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Family and personal medical history and risk of meningioma

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Abstract

Object—Little is known about the epidemiology of meningioma, the most frequently reported primary brain tumor in the US. The authors undertook a case-control study to examine the relationship between family and personal medical history and meningioma risk.

Methods—The authors compared the personal and first-degree family histories of 1124 patients with meningioma (age range 20–79 years) in Connecticut, Massachusetts, North Carolina, the San Francisco Bay Area, and 8 Houston counties between May 1, 2006, and February 26, 2010, and the histories of 1000 control individuals who were frequency-matched for age, sex, and geography.

Results—The patients were more likely than the controls to report a first-degree family history of meningioma (OR 4.4, 95% CI 1.6–11.5), and there was an even stronger association in younger cases. The patients were less likely than controls to report immune conditions including allergy (OR 0.6, 95% CI 0.5–0.7) but were more likely to report a history of thyroid cancer (OR 4.7, 95% CI 1.02–21.5) or leukemia (OR 5.4, 95% CI 1.2–24.1) (most after radiotherapy). Among women, patients were more likely than controls to report hormonally related conditions—uterine fibroid tumors (OR 1.2, 95% CI 1.0–1.5), endometriosis (OR 1.5, 95% CI 1.5–2.1), and breast cancer (OR 1.4, 95% CI 0.8–2.3).

Conclusions—The influence of genetics, the immune system, and radiation near the head on meningioma risk is suggested in the authors' findings; the role of hormones is intriguing but requires further study.

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Keywords

allergy; cancer; epidemiology; family history; hormones; immune factors; meningioma; radiation; oncology

Meningiomas accounted for 33.8% of all primary brain and CNS tumors reported in the US between 2004 and 2006 and thus represent the most frequently diagnosed primary brain tumor in adults.[5] Despite this, few studies have examined risk factors for this lesion, which is frequently associated with neurological complications and decreased quality of life.[20–27,29,33]

Family history studies suggest a role for inherited susceptibility for meningioma in addition to mutations in the *NF2* gene.[11,12,18] Genetic variants in genes involved in the DNA repair pathway, some of which appear common to a number of tumor types, have been implicated, but not confirmed.[3,28] Of note, the environmental risk factor most strongly associated with a diagnosis of meningioma remains exposure to ionizing radiation. A role for hormones (both endogenous and exogenous) and meningioma risk has been hypothesized but less clearly defined.[1,6–10,14–17,34]

The increased emphasis on research dedicated to the study of brain tumors, coupled with the advent of new tools in genetic and molecular epidemiology, makes this an ideal time to advance knowledge of intracranial meningioma. The goal of our Meningioma Consortium Study was to comprehensively examine environmental, genetic, pathological, and clinical variables associated with meningioma risk for the first time in a large epidemiological study. This report compares familial and personal medical histories of meningioma and cancer and other medical conditions in 1124 patients and histories of 1000 control individuals in our ongoing project.

Methods

Study Design

Eligible individuals include all persons diagnosed with a histologically confirmed intracranial meningioma among residents of the states of Connecticut, Massachusetts, and North Carolina, as well as the Alameda, San Francisco, Contra Costa, Marin, San Mateo, and Santa Clara counties of California, and the Brazoria, Fort Bend, Harris, Montgomery, Chambers, Galveston, Liberty, and Waller counties of Texas from May 1, 2006, to February 26, 2010. Cases were identified through the Rapid Case Ascertainment systems and state cancer registries of the respective sites, and patients were between the ages of 20 and 79 years at time of diagnosis. Control individuals were selected by an outside consulting firm in a random-digit-dialing process (Kreider) and were matched to cases by a 5-year age interval, sex, and state of residence. Study patients with a history of meningioma and/or a brain lesion of unknown outcome were excluded. Patients spoke English or Spanish. The study, consent forms, and questionnaire were approved by the Human Investigation Committees at the Yale University School of Medicine, Brigham and Women's Hospital, the University of California at San Francisco, the M. D. Anderson Cancer Center, and the Duke University School of Medicine.

The locations were selected because they represent sites where population-based case-control studies could be undertaken, generally because they are part of the SEER (Surveillance, Epidemiology, and End Results) Program of the National Cancer Institute (that is, Connecticut, North Carolina, and the San Francisco Bay Area) or because they have

Rapid Case Ascertainment systems in place (all 5 sites). In addition, the investigators at all 5 sites have long-standing experience with conducting cancer case-control studies.

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 controls identified by Kreider were sent an introductory letter. Approximately 1–2 weeks later, a trained interviewer contacted the potential study individual by telephone to administer the interview. Prior to the interview, women were sent picture booklets of exogenous hormones to allow them to review products used in the past. Men received the Norwood-Hamilton Scale to enable them to identify the stage of male pattern baldness, if applicable. Interviews took an average of 52 minutes. Proxies provided information for 8 patients and no controls. The questionnaire included detailed questions on family history of cancer, pregnancy and menstrual history, exogenous hormone history, demographics, medical and screening history, and smoking and alcohol consumption. Risk factor and screening information was truncated at the date of diagnosis for patients and the date of interview for controls (hereafter referred to as the reference date). With respect to family history of cancer, patients were asked to indicate the type of cancer, age at onset, and laterality (as appropriate) of up to 3 cancers for all male and female first-degree relatives (mother, father, sisters, brothers, daughters, and sons) and select second-degree relatives (maternal and paternal grandmothers and grandfathers). Patients were questioned about additional relatives, such as aunts and uncles, with a history of cancer or other tumors. The current age or age at death was obtained for all relatives. In addition to the questionnaire, after written consent was obtained, patients were asked to provide a blood or saliva specimen for DNA analyses. Patients were asked to grant permission access to a paraffin-embedded tumor block from their surgery.

To date, 1755 eligible patients and 1652 eligible controls have been identified. Ninety-eight percent of eligible patients had a consenting physician. Among those cases, 65% of the patients participated in the interview portion of the study, whereas 53% of eligible controls participated in the interview. Four hundred seventy-four patients were ineligible due to out-of-state residency (48 cases), language (50 cases), recurrent meningioma (56 cases), incarcerated (1 case), age (49 cases), spinal meningioma (75 cases), pathological specimen unavailable for review (56 cases), mental or medical (that is, deaf) illness (79 cases), death (51 cases; cause of death other than meningioma), and another pathology (such as lung metastasis) (8 cases). Fifty-seven controls were ineligible due to out-of-state residency (5 cases), language (6 cases), a history of previous brain tumor unknown pathology (7 cases), age group (1 case), mental or medical illness (37 cases), or death (1 case). Ninety and seventy-four percent of interviewed patients and control individuals, respectively, agreed to provide a blood/saliva specimen. The sample used in this analysis includes 1124 patients and 1000 control individuals.

Statistical Analysis

The initial portion of the statistical analysis included descriptive statistics. We used t-tests, chi-square analysis, and Fisher exact tests to examine the association between the risk of meningioma and independent covariates. To assess the odds of a meningioma being associated with a particular risk factor, conditional logistic regression was used to provide maximum likelihood estimates of the odds ratios (adjusted for age and sex) with 95% confidence intervals using the statistical package PC-SAS version 9.2.

Results

Descriptive statistics are provided in Table 1. The mean age of patients was 57.6 years and that for controls was 57.8 years (p = 0.26). The majority of patients were female and white. Patients and control individuals were well matched for age and race, but a greater proportion of patients were female. Control individuals were more likely to have 16 or more years of schooling and to have a salary exceeding $75,000.

Personal Medical History

Table 2 compares reported medical histories for patients and controls. Among women, the risk of uterine fibroids and endometriosis was statistically greater for patients than for controls. The risks of breast, ovarian, and endometrial cancer were elevated in patients compared with controls but the risk did not reach statistical significance. Among men, there was no intergroup difference in the risk of prostate cancer. Patients were more likely to report a history of leukemia or thyroid cancer than were controls but no more likely than controls to report a history of lung cancer, colon cancer, or melanoma. Of those who reported a history of leukemia, 9 (90%) of 10 patients and 1 (50%) of 2 controls reported receiving radiation treatment to the head for leukemia. Nine (75%) of 12 patients with a previous diagnosis of thyroid cancer reported receiving radioactive iodine or radiation therapy as part of treatment, whereas 1 (50%) of 2 controls reported such treatments. Five patients had NF2 syndrome; no controls reported this condition. One patient and no control individual reported a history of NF1 syndrome.

Patients were significantly less likely to report a number of conditions related to the immune system, including allergy (OR 0.6, 95% CI 0.5–0.7), asthma (OR 0.7, 95% CI 0.6–0.9), and chicken pox (OR 0.6, 95% CI 0.5–0.8). In addition, although not statistically significant, patients also reported lower rates of eczema and shingles. Patients and controls did not differ with respect to vascular conditions such as myocardial infarction or stroke, or other conditions such as diabetes or depression.

Family History of Cancer

Patients and controls had similar family sizes with no differences in the average number of brothers, sisters, or children. The average ages of patients' and controls' parents did not differ. After removing persons that reported a diagnosis of NF2, a known genetic syndrome associated with meningioma, patients were still significantly more likely than controls to report a first-degree family history of intracranial meningioma (OR 4.4, 95% CI 1.6–11.5) (Table 3). Patients with only a second-degree family history of meningioma had an elevated but not statistically significant risk compared with controls (OR 3.2, 95% CI 0.7–15.5). An inverse association was suggested between age at onset and meningioma risk with patients aged 55 years or younger at 5.4 times (95% CI 1.2–24.3) the risk in controls compared with 3.8 times (95% CI 1.1–13.2) the risk in patients older than 55 years. Men and women were equally likely to report a family history of meningioma.

With respect to other cancers, an elevated risk of meningioma was associated with a first-degree family history of breast cancer, but this risk did not reach statistical significance for either female (OR 1.2, 95 CI 0.9–1.7) or male (OR 1.3, 95% CI 0.8–2.1) patients. Patients with meningioma cases were more likely to report a family history of lung, colon, and cervical cancer than were controls.

Discussion

This is the largest case-control study to examine the relationship between family and personal medical history and meningioma risk. The results indicate the importance of a

positive family history of meningioma and suggest that individuals with first-degree family members diagnosed at a young age are at even greater risk. Our findings confirm those suggested by earlier analyses based primarily on data drawn from Scandinavian tumor registries.[11,12,18] The findings provide evidence that there exists an inherited gene (or genes) for meningioma, in addition to the already well-defined *NF2* gene. These findings are important because, despite the fact that up to 1% of the adult population may harbor a meningioma,[32] the total number of families with multiple members diagnosed with meningioma is relatively small (indicating, in part, a wide spectrum of phenotypic expression with respect to clinical importance and hence screening undertaken), and in most such families meningiomas are currently attributed to inherited *NF2* mutations. At present, no family-based linkage studies of meningioma have been reported; our group is currently in the process of identifying families for such an analysis. Of note, data from Israel provide evidence of a genetic predisposition to radiation-associated meningioma,[28] highlighting the role of inherited genetic factors as well as exposure in the development of meningioma.

A statistically significant inverse association between a number of immune conditions including allergy, asthma, and chicken pox with meningioma risk was seen. These findings confirm statistically nonsignificant but suggestive and consistent findings in previous reports with smaller samples sizes (all studies had fewer than 475 meningioma cases).[2,4,30,31] In the sole study of similar size, eczema was significantly inversely related to meningioma risk (OR 0.74, 95% CI 0.60–0.91) but not overall allergy (OR 0.87, 95% CI 0.66–1.44).[35] In our study, the risk of eczema was also reduced but not significantly. The reporting of allergy is heterogenous and subject to a number of biases. Our study required diagnosis by a doctor or health practitioner; the prevalence of allergies was 33% among control individuals, consistent with national rates. The mechanisms that link meningioma risk and immune factors remain unclear. One mechanism suggests that active immune systems that are highly allergic may be better able to recognize and respond to nascent foreign tumors. Other theories posit a more specific mechanism related to allergy, such as the promotion of an active immune rejection of the tumor based on activation of macrophages, mast cells, and eosinophils, which are characteristics of allergy.

Our current study suggests that immune factors may be protective of meningiomas, a finding that is consistent with that of malignant brain tumors. We speculate that individuals with a biased immune response consisting of a primarily humoral, specifically immunoglobulin E, response (characteristic of allergy) may be more capable of preventing nascent meningioma. This immunological bias, whether developed through environmental influences or genetic predisposition, may lead to a lifelong proclivity for hyperresponsiveness to antigens manifesting both as allergies to external antigens and effective tumor immunosurveillance in the brain.

A role for hormones in the risk of meningioma development has been hypothesized but remains ill defined.[6] This association has been suggested by the increased incidence of meningioma in women that is particularly marked prior to menopause.[33] The presence of hormone receptors on some meningiomas, a reported association between breast cancer and meningiomas,[3,9,25] indications that meningiomas change in size during the luteal phase of the menstrual cycle and pregnancy, and in vitro proliferation of meningioma cell lines in culture after exposure to estrogens have been observed. We examined the association between sex-specific conditions and meningioma risk and noted some intriguing preliminary findings. In particular, female patients were more likely than female control individuals to report a personal ($p = 0.12$) and family ($p = 0.07$) history of breast cancer as well as uterine fibroids ($p < 0.05$) and endometriosis ($p < 0.05$). (The risk estimates for ovarian and endometrial cancer are also elevated, but the small numbers preclude definitive conclusions.) Whether these conditions are related or simply share similar risk factors is

unclear; our consortium plans to further explore these findings in a larger sample as well as by meningioma hormone receptor subtype and exogenous hormone exposure. Interestingly, male patients were no more likely than controls to report a history of prostate cancer.

At present, the primary environmental risk factor identified for meningiomas is exposure to ionizing radiation, with reported risks 6–10 times higher than nonexposure to ionizing radiation.[13,19,26,28,33] Evidence of this relationship is noted by the statistically increased risk of meningioma with a personal history of leukemia or thyroid cancer. Of note, in most of the individuals with leukemia the diagnosis was established when they were children and received radiation treatment to the head decades prior to their meningioma diagnosis, a second primary tumor known to be associated with such treatment.[13]

Conclusions

Overall, our findings suggest that a number of factors may be associated with meningioma risk, including inherited genetic variants and immune factors along with environmental exposures such as ionizing radiation as well as, possibly, hormonal factors. Further examination of these factors singly as well as in the form of gene-environment interactions will be necessary to advance the study of meningioma.

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Abbreviation used in this paper

NF neurofibromatosis

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TABLE 1

Descriptive statistics of patients with meningiomas and controls

	No. of Individuals (%)		
Factor	**Patients**	**Controls**	**p Value**
no. of cases	1124	1000	
age (yrs)			
20–29	16 (1.4)	16 (1.6)	
30–39	67 (5.9)	79 (7.9)	
40–49	213 (19.0)	183 (18.3)	
50–59	326 (29.0)	293 (29.4)	
60–69	342 (30.4)	263 (26.4)	
70–79	159 (14.2)	164 (16.4)	
mean ± SD	57.6 ± 11.5	57.8 ± 12.3	0.26
sex			
male	298 (26.5)	317 (31.7)	
female	826 (73.5)	683 (68.3)	0.01
race			
white	931 (82.8)	850 (85.0)	
black	87 (7.7)	43 (4.3)	
Asian	44 (3.9)	44 (4.9)	
other	25 (5.6)	18 (5.8)	0.17
residence			
Connecticut	124 (11.0)	125 (12.5)	
Massachusetts	266 (23.7)	194 (19.4)	
North Carolina	339 (30.2)	267 (26.7)	
California	264 (23.5)	291 (29.1)	
Texas	131 (11.6)	123 (12.3)	0.01
education (yrs)			
≤16	302 (27.0)	170 (17.0)	<0.01
>16	818 (73.1)	828 (83.0)	
income ($)			
≤75,000	697 (62.5)	522 (52.2)	<0.01
>75,000	418 (37.5)	477 (47.8)	

TABLE 2

Personal medical histories of patients with meningiomas and controls*

	No. of Individuals (%)		
Factor	**Patients**	**Controls**	**OR (95% CI)†**
no. of cases	1124	1000	
cancer			
females only			
breast cancer‡	41 (5.0)	25 (3.7)	1.4 (0.8–2.3)
ovarian cancer	2 (0.2)	1 (0.1)	1.6 (0.2–18.3)§
endometrial cancer	10 (1.2)	6 (0.9)	1.4 (0.5–3.8)
cervical cancer	6 (0.7)	7 (1.0)	0.7 (0.2–2.1)
uterine fibroids	239 (29.4)	172 (25.6)	**1.2 (1.0–1.5)**
endometriosis	115 (14.2)	66 (9.8)	**1.5 (1.1–2.1)**
males only			
prostate	13 (4.4)	18 (5.7)	0.6 (0.3–1.4)
males & females			
lung cancer	5 (0.4)	2 (0.2)	2.1 (0.4–11.1)
colon cancer	0 (0)	1 (0.2)	NA
melanoma	18 (1.6)	20 (2.0)	0.8 (0.4–1.5)
glioma	0 (0)	0 (0)	NA
leukemia	10 (0.9)	2 (0.2)	**4.7 (1.0–21.5)**
thyroid cancer	12 (1.1)	2 (0.2)	**5.4 (1.2–24.1)**
vascular disease			
myocardial infarction	42 (4.2)	43 (3.9)	0.9 (0.6–1.4)
stroke	27 (2.7)	37 (3.3)	1.2 (0.7–2.0)
IDDM	21 (2.1)	41 (3.7)	1.8 (1.0–3.0)
NIDDM	83 (8.3)	110 (9.9)	1.2 (0.9–1.6)
immune dysfunction			
allergy	259 (23.2)	329 (33)	**0.6 (0.5–0.7)**
chicken pox	926 (87.9)	881 (92)	**0.6 (0.5–0.8)**
shingles	121 (10.9)	128 (12.9)	0.8 (0.6–1.05)
asthma	144 (12.9)	174 (17.4)	**0.7 (0.6–0.9)**
eczema	100 (9)	109 (11)	0.8 (0.6–1.1)
other			
NF1	1 (0.1)	0 (0)	NA
NF2	5 (0.6)	0 (0)	NA
depression	284 (26.7)	237 (26.1)	1.0 (0.8–1.2)
seizure	44 (4.0)	20 (2.2)	1.7 (1.0–2.9)

*Bolded values indicate significance. Abbreviations: IDDM = insulin-dependent diabetes mellitus; NA = not applicable; NIDDM = non–insulin-dependent diabetes mellitus.

†Adjusted for age and sex.

[‡] No men with breast cancer were reported.

[§] Fisher exact test.

TABLE 3

First-degree family history of cancer in patients with meningioma and controls

	No. of Individuals (%)		
Family History	**Patients**	**Controls**	**OR (95% CI)***
no. of cases	1124	1000	
meningioma (cranial)	24 (2.1)	5 (0.5)	**4.4 (1.6–11.5)**
glioma	9 (0.8)	7 (0.7)	1.1 (0.4–3.0)
breast cancer	165 (14.7)	120 (12.0)	1.2 (0.9–1.6)
ovarian cancer	26 (2.3)	19 (1.9)	1.2 (0.7–2.2)
endometrial cancer	31 (2.8)	23 (2.3)	1.2 (0.7–2.0)
cervical cancer	26 (2.3)	9 (0.9)	**2.5 (1.2–5.3)**
colon cancer	85 (7.6)	74 (7.4)	1.0 (0.7–1.4)
lung cancer	113 (10.0)	76 (7.6)	**1.3 (1.0–1.8)**
melanoma	47 (4.2)	53 (5.3)	0.8 (0.5–1.2)
prostate	70 (6.2)	86 (8.6)	**0.7 (0.5–0.9)**
thyroid	10 (0.9)	8 (0.8)	1.1 (0.4–2.8)
leukemia	32 (2.8)	24 (2.4)	1.1 (0.6–1.9)

*Adjusted for age, sex, and race.