Published in final edited form as:

Mayo Clin Proc. 2019 February ; 94(2): 254–261. doi:10.1016/j.mayocp.2018.07.026.

Factors Associated with Meningioma Detected in a Population-Based Sample

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Abstract

Objective: To determine the frequency of incidental meningioma and identify associated factors in a population-based sample where participants systematically underwent brain imaging.

Patients and Methods: We searched the Mayo Clinic Study of Aging (MCSA), a population-based sample of Olmsted County, Minnesota residents who underwent longitudinal brain MR imaging. Using a text search of radiologists' notes of 2,402 individuals, mean age 75, scanned between August 10, 2005 and July 31, 2014. 52 participants (2%) had at least one meningioma. We estimated the association of selected risk factors with presence of meningioma using odds ratios and 95% confidence intervals from logistic regression models adjusted for age and sex. Based on these results, we moved the most significant variables forward to a multivariable model.

Results: Controlling for age and sex, significant associations with presence of meningioma included higher body mass index [OR (95% CI)], 1.06 (1.01, 1.12), taking NSAIDs 2.11 (1.13 to 3.95), aspirin 1.90 (1.05 to 3.46), and blood pressure lowering medication 2.06 (1.06 to 3.99). Lower risk was associated with male sex 0.51 (0.29 to 0.90), coronary artery disease 0.46 (0.22 to 0.97) and higher self-reported anxiety 0.88 (0.78 to 0.98). Simultaneous adjustment for all of these factors except aspirin in a multivariable model did not attenuate these associations (concordance 0.71).

Conclusions: 2.2% of population-based participants had an incidental meningioma. They were more likely to be female and have higher BMI. Meningioma was also associated with certain

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medications (NSAIDs and blood pressure lowering medications) and inversely with anxiety and coronary artery disease.

INTRODUCTION

Meningioma is the most common brain tumor, accounting for 36.4% of primary CNS tumors¹. Based on autopsy studies, an estimated 2% of the general population has a meningioma². Many of these go undetected as they are most often slow-growing and over 95% are benign³. As such, most clinicians monitor an incidentally discovered meningioma and typically reserve intervention, such as radiosurgery or resection, for cases where the meningioma poses a clear risk due to size, location, or evidence of progression⁴.

Previous epidemiologic studies have identified meningioma cases through linkage to medical records, claims databases, or cancer registries, wherein meningiomas were presumably identified clinically. We found just one previous relatively small study looking for factors associated with incidental meningiomas where population-based subjects were systematically imaged⁵ and found 9 incidental meningiomas (1.7%), all in females, but no other associated factors, highlighting the need for more population-based studies. Therefore, we conducted a cross-sectional analysis looking for incidentally-identified meningioma and associated factors in a larger sample of participants enrolled in the population-based Mayo Clinic Study of Aging (MCSA) where enrollees systematically undergo brain imaging.

METHODS

Patients and Procedures

All participants were enrolled in the population-based MCSA, a longitudinal study of Olmsted County, Minnesota residents who were randomly selected from the defined county population for participation in the study⁶. At baseline and approximately every 15 months thereafter, a study coordinator interviewed MCSA participants regarding their family and medical history and an index of subjective cognitive decline, a physician performed a mental status and neurologic examination, and patients completed neuropsychological testing. Participants without a medical contraindication who agreed to undergo imaging underwent a 3 Tesla brain MRI at the time of, or soon after, each visit (generally within three months)⁶⁻⁸. Mayo Clinic neuroradiologists interpreted all MRI scans and entered the findings in the patient record. We completed a text search of the radiologists' notes for the 2,402 MCSA individuals scanned between August 10, 2005 and July 31, 2014 using the search terms: meningioma, neoplasm, brain lesion, tumor, intracranial tumor, intracranial mass, intracranial lesion, cystic mass, cyst, extra axial, and dural based. Of the 1050 hits, scans with a "probable" or "possible" meningioma were reviewed and a radiation-oncologist (PDB) verified the determination that a meningioma was present⁹. This process identified fifty-two participants (2.2%) with at least one meningioma (Figure 1).

Factors potentially associated with meningiomas that were ascertained for MCSA participants were analyzed. In selecting variables from the MCSA to examine, we chose those that were found significant in previous meningioma studies, examined in previous studies with insufficient sample size, or theoretically of interest. We also included medical

diagnoses and medications that are common, while leaving out a smaller number of variables where a relationship would seem remote (e.g., macular degeneration), redundant (e.g., we chose CAD over angina; calculated BMI over obesity), or where there was a low response rate (e.g., variables added to the MCSA in more recent years). This resulted in inclusion of demographics (age, sex, education) from the nurse interview, body size (height, weight, BMI) from direct measurement at the study visit, ApoE status from a blood draw, self-reported cognition¹⁰ and score on the Short Test of Mental Status¹¹ from the physician evaluation. Medical diagnoses (coronary artery disease [CAD], diabetes, hypertension, stroke, dyslipidemia, cancer), and history of head trauma causing memory loss or loss of consciousness were abstracted from the participant medical records. In addition, current medications at time of visit (includes total number of medications as well as oral diabetes agents, insulin, statins, blood pressure [BP] lowering medications, medications used for chronic heart failure [CHF], warfarin, nonsteroidal anti-inflammatory drugs [NSAIDs including aspirin], aspirin, selective serotonin reuptake inhibitors [SSRIs] and serotonin and norepinephrine reuptake inhibitors [SNRIs] combined, tricyclics, multivitamin use, and use of hormone replacement therapies [HRT-estrogen, HRT-progesterone] were obtained by self report at each visit as was history of ever smoking. Presence of depressive symptoms and anxiety were obtained by self-report using the Beck Depression Inventory-II (BDI-II)¹² and the Beck Anxiety Inventory (BAI)¹³, respectively.

Standard protocol approvals and consents

The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved all the study protocols, which included review of data collected as part of the MCSA. All participants provided written informed consent. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis

The 52 cases with meningioma found on imaging were compared to the 2,350 subjects without a meningioma on several covariates available in the MCSA. First, we created the list of variables of interest described above. Characteristics of interest were analyzed for association with meningiomas using chi-square or fisher's exact test for categorical data and by the Kruskal Wallis test for continuous data. Next, we estimated the association of the selected variables with presence of meningioma using univariate logistic regression models estimating odds ratios (OR) and 95% confidence intervals (CI), and in models adjusted for age and sex. Variables significantly associated with meningioma ($P < 0.05$) from age and sex-adjusted models were then examined simultaneously in a multivariable logistic regression model. Statistical analyses were completed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Demographics and univariate analyses are reported in Table 1. The groups did not differ in terms of age (meningioma group median 75.0 years, no-meningioma group median 75.6

years; $P = .79$) or education (meningioma group median 15.0 years, no-meningioma group median 14.0 years; $P = .46$). Among persons with meningioma, there was a greater frequency of women compared to men (meningioma group 63.5% female, no-meningioma group 47.0% female; $P = .02$). The primary tumor location was in the convexity in 42% (22/52), tentorium/falx in 29% (15/52), skull base in 19% (10/52), and infratentorial for 10% (5/52). The vast majority of tumors were small (90% < 3cm). The groups did not differ in terms of ApoE status or presence of subjective cognitive concerns, which were low in both groups.

Table 2 shows the associations of meningioma status with medical factors, medications, and anthropometric variables, respectively. Controlling for age and sex, significant associations with presence of meningioma included higher BMI [OR (95% CI)], 1.06 (1.01, 1.12), taking NSAIDS (including aspirin) 2.11 (1.13 to 3.95), aspirin 1.90 (1.05 to 3.46), and BP lowering medication 2.06 (1.06 to 3.99). Lower risk was associated with male sex 0.51 (0.29 to 0.90), CAD 0.46 (0.22 to 0.97) and higher BAI total score 0.88 (0.78 to 0.98). When all of these factors except aspirin were put in a single multivariable model, all associations were similar, though BMI was no longer statistically significant (Table 3). The concordance for the multivariable model was 0.71.

DISCUSSION

Meningioma was identified in 2.2% of participants in our population-based sample of mostly older adults from Olmsted County, Minnesota. This is very similar to the 1.7% reported in the only other study examining factors associated with incidental meningioma in a population-based sample that was systematically imaged⁵. The incidence of meningioma in women in the two studies was nearly identical (2.90% in our study and 2.86% in Krampla et al).

Age is a known risk factor⁴, but was not significantly associated with meningioma in our relatively older sample where the median age was 75.6, and the 25th percentile was 71. All subjects in the Krampla study were age 75 so a relationship with age was not examined. Vernooj et al.¹⁴ systematically imaged 2000 subjects in a population-based sample that was somewhat younger, and found a meningioma rate of 0.5% in 45 to 59 year-olds, and 1.6% in those 75 or older. Vernooj et al. did not report their meningioma findings by sex or other associated factors.

BMI has emerged as a consistent finding in this and other studies¹⁵, and is a potentially modifiable risk factor. Some studies have reported height as an independent risk factor separate from weight¹⁶, and a large prospective population study in Norway¹⁷ found height but not weight to be associated with meningioma. In contrast, weight was more strongly associated with meningioma than height in both men and women in our study.

Given the consistent finding of BMI and female sex as risk factors for meningioma, there has been a great deal of interest in examining possible associations with metabolic and hormone-related variables in development of this tumor. Findings have been mixed with regard to any elevated risk for women on hormone replacement therapy^{18,19}. We did not find a relationship between meningioma and current HRT use; but dosage, length of use, or

any past treatment were not available. The percentage of women on estrogen in our meningioma group was greater than that in the no-meningioma group (12.1% vs 7.1%), but the numbers were extremely small. Johnson et al. (2011) looked at numerous hormone-related factors including “never” vs “ever” used HRT, parity, and age at menarche in older mostly-white women in the Iowa Women’s Health Study cohort. They found no association between these factors and clinically-identified meningioma. Instead, they found a significant relationship with uterine fibroids, postulating that insulin resistance and circulating hormones might be shared risk factors.

In spite of the positive association with BMI, there was no association between meningioma and diabetes in our sample. The relationship between metabolic syndrome and meningioma has been of interest, and appears to be complex, with some studies actually finding an inverse relationship between hyperglycemia and clinical meningioma development^{20,21}. We found CAD was associated with lower risk of meningioma, which seems counter to the positive association between meningioma and taking BP-lowering medications, raising the question of potentially spurious associations due to small sample size. Despite this, Seliger et al. (2017) similarly found a significant negative association between history of myocardial infarction and meningioma.

BMI is related to many other cancers as well²², and this may be a potential mechanism for the association with meningioma. However, we did not find a relationship between meningioma and a history of other cancers in our sample. In fact, a history of cancer was almost twice as frequent in our no-meningioma subjects relative to those with meningioma (23.9% vs 12.2%); a finding that was close to significance ($P=.06$).

The reason for the relationship between NSAIDS and aspirin use and meningioma in our study is not clear. However, it is conceivable that some of the participants with a meningioma experienced headaches or other meningioma-related symptoms that they were treating with analgesic medications. That said, the meningiomas were mostly extremely small, therefore unlikely to cause clinical symptoms, and the groups did not differ on self-reported cognitive symptoms. Further, we reported previously that there were no group differences in cognitive impairment on neuropsychological testing or diagnosis of dementia or mild cognitive impairment⁹. The reason for the relationship between higher anxiety scores and meningioma is also unclear but the anxiety scores in both groups were low, with the median for both groups being just one point (out of 63 possible, with scores over 10 suggesting clinically significant anxiety).

The strengths of our study include the detection of mostly small clinically silent meningiomas in a population-based sample that could differ significantly from those in most other studies where tumors were identified through clinical databases, and were potentially subject to referral or selection bias. We used a cross-sectional study design which allows us to describe associations and to generate hypotheses for future larger prospective studies. Potential limitations include the inability to infer any causal contribution of any of the factors we studied to the development of meningioma. In addition, our subjects were older, and development of meningioma in a younger cohort could look different. For example, Johnson et al.¹⁶ found that BMI before age 30 was not predictive of meningioma, whereas

the relationship of BMI with meningioma after age 30 was significant. We looked at variables collected in the MCSA, a study designed to investigate factors related to mild cognitive impairment and dementia, so factors significantly related to meningioma might not have been included. For example, one often-cited potential risk factor is exposure to ionizing radiation²³, which we could not investigate. Our meningioma group was relatively small, so some cell sizes were small. As such, we could have failed to examine potentially significant associations in our study. Our participants were predominantly white, thus, the study may not be generalizable to studies of other races/ethnicities. And, in fact, there is emerging evidence showing higher incidence of meningioma with black race^{24,25}. Finally, given the exploratory nature of the study, we did not correct for multiple comparisons. For this reason, some of the associations identified could be spurious.

Conclusion:

In this population-based sample, incidental meningioma was identified in 2.2% of participants. Variables associated with meningioma in this study include use of NSAIDs and BP lowering medications, higher BMI, and being female. Additional large-sample population-based studies are needed to clarify risk factors for development of meningioma.

Acknowledgments

Grant Support: This study was supported by a grant from the National Institute of Health (U01 AG006786, AG041851, AG011378), the GHR Foundation, Mayo Foundation for Medical Education and Research, and the Mayo Clinic Department of Psychiatry and Psychology Small Grants Program.

Abbreviations and Acronyms:

MCSA	Mayo Clinic Study of Aging
NSAIDs	nonsteroidal anti-inflammatory drugs
MRI	magnetic resonance imaging
BMI	body mass index
HRT	hormone replacement therapy

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FIGURE 1.

Example of meningioma. On the screening non-contrast MRI (Figure 1-A) scan a 2.8 cm extra-axial mass was noted overlying the high right parietal lobe consistent with meningioma. A follow-up MRI (Figure 1-B) scan with contrast revealed an enhancing extra-axial mass with a tiny dural tail again consistent with a meningioma. Three years later this mass was resected and on pathology review was diagnosed as a WHO Grade I Meningioma.

Table 1.

Characteristics of participants by meningioma status

	Meningioma		P-value
	NO (N=2350)	YES (N=52)	
Demographics			
Age (in years)	75.6 (71.0, 81.7)	75.0 (71.1, 81.4)	.79
Male sex	1245 (53.0%)	19 (36.5%)	.02
Education (in years)	14.0 (12.0, 16.0)	15.0 (12.0, 16.0)	.46
Height (cm)	168.9 (161.3, 176.5)	166.4 (161.3, 174.9)	.38
Weight (kg)	78.9 (68.6, 89.9)	80.4 (71.0, 96.0)	.20
Body Mass Index (BMI) (kg/m2)	27.5 (24.7, 30.6)	28.2 (25.7, 32.6)	.05
Presence of an ApoE-4 allele	629 (26.9%)	14 (26.9%)	>.99
History of smoking	1122 (47.7%)	18 (34.6%)	.06
Cognitive Status			
Kokmen Short test of Mental Status	35.0 (33.0, 36.0)	35.0 (32.0, 37.0)	.63
Subjective Memory Complaint—Blessed scale	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	.31
Medical Conditions			
CAD	774 (33.0%)	9 (17.3%)	.02
Angina	656 (27.9%)	12 (23.1%)	.44
Diabetes	405 (17.2%)	7 (13.5%)	.47
Hypertension	1631 (69.5%)	39 (75.0%)	.39
Stroke	100 (4.3%)	3 (5.8%)	.49
Cancer	531 (23.9%)	6 (12.2%)	.06
Head Trauma	172 (8.3%)	3 (6.1%)	.79
Dyslipidemia	1923 (81.9%)	43 (82.7%)	.88
BDI depression, (Total >= 13)	174 (7.4%)	2 (3.8%)	.59
BAI total	1.0 (0.0, 4.0)	1.0 (0.0, 2.0)	.06
Medications			
Medications, total number	7.0 (4.0, 9.0)	6.0 (5.0, 9.5)	.60
Statins	1143 (48.6%)	25 (48.1%)	.94
BP lowering medication	1467 (62.4%)	39 (75.0%)	.06
Coumadin/Warfarin	125 (5.3%)	5 (9.6%)	.20
NSAIDS	1387 (59.0%)	38 (73.1%)	.04
Aspirin or Aspirin-containing meds	1300 (55.3%)	35 (67.3%)	.09
SSRIs or SNRIs	332 (14.1%)	9 (17.3%)	.52
Tricyclic Antidepressants	71 (3.0%)	4 (7.7%)	.08
Antihistamines	208 (8.9%)	4 (7.7%)	>.99
HRT Estrogen (women only)	79 (7.1%)	4 (12.1%)	.29
Multivitamin	1285 (54.7%)	29 (55.8%)	.88

	Meningioma		<i>P</i> -value
	NO (N=2350)	YES (N=52)	
Rheumatologic or AutoImmune Treatments	50 (2.1%)	2 (3.8%)	.31
Oral Agent for Diabetes	307 (13.1%)	4 (7.7%)	.30
Insulin	101 (4.3%)	2 (3.8%)	>.99

Values presented are N (%) for categorical variables and median (Q1, Q3) for continuous variables. *P*-values for categorical variables are either Chi-Square or Fisher's Exact and for continuous variables are Kruskal-Wallis. Data presented above are based on non-missing values for each variable only. CAD = coronary artery disease; BDI =Beck Depression Inventory; BAI =Beck Anxiety Inventory; BP =blood pressure; NSAIDS = nonsteroidal anti-inflammatory drugs; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; HRT =hormone replacement therapy;

Table 2.

Odds ratios from logistic models predicting meningioma status

	Odds Ratio	95% CI	P-value
<u>Demographics</u>			
Male Sex	0.51	0.29 – 0.90	.02
Height (cm)	1.04	0.99 – 1.09	.09
Weight (kg)	1.03	1.01 – 1.04	.01
Body Mass Index (BMI) (kg/m ²)	1.06	1.01 – 1.12	.03
History of smoking	0.65	0.36 – 1.17	.15
<u>Medical Conditions</u>			
CAD	0.46	0.22 – 0.97	.04
Angina	0.85	0.43 – 1.65	.62
Diabetes	0.78	0.35 – 1.76	.55
Hypertension	1.42	0.73 – 2.77	.31
Stroke	1.49	0.45 – 4.95	.51
Cancer	0.48	0.20 – 1.14	.10
Head Trauma	0.75	0.23 – 2.48	.64
Dyslipidemia	1.09	0.53 – 2.26	.81
BDI depression, (Total >= 13)	0.51	0.12 – 2.13	.36
BAI total	0.88	0.78 – 0.98	.02
<u>Medications</u>			
Medications, total number	1.01	0.94 – 1.08	.85
Statins	1.05	0.61 – 1.84	.85
BP lowering medication	2.06	1.06 – 3.99	.03
Coumadin/Warfarin	2.05	0.79 – 5.30	.14
NSAIDS w/aspirin	2.11	1.13 – 3.95	.02
NSAIDS w/o aspirin	1.67	0.74 – 3.76	.22
Aspirin or Aspirin-containing meds	1.90	1.05 – 3.46	.04
SSRIs or SNRIs	1.13	0.54 – 2.39	.75
Tricyclic Antidepressants	2.42	0.84 – 6.92	.10
Antihistamines	0.80	0.28 – 2.24	.67
HRT Estrogen (women only)	1.70	0.57 – 5.03	.34
Multivitamin	0.98	0.56 – 1.71	.93
Rheumatologic or AutoImmune Treatments	1.62	0.38 – 6.87	.52
Oral Agent for Diabetes	0.59	0.21 – 1.64	.31
Insulin	0.90	0.22 – 3.75	.88

All models were adjusted for age and sex except for HRT Estrogen, which is only adjusted for age. All categorical variables presented are Yes/No with No being the reference level for the odds ratios. Odds ratios for continuous variables correspond with a one unit change. CAD = coronary artery disease; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; BP = blood pressure; NSAIDS = nonsteroidal anti-inflammatory drugs; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; HRT = hormone replacement therapy

Table 3.

Multivariable logistic model predicting meningioma status

	Odds Ratio	95% CI	P-value	c-statistic
				0.71
Male	0.50	0.28 – 0.90	.02	
NSAIDS	2.08	1.10 – 3.93	.02	
Body Mass Index (BMI) (kg/m2)	1.05	1.00 – 1.11	.06	
BAI Total	0.89	0.79 – 0.99	.03	
CAD	0.34	0.16 – 0.73	.01	
BP lowering medication	2.05	1.06 – 3.98	.03	

All categorical variables presented are Yes/No with No being the reference level for the odds ratios. Odds ratios for continuous variables correspond with a one unit change. . CAD = coronary artery disease; BDI =Beck Depression Inventory; BAI =Beck Anxiety Inventory; NSAIDS = nonsteroidal anti-inflammatory drugs; BP =blood pressure