR: 1.54; 95% CI: 1.17–2.03) than those who had neither diabetes nor hypertension. Smoking status, alcohol use, moderate activity, vigorous activity, and hours of sitting were not associated with meningioma (Supplementary Table 1).

An analysis stratified by ethnicity revealed that increased BMI and weight were significantly associated with meningioma in Japanese Americans (*P* = 0.004 and *P* = 0.01, respectively), but BMI change (percent) and average annual BMI change were not (P-trend = 0.22, 0.11, respectively; Supplementary Table 2). Average annual BMI change was associated with meningioma risk in whites (P-trend = 0.04). In addition, hypertension was significantly associated with meningioma among Japanese Americans (OR: 1.63; 95% CI: 1.17–2.27) and Native Hawaiians (OR: 1.86; 95% CI: 1.02–3.40). A combination of both hypertension and diabetes was associated with a particularly increased risk among Japanese Americans (OR: 2.00; 95% CI: 1.04–3.87). These associations, however, did not differ significantly across race/ethnicity (*P* values for heterogeneity ≥ 0.17).

In women, older age at first birth was inversely associated with risk of meningioma (P-trend = 0.004; Table 3). Oral contraceptive use was positively associated with meningioma (OR: 1.24; 95% CI: 1.01–1.51), but there was no dose response trend of increasing risk with increasing duration of use (P-trend = 0.14). Compared with premenopausal women, risk was higher among those who had a surgical menopause by oophorectomy (OR: 1.67; 95% CI: 1.06–2.63), but this association was not significant among those women who were not HT users (OR: 1.95; 95% CI: 0.99–3.85). Current use of menopausal estrogen alone showed a borderline significant association with increased risk compared with no estrogen use (with or without past or current progesterone use, OR: 1.27; 95% CI: 0.98–1.64). Combined use of current estrogen and progesterone was not associated with meningioma (OR: 1.02; 95% CI: 0.77–1.34). Longer duration of estrogen use was significantly associated with risk (per 5 y, OR: 1.07; 95% CI: 1.01–1.15), but this was not significant among those who had a surgical menopause (per 5 y, OR: 0.96; 95% CI: 0.81–1.14).

Discussion

This study sought to evaluate factors associated with meningioma risk in a large ethnically diverse population. We found that higher BMI, higher weight, hypertension, and oral contraceptive and menopausal estrogen use were associated with increased meningioma risk.

A positive association between higher BMI and meningioma risk has been observed in several studies in predominantly white populations.[10–13,18–21] The association between BMI and meningioma seemed stronger among men than among women in our study, but this did not yield a significant *P* value for heterogeneity. Two other studies did not find an association between BMI and meningioma in men, possibly due to relatively few male cases (both *N* = <55).[12,18] However, a multicenter case-control study in men with meningioma (*N* = 456) found a significant association between BMI and risk of meningioma.[21] Three meta-analyses also found a positive association between increased BMI and meningioma risk, 2 of which found the association to be present among both men and women.[10,22,23] Our findings are consistent with these published findings.

In our study, the association between BMI and meningioma seems to be particularly strong in Japanese Americans. We did not observe any other significant associations among other ethnicities with regard to BMI, which may be due to a relatively higher prevalence of higher BMI among African Americans, Latinos, and Native Hawaiians compared with whites and Japanese Americans resulting in less statistical power. The positive association between obesity and meningioma may be explained by higher levels of circulating estrogen that may result from more adipose tissue known to produce estrogen, which is known to promote meningioma development.[24–27] More adipose tissue may also increase levels of insulin and insulin-like growth factor 1, leading to stimulation of cancer cell growth in breast cancer and may thus contribute to meningioma development in a similar manner.[28]

Metabolic syndrome, which is characterized by dyslipidemia, obesity, increased systolic blood pressure, and increased fasting plasma glucose concentrations, has previously been associated with increased meningioma risk.[19,29,30] This may be due to chronic low-grade inflammation, decreased antioxidant defense mechanisms, and increased oxidative stress associated with metabolic syndrome.[31,32] Apart from obesity, this study found a positive association between hypertension and meningioma, which was also identified in a nested case-control study within a cohort from the UK.[19] There currently seems to be no explanation for the association between hypertension and meningioma. The association was stronger in individuals with both hypertension and diabetes. However,

Table 2 Association between anthropometric factors, diabetes, and hypertension with meningioma

	Men		Women		P for Heterogeneity	Overall	
	Cases/Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)		Cases/Controls	OR (95% CI)
BMI (kg/m²)							
<25	60/789	1.00 (ref.)	250/2703	1.00 (ref.)	0.3175	310/3492	1.00 (ref.)
25–<30	111/1003	1.44 (1.02–2.02)	236/2268	1.15 (0.94–1.41)		347/3271	1.21 (1.02–1.44)
≥30	41/346	1.50 (0.95–2.35)	182/1653	1.16 (0.92–1.47)		223/1999	1.22 (0.99–1.50)
P-trend		0.0483		0.1794			0.0410
BMI (kg/m²) per 5-unit increase	1.09 (0.91–1.31) 0.3365		1.07 (0.99–1.16) 0.0941		0.5362	1.07 (1.00–1.15) 0.0686	
BMI at age 21 (kg/m²) *							
<20.0	31/365	1.00 (ref.)	224/2246	1.00 (ref.)	0.7633	255/2611	1.00 (ref.)
20.0–<22.2	64/647	1.19 (0.75–1.88)	217/2217	1.00 (0.82–1.23)		281/2864	1.03 (0.85–1.24)
≥22.2	105/1021	1.22 (0.79–1.88)	176/1680	1.04 (0.84–1.30)		281/2701	1.06 (0.88–1.29)
P-trend		0.4310		0.7387			0.5488
BMI at age 21 (kg/m²) per 5-unit increase	1.04 (0.82–1.33)		1.02 (0.89–1.16)		0.7104	1.02 (0.91–1.15)	
Height (cm)**							
≤Q1	33/406	1.00 (ref.)	111/1076	1.00 (ref.)	0.4580	144/1482	1.00 (ref.)
>Q1–≤Q2	48/538	0.99 (0.60–1.63)	163/1737	0.89 (0.68–1.17)		211/2275	0.93 (0.73–1.18)
>Q2–≤Q3	84/695	1.23 (0.75–2.04)	267/2530	0.97 (0.74–1.27)		351/3225	1.05 (0.83–1.33)
>Q3	50/509	1.03 (0.58–1.84)	136/1388	0.87 (0.63–1.20)		186/1897	0.92 (0.70–1.22)
P-trend		0.7376		0.5717			0.8801
Height (cm) per 10 cm increase	1.26 (0.99–1.59) 0.0622		0.94 (0.81–1.08) 0.3491		0.0143	1.02 (0.90–1.15) 0.7474	
Weight (kg)**							
≤Q1	31/515	1.00 (ref.)	169/1871	1.00 (ref.)	0.1027	200/2386	1.00 (ref.)
>Q1–≤Q2	59/547	1.86 (1.15–3.03)	141/1413	1.12 (0.87–1.45)		200/1960	1.25 (1.00–1.56)
>Q2–≤Q3	59/537	1.89 (1.12–3.19)	180/1718	1.21 (0.94–1.57)		239/2255	1.32 (1.05–1.66)
>Q3	63/541	2.08 (1.20–3.60)	179/1641	1.23 (0.93–1.63)		242/2182	1.37 (1.07–1.75)
P-trend		0.0275		0.1315			0.0173
Weight (kg) per 5 kg increase	1.03 (0.97–1.10) 0.2785		1.03 (1.00–1.06) 0.0950		0.1302	1.03 (1.00–1.06) 0.0475	
BMI change (%)							
<–5 (weight loss)	10/115	1.60 (0.66–3.87)	21/328	0.61 (0.34–1.07)	0.2920	31/443	0.80 (0.50–1.29)
–5 to <5	13/270	1.00 (ref.)	50/555	1.00 (ref.)		63/825	1.00 (ref.)
5 to <15	50/549	1.80 (0.96–3.41)	109/1099	1.04 (0.72–1.50)		159/1648	1.21 (0.88–1.65)

Table 2 *Continued*

	Men		Women		P for Heterogeneity	Overall	
	Cases/Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)		Cases/Controls	OR (95% CI)
15 to <25	57/466	2.49 (1.32–4.68)	128/1238	1.13 (0.79–1.62)		185/1704	1.40 (1.03–1.91)
25 to <35	33/293	2.61 (1.32–5.13)	96/964	1.12 (0.76–1.63)		129/1257	1.39 (1.00–1.93)
≥35	36/339	2.34 (1.17–4.70)	212/1932	1.17 (0.82–1.68)		248/2271	1.39 (1.02–1.91)
P-trend		0.0160		0.3257			0.0052
Average annual BMI change* **							
<–0.25 (weight loss)	4/38	1.47 (0.49–4.40)	16/159	0.95 (0.52–1.71)	0.3168	20/197	1.08 (0.64–1.81)
–0.25 to <0.25	44/652	1.00 (ref.)	120/1253	1.00 (ref.)		164/1905	1.00 (ref.)
0.25 to <0.50	62/536	1.73 (1.14–2.63)	106/1229	0.93 (0.70–1.24)		168/1765	1.14 (0.90–1.44)
0.50 to <0.75	39/353	1.85 (1.14–3.01)	116/1112	1.12 (0.84–1.49)		155/1465	1.29 (1.01–1.65)
0.75 to <1.0	21/188	1.95 (1.08–3.52)	89/780	1.23 (0.90–1.69)		110/968	1.39 (1.05–1.83)
≥1.0	29/265	1.83 (1.03–3.26)	169/1583	1.12 (0.84–1.50)		198/1848	1.27 (0.98–1.64)
P-trend		0.0311		0.1643			0.0381
Diabetes							
No	180/1913	1.00 (ref.)	592/6003	1.00 (ref.)	0.2364	772/7916	1.00 (ref.)
Yes	35/237	1.40 (0.92–2.11) 0.1131	87/765	1.12 (0.86–1.47) 0.3975		122/1002	1.20 (0.96–1.50) 0.1144
Hypertension							
No	107/1291	1.00 (ref.)	358/3897	1.00 (ref.)	0.2257	465/5188	1.00 (ref.)
Yes	108/859	1.44 (1.07–1.94) 0.0160	321/2871	1.21 (1.02–1.44) 0.0337		429/3730	1.26 (1.09–1.47) 0.0025
Diabetes and hypertension							
No diabetes or hypertension	95/1185	1.00 (ref.)	333/3630	1.00 (ref.)	0.4584	428/4815	1.00 (ref.)
Diabetes and no hypertension	12/106	1.36 (0.71–2.60) 0.3598	25/267	1.05 (0.67–1.66) 0.8250		37/373	1.14 (0.79–1.66) 0.4790
Hypertension and no diabetes	85/728	1.43 (1.04–1.97) 0.0282	259/2373	1.20 (0.99–1.44) 0.0582		344/3101	1.25 (1.07–1.47) 0.0060
Diabetes and hypertension	23/131	2.04 (1.20–3.45) 0.0082	62/498	1.39 (1.00–1.92) 0.0487		85/629	1.54 (1.17–2.03) 0.0022

OR stratified by matching set and adjusted for BMI, alcohol, smoking status, diabetes, hypertension and education.
*BMI at 21 cutoffs determined with 33rd and 66th percentiles among controls.
**Sex-specific height (cm) and weight (kg) cutoffs determined by quartiles among controls
– height: men ≤167.6, >167.6–≤172.7, > 172.7–≤177.8, >177.8; women ≤154.9, >154.9–≤160.0, >160.0–≤165.1, >165.1.
– weight: men ≤70.3, >70.3–≤78.0, >78.0–≤87.5, >87.5; women ≤59.0, >59.0–≤68.0, >68.0–≤78.5, >78.5.
***Average annual BMI change (percent per year).

Table 3 Association between hormonal factors and meningioma among women

	Cases/ Controls	OR* (95% CI)
Age at menarche, y		
≤12	321/3220	1.00 (ref.)
13–14	250/2517	0.97 (0.81–1.17)
>14	89/895	0.98 (0.75–1.27)
P-trend		0.7888
Nulliparity		
No	600/5917	1.00 (ref.)
Yes	77/822	0.96 (0.73–1.25)
		0.7360
Parity		
0	77/800	1.00 (ref.)
1–2	211/2175	0.99 (0.75–1.32)
3–4	225/2228	1.07 (0.80–1.43)
5 or more	155/1461	1.05 (0.77–1.45)
P-trend		0.5600
Age at first live birth, y		
nulliparous	77/822	0.81 (0.60–1.08)
15–20	239/2153	1.00 (ref.)
21–30	304/3179	0.78 (0.64–0.96)
>30	29/398	0.60 (0.39–0.93)
P-trend		0.0040
Ever used oral contraceptive		
No	397/4226	1.00 (ref.)
Yes	251/2256	1.24 (1.01–1.51)
		0.0411
Duration of oral contraceptive use, y		
None	397/4226	1.00 (ref.)
<5	203/1719	1.31 (1.06–1.63)
≥5	47/490	1.08 (0.76–1.52)
P-trend		0.1404
Menopausal status		
Premenopausal	40/484	1.00 (ref.)
Natural menopause	309/3401	1.12 (0.73–1.74)
Surgical menopause (oophorectomy with or without hysterectomy)	135/1033	1.67 (1.06–2.63)
Other surgery that causes periods to stop (hysterectomy, endometrial ablation)	157/1351	1.52 (0.98–2.37)
Period stopped but reason unknown	31/429	0.81 (0.44–1.46)
Menopausal status—no HT use		
Premenopausal	39/476	1.00 (ref.)
Natural menopause	180/1940	1.26 (0.73–2.18)
Surgical menopause (oophorectomy with or without hysterectomy)	28/199	1.95 (0.99–3.85)
Other surgery that causes periods to stop (hysterectomy, endometrial ablation)	60/551	1.56 (0.89–2.74)
Period stopped but reason unknown	16/236	0.78 (0.36–1.68)
Menopausal status—HT use		
Natural menopause	120/1360	1.00 (ref.)
Surgical menopause (oophorectomy with or without hysterectomy)	98/783	1.38 (1.00–1.89)
Other surgery that causes periods to stop (hysterectomy, endometrial ablation)	87/724	1.45 (1.05–2.01)

Table 3 *Continued*

	Cases/ Controls	OR* (95% CI)
Period stopped but reason unknown	6/89	0.94 (0.37–2.34)
Age at menopause, by type		
Premenopausal	40/484	1.00 (ref.)
Natural menopause at age <50	139/1585	1.12 (0.71–1.78)
Natural menopause at age ≥50	164/1782	1.27 (0.79–2.02)
Oophorectomy (with or without hysterectomy) at age <50	101/824	1.72 (1.07–2.74)
Oophorectomy (with or without hysterectomy) at age ≥50	22/149	2.02 (1.07–3.80)
Other surgery (hysterectomy, endometrial ablation) at age <50	134/1130	1.62 (1.03–2.55)
Other surgery (hysterectomy, endometrial ablation) at age ≥50	10/75	1.90 (0.85–4.26)
Limited to postmenopausal women		
Estrogen (E) and progestin (P) use		
Never E use, with or without past or current P use	284/2926	1.00 (ref.)
Past E use, with or without past P use	120/1211	1.09 (0.86–1.38)
Current E use alone	102/820	1.27 (0.98–1.64)
Current E use with P—past or current	89/925	1.02 (0.77–1.34)
P-trend		0.4289
HT use		
Estrogen per 5 year of use		1.07 (1.01–1.15)
Progestin per 5 year of use		0.59 (0.33–1.04)
Estrogen + progestin per 5 year of use		1.05 (0.92–1.20)
Limited to women with surgical menopause		
HT use		
Estrogen per 5 year of use		0.96 (0.81–1.14)
Progestin per 5 year of use		0.32 (0.08–1.29)
Estrogen + progestin per 5 year of use		0.69 (0.41–1.17)

OR stratified by matching set and adjusted for BMI, alcohol, smoking status, diabetes, hypertension, and education.

no association between diabetes alone and meningioma risk was identified in this study, which has even been suggested to be inversely related in a large Swedish cohort.[33] The results from this study suggest that low physical activity levels and smoking status, which are both positively associated with metabolic syndrome, are not associated with meningioma risk.[34,35] Smoking, which was not associated with meningioma risk in this study, has been inversely associated with risk of meningioma in some studies.[13,36]

Oral contraceptive use was associated with increased meningioma risk in this study, which is in line with 2 other relatively large cohort studies from the US and Europe,[13,14] although conflicting results have been reported based on the Million Women Study and a case-control study from the Chicago area.[20,36] Menopausal hormone use has been associated with increased meningioma risk, although our study found only a borderline significant association with sole estrogen use.[14,37–42] Nevertheless, increased duration of estrogen use was significantly associated with meningioma. Consistent with our findings, a Finnish cohort suggested that estrogen use in particular was associated with meningioma, whereas a combination of estrogen and progesterone was not.[41] Another study indicated that use of estrogen and progestin combined therapy resulted in a higher risk than sole estrogen use.[37] These intriguing associations between hormonal contraceptives and menopausal hormone use and meningioma risk may be explained by the fact that the estrogenic components of these agents potentially promote meningioma growth, but the specific contribution of progestin to meningioma risk remains less clear and was clearly negative in our study.[24–27] The inverse association with progestin use may be explained by the relatively older age at enrollment in our cohort compared with other studies, as progesterone receptor–positive meningiomas tend to present at a younger age and may be underrepresented in our cohort.[43]

Some of the study strengths are the inclusion of multiple ethnicities, relatively large size, and extensive information on risk factors and potential confounders. To our knowledge this is the first study comparing risk factors across ethnicity/race in a single study with uniform data collection on risk factors. However, this study also has several limitations. The algorithm used to ascertain meningioma cases and controls using the Medicare and Center on Human Development and Disability (CHDD)

databases has not been validated in the MEC, which might have resulted in outcome misclassification. There is a possibility that the control group might include undiagnosed meningioma, which is present in about 1–2% of individuals.[44] If this occurred, the observed associations in this study might have been attenuated. The administrative claims data also did not permit the differentiation of World Health Organization grades of meningiomas to delineate specific risk factors for high-grade meningioma. Finally, even with our large number, the numbers of cases in each racial/ethnic group and across exposure categories are sparse, which may have resulted in a lack of power to detect a significant association in the analyses stratified by ethnicity.

In conclusion, in this first study of meningioma risk factors among diverse populations, we provided some evidence that body weight, hypertension, and hormonal factors are associated with meningioma with some differences among ethnicities.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

cohort study | meningioma | multiethnic cohort

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References

1. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro Oncol.* 2017;19(Suppl 5):v1–v88.
2. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol.* 2010;99(3):307-314.
3. Zamanipoor Najafabadi AH, Peeters MCM, Dirven L, et al. Impaired health-related quality of life in meningioma patients—a systematic review. *Neuro Oncol.* 2016;19(7):now250.
4. Aboukais R, Zairi F, Baroncini M, et al. Intracranial meningiomas and neurofibromatosis type 2. *Acta Neurochir (Wien).* 2013;155(6):997–1001.
5. Goutagny S, Kalamarides M. Meningiomas and neurofibromatosis. *J Neurooncol.* 2010;99(3):341–347.
6. Asgharian B, Chen Y-J, Patronas NJ, et al. Meningiomas may be a component tumor of multiple endocrine neoplasia type 1. *Clin Cancer Res.* 2004;10(3):869–880.
7. Braganza MZ, Kitahara CM, Berrington de González A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. *Neuro Oncol.* 2012;14(11):1316–1324.
8. Yamanaka R, Hayano A, Kanayama T. Radiation-induced meningiomas: an exhaustive review of the literature. *World Neurosurg.* 2017;97:635–644.e8.
9. Claus EB, Calvocoressi L, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M. Dental x-rays and risk of meningioma. *Cancer.* 2012;118(18):4530–4537.
10. Niedermaier T, Behrens G, Schmid D, Schlecht I, Fischer B, Leitzmann MF. Body mass index, physical activity, and risk of adult meningioma and glioma: a meta-analysis. *Neurology.* 2015;85(15):1342–1350.
11. Johnson DR, Olson JE, Vierkant RA, et al. Risk factors for meningioma in postmenopausal women: results from the Iowa Women's Health Study. *Neuro Oncol.* 2011;13(9):1011–1019.
12. Michaud DS, Bové G, Gallo V, et al. Anthropometric measures, physical activity, and risk of glioma and meningioma in a large prospective cohort study. *Cancer Prev Res (Phila).* 2011;4(9):1385–1392.
13. Claus EB, Calvocoressi L, Bondy ML, Wrensch M, Wiemels JL, Schildkraut JM. Exogenous hormone use, reproductive factors, and risk of intracranial meningioma in females. *J Neurosurg.* 2013;118(3):649–656.
14. Michaud DS, Gallo V, Schlehofer B, et al. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. *Cancer Epidemiol Biomarkers Prev.* 2010;19(10):2562–2569.
15. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol.* 2000;151(4):346–357.
16. Setiawan VW, Virnig BA, Porcel J, et al. Linking data from the Multiethnic Cohort Study to medicare data: linkage results and application to chronic disease research. *Am J Epidemiol.* 2015;181(11):917–919.
17. Park SL, Goodman MT, Zhang ZF, Kolonel LN, Henderson BE, Setiawan VW. Body size, adult BMI gain and endometrial cancer risk: the multiethnic cohort. *Int J Cancer.* 2010;126(2):490–499.
18. Wiedmann M, Brunborg C, Lindemann K, et al. Body mass index and the risk of meningioma, glioma and schwannoma in a large prospective cohort study (The HUNT Study). *Br J Cancer.* 2013;109(1):289–294.
19. Seliger C, Meier CR, Becker C, et al. Metabolic syndrome in relation to risk of meningioma. *Oncotarget.* 2017;8(2):2284–2292.

20. Benson VS, Pirie K, Green J, Casabonne D, Beral V; Million Women Study Collaborators. Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. *Br J Cancer.* 2008;99(1):185–190.
21. Schildkraut JM, Calvocoressi L, Wang F, et al. Endogenous and exogenous hormone exposure and the risk of meningioma in men. *J Neurosurg.* 2014;120(4):820–826.
22. Zhang D, Chen J, Wang J, et al. Body mass index and risk of brain tumors: a systematic review and dose-response meta-analysis. *Eur J Clin Nutr.* 2016;70(7):757–765.
23. Sergentanis TN, Tsivgoulis G, Perlepe C, et al. Obesity and risk for brain/CNS tumors, gliomas and meningiomas: a meta-analysis. *PLoS One.* 2015;10(9):e0136974.
24. Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). *Cancer Causes Control.* 2001;12(1):47–59.
25. Bezemer ID, Rinaldi S, Dossus L, et al. C-peptide, IGF-I, sex-steroid hormones and adiposity: a cross-sectional study in healthy women within the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Causes Control.* 2005;16(5):561–572.
26. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst.* 2003;95(16):1218–1226.
27. Jay JR, MacLaughlin DT, Riley KR, Martuza RL. Modulation of meningioma cell growth by sex steroid hormones in vitro. *J Neurosurg.* 1985;62(5):757–762.
28. Key TJ, Appleby PN, Reeves GK, Roddam AW; Endogenous Hormones and Breast Cancer Collaborative Group. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol.* 2010;11(6):530–542.
29. Schlaich M, Straznicky N, Lambert E, Lambert G. Metabolic syndrome: a sympathetic disease? *Lancet Diabetes Endocrinol.* 2015;3(2):148–157.
30. Edlinger M, Strohmaier S, Jonsson H, et al. Blood pressure and other metabolic syndrome factors and risk of brain tumour in the large population-based Me-Can cohort study. *J Hypertens.* 2012;30(2):290–296.
31. Fernández-Sánchez A, Madrigal-Santillán E, Bautista M, et al. Inflammation, oxidative stress, and obesity. *Int J Mol Sci.* 2011;12(5):3117–3132.
32. Rajaraman P, Hutchinson A, Rothman N, et al. Oxidative response gene polymorphisms and risk of adult brain tumors. *Neuro Oncol.* 2008;10(5):709–715.
33. Bernardo BM, Orellana RC, Weisband YL, et al. Association between prediagnostic glucose, triglycerides, cholesterol and meningioma, and reverse causality. *Br J Cancer.* 2016;115(1):108–114.
34. He D, Xi B, Xue J, Huai P, Zhang M, Li J. Association between leisure time physical activity and metabolic syndrome: a meta-analysis of prospective cohort studies. *Endocrine.* 2014;46(2):231–240.
35. Sun K, Liu J, Ning G. Active smoking and risk of metabolic syndrome: a meta-analysis of prospective studies. *PLoS One.* 2012;7(10):e47791.
36. Lee E, Grutsch J, Persky V, Glick R, Mendes J, Davis F. Association of meningioma with reproductive factors. *Int J Cancer.* 2006;119(5):1152–1157.
37. Andersen L, Friis S, Hallas J, Ravn P, Schrøder HD, Gaist D. Hormone replacement therapy increases the risk of cranial meningioma. *Eur J Cancer.* 2013;49(15):3303–3310.
38. Benson VS, Kirichek O, Beral V, Green J. Menopausal hormone therapy and central nervous system tumor risk: large UK prospective study and meta-analysis. *Int J Cancer.* 2015;136(10):2369–2377.
39. Blitshteyn S, Crook JE, Jaeckle KA. Is there an association between meningioma and hormone replacement therapy? *J Clin Oncol.* 2008;26(2):279–282.
40. Jhawar BS, Fuchs CS, Colditz GA, Stampfer MJ. Sex steroid hormone exposures and risk for meningioma. *J Neurosurg.* 2003;99(5):848–853.
41. Korhonen K, Auvinen A, Lyytinen H, Ylikorkala O, Pukkala E. A nationwide cohort study on the incidence of meningioma in women using postmenopausal hormone therapy in Finland. *Am J Epidemiol.* 2012;175(4):309–314.
42. Wigertz A, Lönn S, Mathiesen T, Ahlbom A, Hall P, Feychting M; Swedish Interphone Study Group. Risk of brain tumors associated with exposure to exogenous female sex hormones. *Am J Epidemiol.* 2006;164(7):629–636.
43. Pravdenkova S, Al-Mefty O, Sawyer J, Husain M. Progesterone and estrogen receptors: opposing prognostic indicators in meningiomas. *J Neurosurg.* 2006;105(2):163–173.
44. Nakasu S, Hirano A, Shimura T, Llena JF. Incidental meningiomas in autopsy study. *Surg Neurol.* 1987;27(4):319–322.