THE ASSOCIATION OF BREAST CANCER AND MENINGIOMA IN MEN AND WOMEN

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OBJECTIVE: An association between breast cancer and intracranial meningioma has been described in women. We sought to determine whether this connection exists in men as well, hypothesizing that causes unrelated to sex may be responsible.

METHODS: We queried state cancer registries that recorded data on breast cancer and meningioma. *International Classification of Diseases for Oncology* codes for breast cancer and meningioma were used. The incidence rate of the second primary tumor was compared between identified meningioma and breast cancer cohorts and the general population for each sex.

RESULTS: Five state registries collected data on men and women from 1995 to 2003. The incidence of meningioma was 2.6 and 0.96 (cases per 100 000) for women and men, respectively, during this period. The incidence of breast cancer was 61 and 0.69 (cases per 100 000) for women and men, respectively, during this period. One man and 439 women were diagnosed with both diseases. The standardized incidence ratio was used to determine the magnitude of association between breast cancer and meningioma. During the study period, the standardized incidence ratio indicated a stronger than expected association between breast cancer and meningioma in women, regardless of which disease was diagnosed first. In every year except one, the standardized incidence ratio indicated no association between breast cancer and meningioma in men, regardless of which disease was diagnosed first.

CONCLUSION: Our results support a strong association between meningioma and breast cancer in women. Conversely, we were unable to show as strong an association in men. This suggests that the connection between these diseases may be dependent on sex.

KEY WORDS: Breast cancer, Meningioma

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An association between meningioma and breast cancer has been reported in the medical literature in small series or case reports (2, 9, 13, 14, 16, 21, 22, 24, 27, 28, 39, 41, 44, 46, 48, 51, 52, 55, 60, 63–66, 70, 76). Larger series have calculated the relative risk for a woman to develop an intracranial meningioma while carrying a diagnosis of breast cancer (or vice versa) to be between 1.5 and 2.0 (1, 3, 36, 60). Other studies have reported lesser degrees of risk (25, 38). The most commonly proposed explanation for this association involves the hormonal receptors present in both tumors, particularly meningiomas (5–8, 10, 11, 15, 17–19, 29, 31, 34, 37, 42, 47, 49, 50, 56, 67–69, 72). Indeed, variation in the levels of sex hormones in women has been reported to influence growth of meningioma (4, 35, 40, 45, 58). Although the risk of breast cancer is many times higher for women than for men, the risk of meningioma is also higher for women than men by at least 2-fold (23, 54). Whether androgen or estrogen receptor activity is responsible for the sex association is unclear, with some investigators showing a similar expression profile for these receptors in meningioma tissue taken from both men and women (43).

Male breast cancer is very rare, with an incidence of approximately 1 case per 100 000 in the United States (33). The additional risk for developing a meningioma is unknown, owing to the relative rarity of both diseases in men. A

ABBREVIATIONS: CI, confidence interval; **ICD-O**, *International Classification of Diseases for Oncology*; **SIR**, standardized incidence ratio

lack of association between these diseases in men would indicate a sex-specific phenomenon (possibly related to hormonal levels, rather than hormone receptor expression). Conversely, an increased risk of having both diseases in men would suggest that factors unrelated to sex drive this association. Pooling data from individual state cancer registries, we determined the incidence of breast cancer and meningioma separately in men and in women and also identified patients diagnosed with both diseases for comparison. Here, we show that the association of breast cancer and meningioma in men is essentially nonexistent, but the association of these diseases in women is indeed quite strong.

PATIENTS AND METHODS

This population-based study received approval from the Institutional Review Board at The University of Texas M. D. Anderson Cancer Center. The state cancer registries of Arizona, Colorado, Massachusetts, New York, and Texas were queried to identify patients with diagnoses of breast cancer and meningioma. These 5 cancer registries were used because they recorded disease-specific *International Classification of Diseases for Oncology* (ICD-O) histology codes for breast cancer and meningioma in both male and female patients (30). These registries were also able to provide numbers of patients per year diagnosed with both diseases. Furthermore, these registries maintained these data for the same time period (1995–2004) of at least 10 years. All registries used are full and sustaining members of the North American Association of Central Cancer Registries. These cancer registries obtain information primarily from hospital reporting, pathology reports, and death certificates, and they adhere to strict standardized criteria for cancer registration (available at http://www.naaccr.org). In general, these registries assign unique patient identifier numbers to keep track of registered patients, thus enabling them to identify patients who are diagnosed with each cancer type.

For meningioma, ICD-O codes 0, 1, and 3 were used; these codes correspond to benign, atypical, and malignant meningiomas, respectively. For breast cancer, ICD-O codes 2 and 3, which correspond to in situ and malignant cancers, respectively, were used. The population of each state for each year studied was obtained from the United States Census Bureau and Centers for Disease Control and Prevention. Only adult populations (18 years of age or older) of each state were used. Patient data was de-identified by the cancer registry. Information on age and race was not available from all registries. In the interest of patient confidentiality (given the relative rarity of having both diagnoses), the specific dates of each diagnosis were unavailable; however, the year each diagnosis was made was available.

The incidence rate of the second tumor (either breast cancer or meningioma) was compared between identified meningioma and breast cancer cohorts and the general population. The incidence rates were calculated with the assumption that the population at risk was followed for 1 year. On the basis of the independent incidence rates of each cancer, an expected incidence rate of each tumor on an annual basis was calculated. The standardized incidence ratio (SIR) was used to determine the magnitude of the association between breast cancer and meningioma. The SIR was defined as follows: $SIR = D/E$, where D is the observed number of events in the cohort, and E is the expected number of events in the cohort (12, 61). The exact 95% confidence interval (CI) was calculated with assumption of a Poisson distribution for the data (61, 62). The statistical analysis was performed using S-Plus 7.1 software.

RESULTS

Data on patients with breast cancer and meningioma were available from the 5 cancer registries for a common 9-year epoch from 1995 through 2003. During this period, a total of 6527 meningiomas and 153 599 breast cancers were diagnosed in women (Table 1). During this same period, a total of 2327 meningiomas and 1668 breast cancers were diagnosed in men (Table 2). The mean incidences (cases per 100 000) of meningioma and breast cancer in women during the study period were 2.6 and 61, respectively. The mean incidences of meningioma and breast cancer in men during the study period were 0.96 and 0.69, respectively.

During the study period, 219 of the 6103 women already diagnosed with meningioma (3.6%) were diagnosed with breast cancer. The mean number of breast cancer cases diagnosed per year in women who already had a diagnosis of meningioma was 24, and the median was 28. The number of women with meningioma expected to develop breast cancer (on an annual basis) during the study period ranged from 0.22 to 0.64, and the cumulative number of expected cases was 3.74 (Table 3). For the 9-year period, the SIR of patients diagnosed with breast cancer in a woman already harboring a meningioma was 58 (95% CI, 51–67). The mean number of breast cancer cases diagnosed per year in women with meningioma was 36, and the median was 37. During this same time period, 320 of the 153 276 women already diagnosed with breast cancer (0.2%) were diagnosed with meningioma (Table 4). The expected number of women developing meningioma who already had a diagnosis of breast cancer (on an annual basis) during the study period ranged from 0.23 to 0.66, and the cumulative expected number of cases was 4. For the 9-year period, the SIR of developing meningioma in a woman already diagnosed with breast cancer was 80 (95% CI, 72–89).

During the study period, 1 of the 2327 men diagnosed with meningioma (0.04%) was diagnosed with breast cancer. The mean number of breast cancer cases diagnosed per year in men during this period was 0.1, and the median was 0. During the study period, the SIR for developing a subsequent breast cancer when already diagnosed with meningioma was 0 for all years except one (1999), in which the 1 case was identified. In this year, the SIR was 443 (95% CI, 12–2785). The expected number of breast cancer cases in men already diagnosed with meningioma was low, ranging from 0.001 to 0.003, with a cumulative expected number of cases over the 9 years of 0.02 (Table 5). During this same period, 0 cases of meningioma were diagnosed in the 1667 men who were already diagnosed with breast cancer. The expected number of meningioma cases developing in male breast cancer patients ranged from 0.001 to 0.003, and the cumulative expected number of cases during the 9-year period was 0.02. The SIR for developing meningioma in men with an existing diagnosis of breast cancer was 0 for all years (Table 6).

DISCUSSION:

The association between breast cancer and meningioma has been described in women, but there has been some debate

TABLE 1. Number of meningiomas and breast cancers reported in women for the 5 state cancer registries during the years 1995–2003

Year	Estimated population	Meningioma		Breast cancer	
		No. of cases	Incidence per 100 000	No. of cases	Incidence per 100 000
1995	26 084 874	419	1.61	14 329	54.93
1996	26 379 461	494	1.87	15 299	58.00
1997	26 702 086	541	2.03	16 351	61.23
1998	27 045 561	594	2.20	16 972	62.75
1999	27 394 254	723	2.64	17 582	64.18
2000	29 586 122	742	2.51	17 990	60.81
2001	28 701 801	934	3.25	18 381	64.04
2002	29 117 340	1018	3.50	18 859	64.77
2003	29 418 348	1062	3.61	17 836	60.63

TABLE 2. Number of meningiomas and breast cancers reported in men for the 5 state cancer registries during the years 1995–2003

Year	Estimated population	Meningioma		Breast cancer	
		No. of cases	Incidence per 100 000	No. of cases	Incidence per 100 000
1995	25 232 122	164	0.65	121	0.48
1996	25 524 835	207	0.81	153	0.6
1997	25 845 021	182	0.7	165	0.64
1998	26 185 320	229	0.87	174	0.66
1999	26 530 052	256	0.96	234	0.88
2000	28 679 108	283	0.99	182	0.63
2001	27 801 066	329	1.18	203	0.73
2002	28 208 700	339	1.2	226	0.8
2003	28 506 808	338	1.19	210	0.74

regarding the strength of this link. We queried 5 state cancer registries to identify patients (male and female) diagnosed with meningioma, breast cancer, or both diseases. Here, we show that women with one disease are at increased risk of being diagnosed with the other, when comparing the number of expected cases with observed cases. However, this risk does not appear to exist in men. These results suggest that the association between meningioma and breast cancer is a sex-specific phenomenon.

Our results indicate that the link between meningioma and breast cancer in women is stronger than previously reported. The cumulative observed rate of breast cancer in patients already diagnosed with meningioma was 80 times the expected rate. Similarly, the cumulative observed rate of meningioma in patients already diagnosed with breast cancer was 58 times the expected rate. However, the link is not apparent in men with either disease. We were able to identify only 1 case of a man who developed breast cancer after being diagnosed with meningioma. No cases of meningioma were identified in men previously diagnosed with breast cancer.

TABLE 3. The standardized incidence ratio for subsequent diagnosis of breast cancer after initial diagnosis of meningioma in women[a]

Year	No. of patients with initial meningioma	Subsequent breast cancer cases		
		Observed no.	Expected no.	SIR (95% CI)
1995	364	18	0.20	90 (53–142)
1996	425	28	0.25	114 (74–162)
1997	496	30	0.30	99 (67–143)
1998	545	28	0.34	82 (55–119)
1999	667	28	0.43	65 (43–94)
2000	697	21	0.42	50 (31–76)
2001	892	28	0.57	49 (33–71)
2002	988	28	0.64	44 (29–63)
2003	1029	10	0.62	16 (8–30)

[a] SIR, standardized incidence ratio; CI, confidence interval.

TABLE 4. The standardized incidence ratio for subsequent diagnosis of meningioma after initial diagnosis of breast cancer in women[a]

Year	No. of patients with initial breast cancer	Subsequent meningioma cases		
		Observed no.	Expected no.	SIR (95% CI)
1995	14 303	47	0.230	205 (150–271)
1996	15 261	59	0.286	206 (155–262)
1997	16 316	40	0.331	121 (86–165)
1998	16 932	37	0.372	99 (70–138)
1999	17 545	47	0.463	101 (75–136)
2000	17 961	37	0.450	82 (58–113)
2001	18 337	26	0.597	44 (28–63)
2002	18 815	14	0.658	21 (12–36)
2003	17 806	13	0.643	20 (11–34)

[a] SIR, standardized incidence ratio; CI, confidence interval.

TABLE 5. The standardized incidence ratio for subsequent diagnosis of breast cancer after initial diagnosis of breast cancer in men[a]

Year	No. of patients with initial meningioma	Subsequent breast cancer cases		
		Observed no.	Expected no.	SIR (95% CI)
1995	164	0	0.001	0 (0–3689)
1996	207	0	0.001	0 (0–3689)
1997	182	0	0.001	0 (0–3689)
1998	229	0	0.002	0 (0–1844)
1999	256	1	0.002	443 (12–2785)
2000	283	0	0.002	0 (0–1844)
2001	329	0	0.002	0 (0–1844)
2002	339	0	0.003	0 (0–1230)
2003	338	0	0.002	0 (0–1844)

[a] SIR, standardized incidence ratio; CI, confidence interval.

This study draws upon a population of over 25 000 000 patients per year for each sex. This is the largest population evaluated to determine the increased risk of developing meningioma in patients diagnosed with breast cancer and vice versa. Despite the large population studied, there are limitations to this analysis, and certain assumptions were made. For example, for each year, it was assumed that the population of each state remained stable. This assumption may be less appropriate for Western states, such as Arizona and Colorado, which are known to have higher migration rates. Although each state registry provided de-identified information on patients, including specific dates of diagnosis of each disease, it is unknown whether or not these patients may have lived previously or subsequently in a different state.

Breast cancer rates vary significantly between age groups and racial groups in the United States. The highest rates are seen in Caucasians, and the lowest rates are seen in Native Americans. Racial differences were not taken into consideration, nor were age ranges, in our study. The incidence of breast cancer increases with age, with incidences ranging from 1.4 cases per 100 000 in women of ages 20 to 24 years to 499 cases per 100 000 in women aged 75 to 79 years. Indeed, our overall breast cancer incidence of approximately 61 cases per 100 000 is somewhat lower than the typically reported rates of breast cancer, which range from 120 to 140 cases per 100 000 (57).

Meningioma is considered a benign brain tumor and has, until recently, not been consistently recorded in either national or state cancer registries. As a consequence, we were limited to the 5 state cancer registries we used in the study because they maintained records of meningioma cases for several years. Although the 5 states combined have a sizable population (approximately 25 million per sex per year of the study), they represent only approximately one-sixth of the total population of the United States. Regional cancer rates may be higher or lower, and thus the generalizability of our results to the total population of the United States may be limited.

Many patients harbor incidental meningiomas that are asymptomatic and may be followed rather than removed (53). This may underestimate the true incidence of meningioma in this study, given that imaging of the brain may not be performed in patients with breast cancer unless they are experiencing neurological symptoms. Additionally, if a patient with either disease is diagnosed and followed solely on an outpatient basis, then the patient may not be captured by a cancer registry (a conceivable scenario in a patient with a small, incidentally found meningioma). Conversely, the increased vigilance in patients diagnosed with breast cancer may have resulted in an increase in the diagnosis of incidental meningiomas, thus artificially elevating the association of these diseases. The reported incidence of meningioma in men and women in the general population is estimated at 3.2 and 7.2, respectively (20). Although the incidences we identified in our study for meningioma were lower, we used data from 5 states, whereas the Central Brain Tumor Registry of the United States uses data from 19 states. Finally, although we were able to identify which disease was diagnosed first (solely as a function of when the disease was reported to the cancer registry), we do not know which disease actually occurred first in these patients. For example, it is possible that a patient may have been harboring an intracranial meningioma for some time before a breast cancer diagnosis. Although we report an increased risk in women of being diagnosed with one disease when already diagnosed with another, a temporal association of these tumors, and any suggestion of one tumor influencing the initiation and development of the other, is dubious at best. Thus, we do not claim an increased risk of developing one tumor as a consequence of the other, only that an association of these diagnoses exists in women and not in men.

The results of our study lend support to the posture of remaining vigilant for intracranial lesions in women diagnosed

TABLE 6. The standardized incidence ratio for subsequent diagnosis of meningioma after initial diagnosis of meningioma in men[a]

Year	No. of patients with initial breast cancer	Subsequent meningioma cases		
		Observed no.	Expected no.	SIR (95% CI)
1995	121	0	0.001	0 (0–3689)
1996	153	0	0.001	0 (0–3689)
1997	165	0	0.001	0 (0–3689)
1998	174	0	0.002	0 (0–1844)
1999	233	0	0.002	0 (0–1844)
2000	182	0	0.002	0 (0–1844)
2001	203	0	0.002	0 (0–1844)
2002	226	0	0.003	0 (0–1230)
2003	210	0	0.002	0 (0–1844)

[a] SIR, standardized incidence ratio; CI, confidence interval.

with breast cancer. Although no such recommendation has been levied by national cancer agencies, an increased index of suspicion regarding an intracranial lesion may be warranted in women diagnosed with breast cancer. Although our results suggest an increased risk of breast cancer in patients diagnosed with meningioma and vice versa, it may be difficult to justify increased screening for breast cancer (beyond what is already recommended for women in the United States) for women diagnosed with meningioma. Any increased screening recommendation would likely come as a consequence of validating these findings in a prospectively followed cohort of patients.

A definite limitation to the study is the relative rarity of breast cancer in men, and this may be attributable to a low index of suspicion for the disease (71). The incidence of breast cancer in men in our study was less than 1 in 100 000. This low incidence may have profound influences on statistical analysis. Thus, we interpreted the 1 case of concomitant breast cancer and meningioma in the male population as lower than the expected number of cases during the 9-year time period. However, it is possible that even with a cumulative study period of 9 years, and an expected incidence of 0.02 cases during this time, the time frame used was not sufficient to adequately document the true incidence of the association. Indeed, the 1 case of breast cancer occurring after meningioma in the male population (in 1999) has a SIR of 443, demonstrating that very small numbers are sufficient to affect the results and subsequent conclusions of this study. Conversely, there were 0 cases of meningioma being diagnosed after breast cancer in men.

The etiology of the apparent sex-specific phenomenon of this association is unclear. Although hormone receptors have been implicated in the development and progression of both tumor types, it is difficult to know for certain what is behind the association of these tumor types in women. Meningiomas have long been known to harbor both progesterone and estrogen receptors (7, 19, 50). Progesterone receptors are more prevalent and more biologically active, however, and are increased in recurrent tumors, suggesting that they play a role in proliferation (59). Estrogen receptors do not appear to play a significant role, as evidence of their presence in meningiomas is much weaker (5, 10, 37, 50). In their study of progesterone and estrogen receptor expression in meningiomas obtained from men and women, Korhonen et al. (43) found an equal rate of expression of these receptors in tumors obtained from both sexes. They concluded that the higher incidence of meningioma in women could not be explained by differences in receptor expression.

Similarly, breast cancers harbor estrogen and progesterone hormone receptors, but the expression rate is somewhat variable, with the rates of expression commensurate with increases in patient age (33). Male breast cancer has some similarities to female breast cancer, including histological subtypes (although lobular cancers are less common in men), but estrogen and progesterone receptors are expressed at a significantly higher rate, and *Her2-neu* is expressed at a lower rate (26, 32, 33, 73–75). Increased hormone receptors present in male breast cancers seem to belie the lack of association with meningioma seen in women; thus, despite our results supporting a significantly higher association of meningioma and breast cancer in women, it is difficult to attribute this relationship definitively to hormonal receptor differences between the sexes. Still, hormonal differences may be responsible, since women have a much higher lifetime exposure to estrogen and progesterone than do men. Thus, despite similarities in receptor expression, hormone exposure may be the definitive difference and may explain the apparent sex-related phenomenon.

CONCLUSION

This population study indicates that the association between breast cancer and meningioma is very strong in women. However, the same association was not observed in men. This difference suggests that the association of these diseases is peculiar to women. This phenomenon may be a consequence of the higher cumulative exposure to hormones experienced by women throughout their lifetimes.

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COMMENTS

Rao et al. pose an interesting question: is the coincidence of meningiomas and breast cancer tumors sex-specific? If there is an underlying genetic mechanism linking the 2 tumors, the coincidence should hold for males and females. Because of the low incidence of breast cancer in men, this question can be answered only by surveying a large patient population. To this end, the authors reviewed the cancer registries in 5 states. They do a very good job of explaining the shortcomings of this approach.

Although the incidence of breast cancer was considerably lower in men than in women, the authors were able to identify 1668 cases of breast cancer in men. During the study period, 1 man with a known meningioma was diagnosed with breast cancer. The expected incidence for the study period was 0.02. The authors did find a robust relationship between meningiomas and breast cancer in women. No such relationship was found in men, although the authors point out that a longer follow-up time might reveal a weak correlation. The reader must wonder about the possibility of a beta error in this study. Is it possible that a larger population of men with breast cancer or a longer follow-up period would reveal a less robust coincidence in men?

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The association between breast cancer and meningioma in women has been appreciated for a long time. Quantification of the degree of this association has been lacking. This study addresses this need. Although the weaknesses of a retrospective study of databases are real, the authors appreciate them, acknowledge them, and account for them as well as possible.

This study is a real contribution to my practice. I frequently treat both of these diseases individually and sometimes in tandem in female patients, and I will be able to tackle a discussion about their coincidence with real facts now. Even though meningiomas are sometimes detected in patients with known breast cancer, these tumors are often the last thing that a patient with breast cancer concerns herself with.

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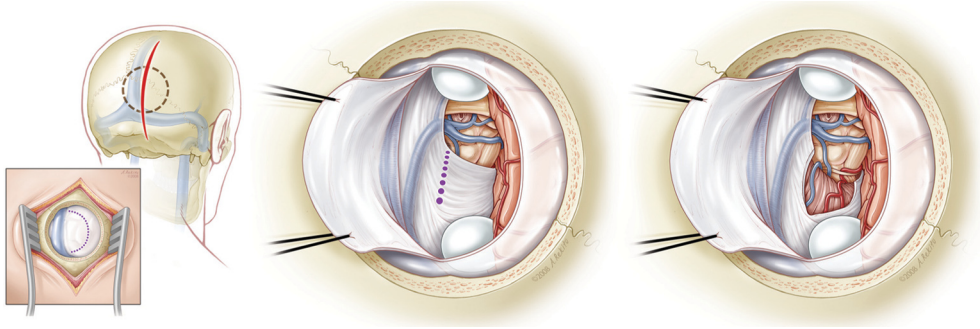

Drawings depicting the interhemispheric occipital transtentorial approach. See page 556.