The Association between Breast Carcinoma and Meningioma in Women

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BACKGROUND. Published case reports of a possible association between meningioma and breast carcinoma are not uncommon in the literature. Four published analytic studies have addressed this suggested association specifically. Three of these studies reported significant associations, with relative risk estimates mostly between 1.5 and 2.0. The other study reported relative risk point estimates near 1.5, but confidence intervals included 1.0. The current study was a population-based, retrospective cohort analysis that evaluated the risk of subsequent breast carcinoma in women who were diagnosed with meningioma and the risk of subsequent meningioma in women who were diagnosed with breast carcinoma.

METHODS. The measure of association is the relative risk and is reported as the standardized incidence ratio (SIR). Using western Washington State cancer registry data and intercensal population estimates for western Washington State, incidence rates of second primary tumor were compared between identified meningioma and breast carcinoma cohorts and the general population for the years 1992–1998.

RESULTS. The risk of breast carcinoma after patients were diagnosed with meningioma (SIR) was 1.54 (95% confidence interval [95% CI], 0.77–2.75). The risk of meningioma after patients were diagnosed with breast carcinoma was 1.40 (95% CI, 0.67–2.58), and the risk of meningioma after patients were diagnosed with invasive breast carcinoma was 1.64 (95% CI, 0.79–3.02). In each combination for age groups ages $>$ 50 years, risks were elevated, but the confidence intervals included 1.0.

CONCLUSIONS. These results suggest that the risk of meningioma among women who have experienced breast carcinoma and the risk of breast carcinoma among women who have experienced meningioma are elevated moderately. Shared risk factors may account for the relatively week bidirectional associations seen in this and other studies. ***Cancer* 2002;94:1626–35.** *© 2002 American Cancer Society.*
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Published case reports as early as 1929 suggested a possible association between meningioma and breast carcinoma. In the intervening years, several clinical reports of patients who developed both meningioma and breast carcinoma have been published. Since 1980, at least 12 case reports have been published in English language journals in which 56 individuals with diagnoses of both breast carcinoma and meningioma were described.[1–11] Before 1980, 17 additional patients were reported in English language journals.[12] The clinical literature suggests several possible mechanisms to explain the clinical reports. One article posited an association based merely on *collision* tumors in which a malignant tumor (breast carcinoma) metastasizes to a preexisting benign tumor (meningioma).[12] Reports of breast carcinoma and meningioma in situations where the presence of

pathologically confirmed *collision* tumors could not be demonstrated prompted explanations suggesting that meningioma may result as a direct metastasis of breast carcinoma. Several case reports described meningioma as a pathologically confirmed, metastatic product of breast carcinoma.[1–3] However, at least one case report suggested the opposite relation, with meningioma preceding and serving as the source for breast malignancy.[4]

The clinical literature also has suggested that the association may not be based on metastatic events but, rather, on common risk factors.[5] This line of reasoning follows from several pieces of evidence. First, both breast carcinoma and meningioma occur much more frequently in women than in men. Second, both tumors occur more frequently as age increases. In addition, increased tumor growth has been observed during pregnancy for both meningioma and breast carcinoma, suggesting hormone-induced stimulation.[13] Recent efforts to determine shared genetic predisposition for these two types of neoplasms have provided more information but have neither dismissed nor supported the reported link between the two tumors. In particular, although the *BRCA1* and *BRCA2* genes have been linked to familial and sporadic forms of breast carcinoma, an analysis of *BRCA1* and *BRCA2* genes in patients with sporadic meningiomas has suggested that alterations of the BRCA1 and *BRCA2* genes are not common pathogenetic events in the development of meningioma.[13]

It is possible that an association between breast carcinoma and meningioma may be due to an overlap in the gene-environment interactions necessary for tumorigenesis. For both tumors, recent research has focused on loss of heterozygosity (LOH), or the loss of one allele in a tumor cell from a chromosome region for which individual normal cells are heterozygous: It is believed that LOH promotes tumorigenesis through a process whereby the expression of the disease occurs with the loss of the normal (or protective) allele through possible pathways, such as gene-environment interactions or by environmental causes alone.[14]

Two chromosomal regions, 1p13–p21 and 22q11–q13, frequently exhibit LOH in breast carcinoma, meningioma, and other types of tumor.[15,16] At least three tumor suppressor inactivation genes have been identified on the long arm of chromosome 22.[15] Observed associations between breast carcinoma and meningioma may be due to the activation (or inactivation) of genes in these regions. However, the tumorigenesis pathways may diverge for breast carcinoma and meningioma, because other unrelated chromosomal regions have been proposed as critical events. For example, it is hypothesized that the 14q24 to 14q32 region is the critical region responsible for immortalizing cells, resulting in the most aggressive forms of meningioma, yet this region has not been implicated in the development of breast carcinoma.[15]

Current genetic investigations and clinical reports appear to assume that an association between breast carcinoma and meningioma already has been established. However, the literature includes only six studies that have sought to quantify the association between primary malignancies and meningiomas.[17–22] Specific consideration of the association between breast carcinoma and meningioma has been reported in four studies (Table 1): Three of these studies found a significant association between the two tumors.[17,18,22] The other study did not find a statistically significant association.[21]

The objective of the current study was to quantify the association between breast carcinoma and meningioma in women by using population-based data. The hypotheses tested were 1) that a diagnosis of breast carcinoma places a woman at increased risk for a subsequent diagnosis of primary meningioma and 2) that a diagnosis of meningioma places a woman at increased risk for a subsequent diagnosis of primary breast carcinoma.

MATERIALS AND METHODS

This study was a population-based, retrospective cohort analysis. The study population included all the female residents age $\geq$ 15 years who resided in the 13 counties of western Washington State, where the Cancer Surveillance System (CSS) at the Fred Hutchinson Cancer Research Center (FHCRC) collects data on malignant neoplasms and on some nonmalignant neoplasms. The study period was 1992–1998. During the study period, the average total population of age-eligible women in the 13-county area was nearly 1,473,000 women.[23]

Since 1974, CSS has collected data on the incidence, treatment, and outcomes for all patients with newly diagnosed breast carcinoma. Since 1991, CSS has collected the same data for patients with primary meningioma. CSS data-collection staff members abstract data on $>$ 95% of patients with neoplasms, with the remaining data abstracted by hospital tumor registry personnel. Diagnosis and treatment data are obtained from individual medical and hospital records. CSS staff members as well as Surveillance, Epidemiology, and End Results Program representatives carry out all case-finding and quality-control procedures.[24] The tumor registry collects confidential information and assigns a unique number to each individual that includes a sequence code to identify additional neoplasm diagnoses in the same individual. Follow-up

TABLE 1
Published Associations between Meningioma and Breast Carcinoma or Other Primary Malignancies

Association examined	Results	Reference
Meningioma and breast carcinoma	Obs, 8; Exp, 3.4; O/E, 1.76 ($P < 0.05$)	Schoenberg et al. [18] (Data from Connecticut Tumor Registry)
Meningioma then breast carcinoma	Obs, 11; Exp, 9.9; O/E, 1.1 ($P > 0.05$)	Emry[22] (Data from Los Angeles County Cancer Surveillance Program)
Breast carcinoma then meningioma	Obs, 37; Exp, 10.5; O/E, 3.5 ($P < 0.001$)	—
Meningioma then breast carcinoma (all women)	RR, 1.54 (95% CI, 0.97–2.34)	Helseth et al.[17]
Meningioma then breast carcinoma (women age 50–64 yrs)	RR, 1.92 (95% CI, 1.02–3.29)	Helseth et al.[17]
Breast carcinoma then meningioma (all women)	RR, 1.75 (95% CI, 1.08–2.68)	Helseth et al.[17]
Meningioma then breast carcinoma	RR, 1.76 (95% CI, 0.74–2.50)	Jacobs et al.[21] (data from Kansas Cancer Data Service)
Meningioma and extraneural malignancies	OR, 3.52 ($P < 0.01$)	Bellur et al.[20]
Intracranial tumors and breast carcinoma (meningioma accounted for 54% of confirmed tumors)	RR, 1.83 (95%CI, 1.4–2.5)	Adami et al.[19]

Obs: observed; Exp: expected; O/E: observed/expected ratio; RR: relative risk; 95%CI: 95% confidence interval; OR: odds ratio.

information is collected annually using data from a variety of sources, such as hospital records, the Washington State Department of Motor Vehicles, the Health Care Financing Administration, Washington State death records, voter registration, Social Security information, and the National Death Index. To protect patient privacy, CSS did not provide the day of diagnosis. Therefore, it was necessary to assume that all diagnoses occurred on the 15th day of each diagnosis month. Exact birth dates (day, month, and year) were provided.

This study posed minimal risk to study participants, because the cancer registry did not provide data that would permit identification of individuals; therefore, informed consent was not required by the Institutional Review Board (IRB). After FHCRC IRB approval of the study design, two data sets were provided. One contained information for all primary breast carcinoma diagnoses recorded by the registry since 1974. The other data set contained all primary meningioma diagnoses recorded by the registry. The meningioma data included incidental coding of meningioma diagnoses before 1991. If a person was diagnosed with another primary malignancy and then developed meningioma, then reports of the meningioma diagnosis may have been submitted to CSS. Diagnoses before 1991 are recorded in the CSS data but do not reflect complete surveillance for meningioma and, thus, were not used here. Each data set was reduced to primary diagnoses of the respective disease between 1992 and 1998. Although ascertainment of meningioma occurred starting in 1991, we decided in advance to exclude 1991 data to ensure the most complete ascertainment of each disease for every year of the study. Each of these data sets alone was used to determine the number of all primary breast carcinomas and primary invasive breast carcinomas or primary meningiomas, respectively. Using this method, two cohorts were defined. The meningioma cohort consisted of 598 women who were diagnosed with any type of primary central nervous system (CNS) meningioma. Similarly, a breast carcinoma cohort was formed that consisted of 21,551 women who were diagnosed with any type of primary breast carcinoma. Because of the possibility that more aggressive breast tumors may be more likely to result in a subsequent diagnosis of meningioma, a subcohort consisting of 18,349 women who had been diagnosed with primary invasive breast carcinoma also was identified.

To determine the number of women who had diagnoses of both diseases, the original two data sets were linked using the unique cancer registry number from which the neoplasm sequence number had been removed. In linking the data sets, no restrictions on year of diagnosis were employed, and it was determined that 35 women who were recorded in the registry had diagnoses of both diseases. Subsequently, the data set was restricted to include only those women for whom the diagnoses of both primary breast carcinoma and meningioma occurred within the study period. Among the women in each of the two cohorts, 24 women had diagnoses of both primary

CNS meningioma and primary breast carcinoma during 1992–1998. A total of three women with concurrent diagnoses (defined as diagnoses of both meningioma and breast carcinoma within the same 30 day period) were excluded, because these women would have contributed to the counts for each disease but would not have contributed any length of time at risk (person-years) to the denominator of each incidence rate, arbitrarily increasing the relative risk estimates. No diagnosis of either disease occurred at autopsy.

For women in the meningioma cohort, the length of time at risk (person-years) for breast carcinoma diagnosis was measured as the time from meningioma diagnosis to one of four possible end points: diagnosis of breast carcinoma, death, lost to CSS follow-up, or the end of the study (December, 1998). Similar methods were used to determine person-years at risk for women in the breast carcinoma cohort and in the invasive breast carcinoma subcohort.

To determine the expected number of patients with the relevant second tumor, we calculated population rates of primary meningioma, primary breast carcinoma, and primary invasive breast carcinoma in western Washington State women using CSS data for 1992–1998 and using intercensal population estimates provided by the Washington State Department of Health as the population person-years at risk.[23] The summation of the annual intercensal population estimates from 1992 through 1998 represents the total accumulated person-years at risk. Washington State intercensal population estimates are reported as 5-year age groups, so we were able to determine corresponding age group specific incidence rates of all diagnoses.

All data cleaning and analyses were performed using Stata statistical software (release 6.0; Stata Corporation, College Station, TX). The measure of association was the relative risk and is reported as the standardized incidence ratio (SIR). We compared the observed number of breast carcinomas in the group of women who had first been diagnosed with meningioma to the expected numbers of breast carcinomas among women with a diagnosis of meningioma. The expected number of breast carcinomas in the meningioma cohort was determined by multiplying 5-year age and calendar year strata of person-years at risk by the corresponding 5-year age group specific incidence rates of breast carcinoma in the female population. SIRs were calculated as the ratio of observed to expected numbers of breast carcinomas using intercensal population estimates of women age $\geq$ 15 years living in the 13 county area of Washington State as the standard population. Exact 95% confidence intervals (95%CI) were calculated with the assumption of a Poisson distribution for the data.[25] We calculated SIRs for meningioma in the breast carcinoma cohort and the invasive breast carcinoma subcohort using the same method.

RESULTS

The age distributions for meningioma and for both breast carcinoma diagnoses in the study population were consistent with the currently accepted, descriptive epidemiology of both diseases (Table 2). The greatest number of diagnoses for each disease occurred in women age 50–80 years, even though they make up a relatively small percentage of the general population of adult women. The occurrence of both diseases in the same individual was most common for women age $\geq$ 65 years. Due to the race distribution in western Washington State, it was only possible to examine associations between meningioma and breast carcinoma for white women.

In the study, a total of 24 women were identified with diagnoses of both meningioma and breast carcinoma during the years 1992–1998. For 10 of these women, the diagnosis of breast carcinoma occurred first; for 11 women, the diagnosis of meningioma occurred first; and, for 3 women, we classified the diagnoses as concurrent (Table 3). For nonconcurrent diagnoses, regardless of which diagnosis occurred first, $>$ 70% of the women had the subsequent diagnosis at least 7 months after the first diagnosis. Among women who were diagnosed with meningioma first, the elapsed time until they were diagnosed with breast carcinoma appeared to peak after approximately 2 years. For women who were diagnosed first with primary breast carcinoma, followed by meningioma, the elapsed time between diagnoses was distributed evenly over the 7-year follow-up.

The greatest incidence of meningioma or breast carcinoma occurred in women between the ages of 50 years and 80 years (Table 4). This relation was most evident for women in the breast carcinoma cohort and the invasive breast carcinoma subcohort, in whom the incidence rates were greatest between the ages of 50 years and 79 years. The peak incidence rate for meningioma or breast carcinoma in the study population occurred in women age 65–79 years.

The observed number of breast carcinoma diagnoses in the meningioma cohort was 11.0, whereas the expected number of breast carcinoma diagnoses was 7.16. These values resulted in an SIR of 1.54 (95%CI, 0.77–2.75) for the diagnosis of breast carcinoma in adult women after a previous diagnosis of meningioma (Table 5). The risk was greatest among women age 50–64 years; however, the confidence intervals for all age specific risk estimates included 1.0.

TABLE 2
Characteristics of Women Diagnosed with Meningioma, Women Diagnosed with Breast Carcinoma, and Women in the General Population from Which the Diagnoses Arose 1992–1998

Characteristic (at time of first diagnosis)	Any meningioma diagnosis (N = 598 women) (%)	Any breast carcinoma diagnosis (N = 21,551 women) (%)	Any invasive breast carcinoma diagnosis (N = 18,349 women) (%)[a]	Both meningioma and breast carcinoma diagnoses (N = 24 women) (%)	Percent of general population age > 15 yrs[b]
Age group (yrs)					
15–34	32 (5.4)	379 (1.8)	334 (1.8)	0 (0)	35.6
35–49	152 (25.4)	4818 (22.4)	3937 (21.5)	2 (8.3)	31.4
50–64	158 (26.4)	6766 (31.4)	5644 (30.8)	7 (29.2)	16.4
65–79	192 (32.1)	7138 (33.1)	6178 (33.7)	11 (45.8)	12.0
80+	64 (10.7)	2450 (11.4)	2256 (12.3)	4 (16.7)	4.6
Race					
White (includes Hispanic)	424 (70.9)	19,786 (91.8)	16,941 (92.3)	23 (95.8)	88.0
Black	19 (3.2)	467 (2.2)	397 (2.2)	0	3.5
Asian/Pacific Islands	30 (5.0)	739 (3.4)	606 (3.3)	0	7.1
Other	3 (0.5)	143 (0.7)	135 (0.7)	0	1.4
Unknown	122 (20.4)	413 (1.9)	270 (1.5)	1 (4.2)	—
Marital status					
Single	51 (8.5)	1678 (7.8)	1411 (7.7)	—	—
Married	277 (46.3)	12,153 (56.4)	10,172 (55.4)	—	—
Divorced/Separated	47 (7.9)	2283 (10.6)	1985 (10.8)	—	—
Widowed	112 (18.7)	4130 (19.1)	3698 (20.2)	—	—
Unknown	111 (18.6)	1319 (6.1)	1083 (5.9)	—	—

[a] Pathologic classification of tumor type was according to the International Classification of Diseases for Oncology, second edition, 1990.[26]
[b] General population percentage were based on Washington State intercensal estimates 1992–1998 (those age < 15 years account for 21.5% of the total population).

The overall estimate of the risk of a diagnosis of meningioma in women with a previous diagnosis of any breast carcinoma was 1.40 (95% CI, 0.67–2.58) (Table 6). Except for women age ≤ 34 years, the point estimates for the age group specific risk of meningioma indicated elevated risk, although the confidence intervals were quite large and indicated that the results were not statistically significant. Even though the observed and expected numbers of meningioma diagnoses were small for each age group, there was a suggestion of increasing risk in older age groups. When the analysis was restricted to women with invasive breast carcinoma, the risk of a subsequent diagnosis of meningioma increased from 1.40 to 1.64 (95% CI, 0.79–3.02) (Table 7). Moreover, each age group specific estimate for women age > 34 years increased, and the increased risk at older ages was maintained. Once again, although all age specific point estimates were elevated, the confidence intervals included 1.0.

DISCUSSION

The CSS registry in Washington State is unique, in that, since 1991, data on the population incidence of the usually benign tumor, meningioma, have been collected. Therefore, western Washington State CSS data allowed for a population-based investigation of whether women who develop either primary meningioma or primary breast carcinoma have an increased risk of developing the other disease. Case reports of separate tumors occurring in combination are frequent, and it is difficult to know whether these occurrences are random events or represent an association between the tumors.[27] In this study, the overall relative risk point estimates ranged from 1.40 to 1.64. However, our results did not indicate statistically significant associations between the risk of meningioma in women who were diagnosed previously with breast carcinoma or the risk of breast carcinoma in women who were diagnosed previously with meningioma.

Data collection for this study occurred at a time when the use of advanced imaging techniques (computed tomography and magnetic resonance imaging) was increasingly common. The use of these imaging techniques has the potential to introduce bias, because asymptomatic tumors are more likely to be diagnosed, especially in persons with previously diagnosed disease. Information bias that results when women who have been diagnosed with one disease are

TABLE 3
Characteristics of Women Diagnosed with Both Meningioma and Breast Carcinoma 1992–1998

Characteristic (at time of first diagnosis)	Both meningioma and breast carcinoma diagnoses (*N* = 24 women) (%)	Meningioma diagnosed first followed by breast carcinoma (*N* = 11 women) (%)	Breast carcinoma diagnosed first followed by meningioma (*N* = 10 women) (%)	Concurrent meningioma and breast carcinoma (*N* = 3 women) (%)
Age group (yrs)				
15–34	0 (0)	0	0	0
35–49	2 (8.3)	1 (9)	1 (10)	0
50–64	7 (29.2)	5 (45.5)	2 (20)	0
65–79	11 (45.8)	5 (45.5)	5 (50)	1 (33.3)
80+	4 (16.7)	0	2 (20)	2 (66.7)
Race				
White (includes Hispanic)	23 (95.8)	10 (91)	10 (100)	3 (100)
Black	0	0	0	0
Asian/Pacific Islands	0	0	0	0
Other	0	0	0	0
Unknown	1 (4.2)	1 (9)	0	0
Marital status				
Single	2 (8.3)	1 (9.1)	0	0
Married	7 (29.2)	3 (27.3)	5 (50)	0
Divorced/separated	4 (16.7)	3 (27.3)	1 (10)	1 (33.3)
Widowed	8 (33.3)	2 (18.2)	4 (40)	2 (66.7)
Unknown	3 (12.5)	2 (18.2)	0	0

TABLE 4
Population Incidence of Meningioma, Breast Carcinoma, and Invasive Breast Carcinoma

Age group (yrs)	Person years	Meningioma		Breast carcinoma		Invasive breast carcinoma	
		No. of women	Incidence per 100,000	No. of women	Incidence per 100,000	No. of women	Incidence per 100,000
15–34	3,661,164	32	0.9	379	10.4	334	9.1
35–49	3,236,484	152	4.7	4818	149	3937	121
50–64	1,705,669	158	9.3	6766	397	5644	331
65–79	1,236,341	192	15.5	7138	577	6178	500
80+	470,415	64	13.6	2450	521	2256	480
Total	10,310,073	598	5.8	21,551	209	18,349	178

followed more closely cannot be ruled out. In addition, if medical monitoring is more intensive when a person is diagnosed with either breast carcinoma or meningioma, then it is expected that otherwise asymptomatic conditions would be diagnosed more frequently proximate to the first diagnosis. A peak in second primary neoplasm diagnosis within the year after the first diagnosis did not occur for either breast carcinoma or meningioma.

The total period for the study was 84 months, and the diagnosis of subsequent meningioma or breast carcinoma after this time could not be assessed. Meningiomas are very slow-growing tumors.[28] This study period may have been insufficient to determine with accuracy a possible association between breast carcinoma and meningioma occurring many years later. Consistently, we detected an association between breast carcinoma and meningioma, but the study was limited by the number of women who experienced both tumors The combination of small numbers of women with both tumors and the potentially too short follow-up may explain the large confidence intervals.

This study also was limited in the analysis of specific directions of disease (meningioma followed by breast carcinoma and breast carcinoma followed by meningioma). The diagnosis of each disease was used as the proxy measure of occurrence of the disease. With the available data, there was no way to determine

TABLE 5
Incidence of Breast Carcinoma in Women Originally Diagnosed with Meningioma

Age group (yrs)	Women with initial meningioma		Subsequent breast carcinoma		
	No.	Person-years at risk	Observed no. of breast carcinomas	Expected no. of breast carcinomas	Standardized incidence ratio (95% CI)
18–34	32	57	0	0.01	0
35–49	152	448	1	0.67	1.50 (0.04–8.36)
50–64	158	496	5	1.99	2.51 (0.81–5.85)
65–79	192	569	5	3.29	1.52 (0.49–3.54)
80+	64	228	0	1.20	0
Total	598	1798	11	7.16	1.54 (0.77–2.75)

95%CI: 95% confidence interval.

TABLE 6
Incidence of Meningioma in Women Originally Diagnosed with Any Breast Carcinoma

Age group (yrs)	Women with initial breast carcinoma		Subsequent meningioma		
	No.	Person-years at risk	Observed no. of meningiomas	Expected no. of meningiomas	Standardized incidence ratio (95% CI)
18–34	379	759	0	0.01	0
35–49	4818	12,602	1	0.59	1.69 (0.04–9.41)
50–64	6766	20,355	2	1.91	1.05 (0.13–3.78)
65–79	7138	22,376	5	3.48	1.44 (0.47–3.35)
80+	2450	8287	2	1.14	1.76 (0.21–6.34)
Total	21,551	64,379	10	7.13	1.40 (0.67–2.58)

95% CI: 95% confidence interval.

TABLE 7
Incidence of Meningioma in Women Originally Diagnosed with Invasive Breast Cancer Carcinoma.

Age group (yrs)	Women with initial invasive breast carcinoma		Subsequent meningioma		
	No.	Person-years at risk	Observed no. of meningiomas	Expected no. of meningiomas	Standardized incidence ratio (95% CI)
18–34	334	665	0	0.01	0
35–49	3937	10,337	1	0.49	2.06 (0.05–11.48)
50–64	5644	16,853	2	1.58	1.27 (0.15–4.57)
65–79	6178	19,253	5	3.00	1.67 (0.54–3.89)
80+	2256	7,431	2	1.02	1.96 (0.24–7.07)
Total	18,349	54,593	10	6.10	1.64 (0.79–3.02)

95% CI: 95% confidence interval.

whether the presence of meningioma was occult and, thus, whether the occurrence of meningioma actually preceded the occurrence of breast carcinoma in the two breast carcinoma cohorts.

Another limitation of the current study was the inability to account for women who no longer resided in western Washington State. The person-years at risk calculations were dependent on good ascertainment of vital status after a diagnosis of either condition. To determine whether migration out of the CSS data collection area may have resulted in underestimates of the person-years at risk, we examined U.S. Census Bureau migration patterns for Washington State. The most recently available migration pattern data cover

the time period between 1985 and 1990.[29] Among persons age ≥ 5 years, 74% resided in the same county of Washington State, and 84% continued to reside in Washington State. These statistics include persons of all ages > 5 years; data restricted to adult populations were not available. It seems reasonable to assume that migration patterns are related to age and that children and young families constitute the greatest percentage of persons who change residence. For these reasons, it does not appear that migration out of western Washington State, especially for older women, was an important influence in our study.

Annual vital status information was collected for 68% of the women in the meningioma cohort. The reported mortality rate at follow-up was 23%. The mortality cause was not available from the CSS data unless it was from a neoplastic disease for which the registry collects data. It is assumed that the majority of observed mortality occurred as a result of age. Annual vital status information was collected for 94% of the women in the breast carcinoma cohort. The reported mortality rate at follow-up was 20%. We assumed that all women contributed fully to the person-time during follow-up unless they were deceased. Succinctly, the follow-up end point of mortality was well ascertained, but loss to follow-up due to migration would have resulted in an overestimate of the true person-time under surveillance for the second tumor; hence, the SIRs would be underestimated. However, because the results suggested moderately elevated risks, loss to follow-up did not appear to be a driver of the analytic results.

By defining the study period as 1992–1998, we intended to assess accurately the accumulated person-time at risk. The exclusion of diagnoses that occurred outside the study period was necessary to prevent bias caused by the accumulation of time at risk only for those women who had been diagnosed with one of the diseases and not for all of the women who had been diagnosed with both breast carcinoma and meningioma. This restriction resulted in a reduction in the number of women with diagnoses of both diseases from 35 women to 24 women. These small numbers of women had a prominent influence on this analysis. Although the point estimates suggest an association, the 95%CIs represent a large range of possible results. A future analysis using additional data from other cancer registries or the same data, but over a larger study period, would be helpful in improving confidence in the risk estimates.

The current study adds further evidence to the suggestion that, if the two tumors are related, then it is probably only because they share common risk factors. None of the risk estimates reported here is sufficiently different to indicate a specific pathway of association. For example, if meningioma is a risk factor for the development of breast carcinoma, but not the reverse, then one would expect that the relative risk of breast carcinoma in the meningioma cohort would be notably larger than the risk of meningioma in the breast carcinoma cohorts.

The shared risk factors hypothesis suggests that the tumors are not associated causally. Rather, any association between the two tumors rests on nonspecific mechanisms, such as age, gender, hormone induction, and possibly other demographic characteristics that are common to both tumors. The results from studies by Helseth et al. and Jacobs et al. suggested a nonspecific mechanism of association.[17,21] Jacobs et al. did not find evidence for a statistically significant association for the risk of breast carcinoma in women who were diagnosed with meningioma (standardized mortality ratio, 1.43; 95% CI, 0.74–2.50). The estimate presented here was similar (SIR, 1.54; 95% CI, 0.77–2.75). Helseth et al. reported a significant association between breast carcinoma and meningioma when breast carcinoma was diagnosed first (SIR, 1.75; 95% CI, 1.08–2.68). The association when meningioma was diagnosed first was nearly significant (SIR, 1.54; 95% CI, 0.97–2.34). However, none of the age group specific relative risks reported by Helseth et al. were significant except for women age 50–64 years who were diagnosed with meningioma first. Because all of the risk estimates reported by Helseth et al. represent approximately the same level of association regardless of which disease was diagnosed first, that study tends to support an association on the basis of shared risk factors.

In the study by Helseth et al., 9 of 12 meningiomas were incidental findings at autopsy.[17] Those tumors did not represent medically evident conditions that lead to diagnosis or treatment, and it is possible that the inclusion of such diagnoses at autopsy produced the statistically significant relative risks. In contrast, all of the meningioma diagnoses in the current study were me from living women who contributed to the person-years at risk in the appropriate cohort even if they were asymptomatic at the time of diagnosis.

Emry found a large increased risk of meningioma in women who were diagnosed previously with breast carcinoma (observed/expected ratio, 3.5; $P < 0.001$), whereas the risk of breast carcinoma in women who were diagnosed with meningioma was not significant (observed to expected tumor ratio, 1.1; $P > 0.05$).[22] The Emry study relied on Los Angeles County Cancer Surveillance Program (CSP) data: At the time of that study, CSP data only included incidence of meningioma and/or breast carcinoma. Follow-up data were

not available, and it was necessary to model the person-years at risk using SEER cancer rates for the U.S. population and estimates of mortality. In our study, follow-up data, including mortality, were available for all individuals who continued to reside in Washington State, and the population rates for all diseases were determined using the registry data and the intercensal population estimates from which the diagnoses arose.

The statistical association between breast carcinoma and meningioma was reported first by Schoenberg et al., who published an observed to expected estimate of 1.76 ($P < 0.05$).[18] In that study, only the association between the two diseases was examined, that is, the diagnosis of either breast carcinoma or meningioma followed by the diagnosis of the other disease was included in the same risk calculation. In addition, the estimate was based on a small number of observed tumors (8) and expected tumors (3.4), and the results represent one of the few significant associations from several comparisons of many different tumor combinations.

The published case reports of meningioma and breast carcinoma in the same individual suggest that the pathologic classification of the first tumor may influence the risk of the occurrence of the second tumor. This reasoning seems logical, in that a more aggressive tumor may be more likely to metastasize. Specifically, the CNS is a common metastatic site for breast tumors.[22] Pathologic confirmation of tumor type is collected in the CSS registry. Of the 24 women for whom the diagnoses of breast carcinoma and meningioma occurred during the study period, 22 meningiomas were classified as benign (the tumor type was missing for 2 diagnoses). For the breast carcinoma diagnoses, 4 women had in situ tumors, 18 women had malignant tumors, and 1 woman had a metastatic tumor. These breast carcinoma tumor types in the women with both diagnoses followed the same general distribution that was seen in the entire 21,551-member breast carcinoma cohort. Because more aggressive tumors are no more common in women with diagnoses of both tumors than in women with only breast carcinoma or meningioma, the data suggest that tumor type probably is not related to the likelihood of developing of a second primary neoplasm for these two diseases.

To assess whether the suggested risk factor for meningioma, radiation treatment, influences the likelihood of the occurrence of both diseases, we examined the treatment information contained in the CSS data base, including the type of surgery and various treatment modalities for women with a diagnosis of breast carcinoma. Treatment information for women with a diagnosis of meningioma is not collected actively but is coded when available. When either breast carcinoma or meningioma is diagnosed first, the treatment codes do not suggest that radiation treatment is a clear factor in subsequent risk of development of the other tumor. Of the 10 women who had a subsequent diagnosis of meningioma after a diagnosis of breast carcinoma, only 4 women were treated with beam radiation during breast carcinoma treatment, whereas 6 women had no radiation treatment of any kind. This prevalence of beam radiation treatment in women who had both tumors is not significantly different than for women in the entire breast carcinoma cohort. Of the 11 women who had a subsequent diagnosis of breast carcinoma after a diagnosis of meningioma, 2 women were treated with beam radiation, 6 women had no radiation treatment of any kind, and 3 women had missing information. This pattern of beam radiation, no radiation, and missing data for women diagnosed with meningioma and subsequent breast carcinoma is not significantly different than for the entire meningioma cohort. The treatment code information does not suggest that radiation treatment is related to the subsequent risk of developing these second primary neoplasms.

The persistence of case reports on the suggested association and genetic investigation of the common tumorigenesis pathways continue. Several case reports have been published in the 1990s, with the most recent published in 1998.[3,5,8,9,11] These case reports imply that a significant association is present, whereas analytic studies have provided, at best, equivocal confirmation of the association. Even though it was limited by its small sample size, the current study suggests that any such association is probably modest. Further analysis using larger sets of population-based data that include longer follow-up may be necessary to fully detect this association. Shared risk factors may account for the relatively week bidirectional associations seen in this study and in other studies.

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