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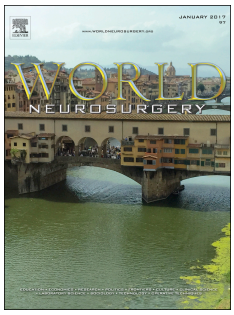

Increased Risk of Subsequent Meningioma Among Women with Malignant Breast Cancer

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PII: S1878-8750(20)30674-4

DOI: https://doi.org/10.1016/j.wneu.2020.03.203

Reference: WNEU 14662

To appear in: *World Neurosurgery*

Received Date: 17 February 2020

Revised Date: 27 March 2020

Accepted Date: 28 March 2020

Please cite this article as: Lopez-Rivera V, Zhu P, Dono A, Lee S, Chen PR, Ballester L, Sheth SA, Esquenazi Y, Increased Risk of Subsequent Meningioma Among Women with Malignant Breast Cancer, *World Neurosurgery* (2020), doi: https://doi.org/10.1016/j.wneu.2020.03.203.

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Conflict of Interest: None.
Disclosure of Funding: None.

Abstract word count: 219
Manuscript word count: 2,778
Number of Tables and Figures: 5
Number of References: 24

Associated Risk of Subsequent Meningioma in Women with Breast Cancer

Abstract

Objective

Despite the increasing evidence of the association between breast cancer and meningioma in women, the relationship between these tumors remains improperly examined. In this study, we aim to identify the socio-demographic and clinicopathological features of women with breast cancer associated with a higher risk of developing a meningioma.

Methods

The Surveillance, Epidemiology, and End Results database (18 registries) was used to identify women with breast cancer as their first neoplasm. The risk of subsequent meningioma was reported as the standardized incidence ratio (SIR) and was analyzed by socio-demographic and clinicopathological subgroups. Results are given as SIR [95% CI].

Results

A total of 564,516 women diagnosed with breast cancer between 2004-2016 were included for analysis. A 26% increased risk of meningioma development (SIR 1.26 [1.19-1.33]; $P<0.05$) was found in the cohort compared to the general population. Patients between ages 18-49 (SIR 2.16 [1.78-2.61]; $P<0.05$) and those with a more advanced tumor stage (Stage IV, SIR 2.39 [1.71-3.25]; $P<0.05$) were at a higher risk. Hormone receptor expression and treatment modality subgroups were at a similar risk compared to the general population.

Conclusion

Our study corroborated the known association between these tumors and found a 26% risk of meningioma development in women with breast cancer, with younger patients and those with a more aggressive disease having a higher than expected risk.

Short Title: Meningioma and Breast Cancer in Women

Keywords: Breast Cancer; Meningioma; Standardized Incidence Ratio; SEER

Introduction

The postulated association between breast cancer and meningioma in women has been increasingly described over the past decades.[1–9] Meningioma tumor growth during pregnancy, physiologic changes in the menstrual cycle and use of exogenous hormones have pointed out the shared risk factors by these two tumors.[1,2,4,10–14] Despite the growing evidence from retrospective studies, the demographic, socioeconomic, and tumor characteristics of breast cancer patients that may influence meningioma development remain largely unknown.

In the present study, we examined the overall risk of subsequent meningioma in breast cancer patients, identifying socio-demographic and clinicopathological characteristics of breast cancer patients associated with a higher risk compared to the general population and among patients in the cohort.

Methods

Study Population

The Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute collects data on demographics, tumor features, treatment, and survival outcomes from approximately 28% of the population in the United States.[15] The SEER 18 registries 2000-2016 (November 2018) was queried to identify cases of newly diagnosed breast cancer in women from January 2004 to December 2016, as records of meningioma tumors in the SEER database were not reliable or available until January 2004.

Breast cancer was defined by the *International Classification of Diseases for Oncology*, third edition (ICD-O-3), coded as ICD-O-3 8500-8549 for ductal or lobular histology, malignant behavior, and topography codes C500-C509. Meningioma was defined by ICD-O-3 codes 9530-9539, and a benign, atypical or malignant behavior. The exclusion criteria are presented in **Figure 1**. Patients were categorized in 2 main groups: those who developed breast cancer and meningioma (BC-M) and those who only developed breast cancer (BC).

SEER Coding and Variable Definitions

Patient socio-demographics extracted from the SEER database included age at diagnosis, year of diagnosis, race/ethnicity, marital status, and insurance status (available since 2007). Age was analyzed as an ordinal variable (18-49, 50-59, 60-69, 70-79, >79 years). Clinicopathologic

characteristics included tumor size, tumor stage (AJCC Cancer Staging Manual), estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status (available since 2010), and histologic subtype. Borderline ER, PR, or HER2 statuses were considered as positive for analysis. For records with tumor size coded as a range, the median was used for analysis (e.g., For a 0-20mm range, a 10mm size was assigned), while those with a possible miscoding (i.e., tumor size of 200mm or greater) were included in the unknown group.

Records with a diagnostic confirmation coded as "Radiography without microscopic confirm" refer to cases diagnosed based on imaging alone (e.g., CT/MRI) without a positive histology/cytology report. Data on the type of imaging modality used at diagnosis or during follow-up are not available in the SEER database. Surgical procedures were identified using the site-specific codes (SEER Program Coding and Staging Manual 2018) for breast and meninges and were categorized into 6 groups, respectively.

Subsequent meningioma development

To assess the degree of association between breast cancer and subsequent meningioma, the standardized incidence ratio (SIR) was used and calculated as the number of observed meningioma cases in the cohort divided by the number of meningioma cases expected in the general population. Using the SEER*Stat MP-SIR session and SEER*Stat Rate session, meningioma incidence referent rates were generated and used for calculation of the expected number of cases adjusting for age, race/ethnicity, and year of diagnosis. Multiple outcome analysis was used for the SIR calculation to account for multiple tumor occurrence.

According to SEER, a synchronous tumor is considered to occur within 2 months after the initial diagnosis of the first tumor. To be compliant with this definition, patients with synchronous breast cancer and meningioma were excluded from our cohort using a 3-month latency exclusion period. Thus, patients in the BC-M cohort were confirmed to have first developed breast cancer followed by a meningioma at least 3 months apart from the initial breast cancer diagnosis, ensuring the accuracy of the SIR calculation. The time at risk for meningioma development was measured using person-years risk and was calculated to any endpoints occurring as following: diagnosis of meningioma, loss of follow-up, death, or end of the study.

Statistical Analysis

The Mann-Whitney U test and Pearson's chi-squared test were used to compare the socio-demographic and clinical features between patients in the BC group and BC-M group. Simple linear regression was used to determine the trends in the diagnosis of breast cancer and meningioma cases and the use of imaging alone vs microscopic/macroscopic evaluation in the diagnosis of meningioma (see Supplementary Material).

To identify characteristics of patients that are more prone to develop a meningioma, we stratified the cohort by age, race/ethnicity, marital status, insurance status, tumor stage, ER, PR, and HER2 statuses, and clinical treatments to evaluate the individual risk of the subgroups. Additionally, we examined the latency period from breast cancer diagnosis to the study endpoint. 95% confidence intervals [95% CI] for the SIR were calculated using the exact Poisson method.[16] In addition, we conducted a sensitivity analysis using multivariable binary logistic regression models to identify potential predictors of developing meningioma among the cohort accounting for three sets of adjustments, respectively (see Supplementary Material).

Statistical analyses were performed with SEER*Stat software (MP-SIR session) for SIR calculation (version 8.3.6; Surveillance Research Program, National Cancer Institute, Bethesda, MD [http:// www.seer.cancer.gov/seerstat/]), Stata IC (Release 15.0, StataCorp, College Station, TX), Prism 7 (GraphPad, La Jolla, CA), and SAS (version 9.4, SAS Institute). All *p*-values were two-sided and considered statistically significant as $P < 0.05$.

Ethics Statement

This study was reviewed by the Institutional Review Board (Committee for the Protection of Human Subjects) and was determined to be exempt from review by the committee.

Results

Study Population Characteristics

Among 564,516 women identified with breast cancer as their first neoplasm between 2004-2016, the median age at diagnosis was 60 years [IQR, 50-70 years], and 69% were non-Hispanic White. The most common breast cancer histology subtype was infiltrating ductal carcinoma, and 78% and 67% of patients had a positive ER and PR expression status, respectively. 44% had a HER2 negative status in the cohort, and among patients in the 2010-2016 subset, 79% had a negative HER2 status. Patients in the BC-M cohort were older (BC vs

BC-M, 60 years vs 63 years; *P*<0.001), more commonly non-Hispanic White (BC vs BC-M, 69.1% vs 74.1%; *P*<0.001), and more often treated with radical mastectomy (BC vs BC-M, 19.1% vs 23.1%; *P*<0.001). Socio-demographic and tumor characteristics of breast cancer patients in the cohort are described in **Table 1**.

Of 1,159 patients in the BC-M group, the majority were between 50-59 years of age (28%) and were non-Hispanic White (74%). Meningioma histologic subtype was not specified in 88% of patients, over half of patients had a meningioma tumor size between 10-50 mm, and 2% had meningiomatosis. 759 (64%) patients were diagnosed based on radiology findings alone while 399 (34%) patients were diagnosed either by macroscopic (i.e., direct visualization) or microscopic examination (i.e., positive histology). Treatment strategies included surgical resection and radiotherapy in 30% and 8% of patients, respectively. Socio-demographic, tumor features and clinical treatments of patients in the BC-M group are detailed in **Table 2**.

Standardized Incidence Ratio of Meningioma

The cohort was followed for a total of 2,894,335.68 person-years and the SIR for meningioma was 1.26 (95% CI [1.19-1.33]; P<0.05), representing a 26% increased risk in the cohort when compared to the general population. This finding remained significant within the first 5 years (3-59 months) following the breast cancer diagnosis, but lost significance beyond 5 years after breast cancer diagnosis. The risk of subsequent meningioma found in our cohort was the highest among other breast cancer and tumor behavior cohorts (See **Supplementary Table S1**). The trend of meningioma risk by year of diagnosis was stable over the course of the study (**Figure 2**), although in patients diagnosed late in the study (2014-2016) a short follow-up period may have contributed to a wide CI of the SIR.

As shown in **Table 3,** there was a two-fold risk of meningioma among patients between 18-49 years of age (SIR 2.16; [1.78-2.61]; P<0.05), and an increased 24% risk in non-Hispanic White (SIR 1.24 [1.16-1.32]; P<0.05). Patients with a divorced marital status (SIR 1.57 [1.33-1.84]; P<0.05), an uninsured status (SIR 2.47 [1.41-4.02]; P<0.05), and a more advanced tumor stage (Stage IV, SIR 2.39 [1.71-3.25]; P<0.05) had an increased risk. A risk of subsequent meningioma was found whether the breast cancer tumor had a positive or negative ER/PR status and regardless of the treatment modality (radiotherapy or chemotherapy).

There were predictors related to demographic, socio-economic, and treatment features that were associated with a higher likelihood of developing a meningioma among patients in the cohort (Please see details in **Supplementary Table S2**).

Trends in Diagnosis of Breast Cancer and Meningioma Cases

The proportion of patients diagnosed with breast cancer over time remained comparable in the study (7% vs 7%, 2004 vs 2016; P= 0.0390), while the proportion of patients diagnosed with a meningioma significantly increased late in the study (1% vs 16%, 2004 vs 2016; P<0.0001) (**Supplemental Figure 1**). When evaluating the trends in the diagnostic confirmation of meningiomas (**Supplemental Figure 2**), there was an increase in the use of imaging alone (50% vs 70%, 2004 vs 2016; P=0.0330) while macroscopic/microscopic visualization of the tumor was less often used towards the end of the study (50% vs 30%, 2004 vs 2016; P=0.0287). There was a difference in the diagnostic confirmation of meningiomas between age subgroups, as a higher proportion of patients in the younger subgroup were diagnosed by microscopic/macroscopic evaluation compared to elderly patients (40% vs 16%, 18-49 years vs 80+ years; P<0.0001). There were no differences in the diagnostic confirmation of meningiomas between tumor staging subgroups.

Discussion

In this study of over 500,000 female patients with breast cancer, we identified nearly 1,200 patients that had a subsequent meningioma. In our cohort, there was a 26% increased risk of developing a meningioma. Younger patients (18-49 years), those with a divorced marital status, and patients with a more aggressive tumor stage had a higher risk than expected, while treatment and hormone expression subgroups had an elevated yet comparable risk.

Prior studies have explored the association between breast cancer and meningioma using state and national cancer registries. However, these studies were limited by the inability to adjust the incidence rates of meningioma for age, race, and year of diagnosis when calculating the expected number of cases for the SIR calculation.[4,6,17] Furthermore, the socio-demographic and clinicopathological features associated with meningioma development in breast cancer patients remained unexplored by these studies. Two previous studies have used the SEER database to study the association between these two tumors – Lavrador et al.[18] evaluated the survival impact

after the diagnosis of any of these two tumors and Milano et al.[17] described clinicopathologic characteristics of breast cancer in women with meningioma.

To the best of our knowledge, this is the first study evaluating patient characteristics associated with a higher risk of meningioma development in breast cancer patients using the SEER database, as in the study by Milano et al.[17] the SIR of meningioma was not calculated. The number of patients in the BC-M group in our study is comparable to the one presented by Lavrador et al., although we did not include patients with synchronous breast cancer and meningioma, as mentioned above.

Sociodemographic Factors

A higher risk of meningioma was found in patients with a younger age (18-49 years, SIR 2.16) compared to the general population, with this trend decreasing with increasing age (**Table 3**). The increased risk in this age group is noteworthy; meningiomas presenting in younger adults is relatively uncommon unless associated with a genetic syndrome, such as neurofibromatosis type II.[1,14,19] In this age subgroup, the status of ER and PR was positive in 74% and 67% of patients, respectively. The use of invasive methods for meningioma diagnosis in patients aged 18-49 years may have been influenced by the need to rule out other tumors due to the expected lower incidence of breast cancer and meningioma in this age subgroup.

The observed risk in divorced and single patients may be explained by a prolonged exposure to estrogen compared to those who were married, as these patients might have been less likely to become pregnant, although data on fertility and use of oral contraceptive is needed to support this assumption. Uninsured and insured patients presented a comparable higher risk of meningioma development within the first 5 years after their initial diagnosis (Table 3), thus decreasing our concern of surveillance bias in our cohort.

Clinicopathological and Treatment Factors

Patients diagnosed with a more aggressive tumor behavior had a higher risk of meningioma than the general population. This finding was evident among patients with a tumor staging IIA-IIIA/IV, with the highest risk in patients with a Stage IV tumor, although this lost significance one year following breast cancer diagnosis. We considered the possibility of misdiagnosis (e.g., dural-based breast metastasis diagnosed as meningioma), and found that all patients with stage IV breast cancer diagnosed with a meningioma survived until the end of the study period. Thus, the expected natural history of brain metastasis and the benign course of

meningiomas may have guided the decision for diagnosis in this subgroup, shown by the comparable use of imaging vs microscopic/macroscopic evaluation between the different tumor staging subgroups.

Regarding the risk of meningioma development and the ER+/PR+ receptor status of breast cancer patients, we found their risk to be similar (ER+: - SIR 1.26 vs ER-: SIR 1.31) (PR+: SIR 1.27 vs PR-: SIR 1.30). The risk of meningioma after breast cancer regardless of ER/PR expression suggests that the observed risk may be related to other factors beyond hormone exposure or receptor status. This was previously suggested by the difference in the incidence of meningioma between men and women with breast cancer despite the equal rate of expression of the estrogen receptor.[6,20] Although not found in our study, other studies have described the relationship between ER/PR expression in breast carcinoma and meningioma.[8,18,21]

The assumption of a treatment-related risk of developing meningioma was considered, as previous studies have described that exposure to ionizing radiation (e.g., patients undergoing radiotherapy) is a risk factor for meningioma.[1,14] In our study, the observed risk of meningioma among patients treated with and without radiotherapy was comparable (SIR 1.26 vs SIR 1.25, No/Unknown RT vs RT)(**Table 3**). When evaluating the cohort for potential predictors of developing a meningioma (**Supplementary Table S2**), increasing age, divorced marital status, and treatment with chemotherapy correlated with an increased likelihood of subsequent meningioma, while a Hispanic race had a decreased likelihood. Treatment with radiotherapy was not associated with meningioma development in the cohort.

Limitations

Our current work has several limitations, most of the which are inherent to its retrospective design and the use of a national cancer registry. First, risk factors related to the incidence of breast cancer (e.g., family history, smoking, number of pregnancies, exogenous hormone use, etc.) are not recorded in the SEER database and thus we were unable to adjust for these variables in our analysis. Second, the increased screening of cancer patients may have resulted in surveillance bias, potentially related to the increasing proportion of meningioma cases diagnosed over the study and the increased reliability of imaging for meningioma diagnosis (see Supplementary Material). However, due to the benign and indolent natural history of meningioma tumors, these may remain silent over years before leading to symptomatic disease, and the true incidence of meningioma may still remain unaccounted for. Finally, most of the

meningioma cases were diagnosed based on radiological findings without histologic confirmation raising the concern for other possible diagnoses, although the natural history and characteristic radiologic features of meningiomas may serve enough to differentiate from other tumors.[22–24]

Despite these limitations, the study design, statistical analysis performed, and use of a large population dataset allow to provide significant evidence on the increased risk of meningioma in breast cancer patients and highlight the characteristics of breast cancer patients associated with a higher risk. Future research should be directed towards evaluating the pathways by which breast cancer tumors induce an increased risk of meningioma.

Conclusions

In this large population study, there was a higher risk of subsequent meningioma in women with breast cancer compared to the general population, particularly in younger patients and those with more aggressive disease. There was no association of subsequent meningioma and radiotherapy treatment for breast cancer. A positive ER/PR status of the breast cancer tumor did not confer additional risk of subsequent meningioma. These findings suggest that non-hormonal factors may play an important role in the association between these tumors. Awareness of the higher than expected incidence of meningioma among breast cancer patients, especially those at risk for metastatic disease and who later develop symptomatic or incidental brain lesions, may serve useful in the clinical decision-making for this patient population.

References

1. Barnholtz-Sloan JS, Kruchko C. Meningiomas: causes and risk factors. *Neurosurg Focus*. 2007;23(4):1-8. doi:10.3171/FOC-07/10/E2
2. Blankenstein MA, van der Meulen-Dijk C, Thijssen JHH. Assay of oestrogen and progestin receptors in human meningioma cytosols using immunological methods. *Clin Chim Acta*. 1987;165(2-3):189-195. doi:10.1016/0009-8981(87)90162-8
3. Caroli E, Salvati M, Giangaspero F, Ferrante L, Santoro A. Intrameningioma metastasis as first clinical manifestation of occult primary breast carcinoma. *Neurosurg Rev*. 2006;29(1):49-54. doi:10.1007/s10143-005-0395-4
4. Custer B, Longstreth JT, Phillips LE, Koepsell TD, Van Belle G. Hormonal exposures and the risk of intracranial meningioma in women: A population-based case-control study. *BMC Cancer*. 2006;6:1-9. doi:10.1186/1471-2407-6-152
5. Kubo M. Association of Breast Cancer with Meningioma: Report of a Case and Review of the Literature. *Jpn J Clin Oncol*. 2001;31(10):510-513. doi:10.1093/jjco/hye109
6. Rao G, Giordano SH, Liu J, McCutcheon IE. The association of breast cancer and meningioma in men and women. *Neurosurgery*. 2009;65(3):483-489. doi:10.1227/01.NEU.0000350876.91495.E0
7. Rubinstein AB, Schein M, Reichenthal E. The association of carcinoma of the breast with meningioma. *Surg Gynecol Obstet*. 1989;169(4):334-336.
8. Sayegh ET, Henderson GA, Burch EA, et al. Intrameningioma metastasis of breast carcinoma. *Rare Tumors*. 2014;6(2):49-52. doi:10.4081/rt.2014.5313
9. Smith FP, Slavik M, MacDonald JS. Association of breast cancer with meningioma: report of two cases and review of the literature. *Cancer*. 1978;42(4):1992-1994. doi:10.1002/1097-0142(197810)42:4<1992::aid-cncr2820420445>3.0.co;2-o
10. Cea-Soriano L, Blenk T, Wallander MA, Rodríguez LAG. Hormonal therapies and meningioma: Is there a link? *Cancer Epidemiol*. 2012;36(2):198-205. doi:10.1016/j.canep.2011.08.003
11. Claus EB, Calvocoressi L, Bondy ML, Wrensch M, Wiemels JL, Schildkraut JM. Exogenous hormone use, reproductive factors, and risk of intracranial meningioma in females. *J Neurosurg*. 2013;118(3):649-656. doi:10.3171/2012.9.JNS12811
12. Lee E, Grutsch J, Persky V, Glick R, Mendes J, Davis F. Association of meningioma with

reproductive factors. *Int J Cancer*. 2006;119(5):1152-1157. doi:10.1002/ijc.21950

13. Qi ZY, Shao C, Huang YL, Hui GZ, Zhou YX, Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: A meta-analysis. *PLoS One*. 2013;8(12). doi:10.1371/journal.pone.0083261

14. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol*. 2010;99(3):307-314. doi:10.1007/s11060-010-0386-3

15. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs excluding AK Custom Data (with additional treatment fields), Nov 2018 Sub (2000-2016) <Katrina/Rita Population Adjustment> - Link based on the N 2018 submission. No Title. www.seer.cancer.gov.

16. Sahai, Hardeo. Khurshid A. *Statistics in Epidemiology: Methods, Techniques, and Applications.* 1 Edition. Boca Raton: CRC Press; 1996.

17. Milano MT, Grossman CE. Meningioma in breast cancer patients population-based analysis of clinicopathologic characteristics. *Am J Clin Oncol Cancer Clin Trials*. 2017;40(1):11-16. doi:10.1097/COC.0000000000000052

18. Lavrador JP, Pinto MV, Lemos LM, Ribeiro C, Santos AP. Meningioma and breast cancer: survival of patients with synchronous and metachronous meningioma and breast cancer. *J Neurooncol*. 2018;136(1):163-171. doi:10.1007/s11060-017-2640-4

19. Claus EB, Calvocoressi L, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M. Family and personal medical history and risk of meningioma: Clinical article. *J Neurosurg*. 2011;115(6):1072-1077. doi:10.3171/2011.6.JNS11129

20. Korhonen K, Salminen T, Raitanen J, Auvinen A, Isola J, Haapasalo H. Female predominance in meningiomas can not be explained by differences in progesterone, estrogen, or androgen receptor expression. *J Neurooncol*. 2006;80(1):1-7. doi:10.1007/s11060-006-9146-9

21. Doyle S, Messiou C, Rutherford JM, Dineen RA. Cancer presenting during pregnancy: radiological perspectives. *Clin Radiol*. 2009;64(9):857-871. doi:10.1016/j.crad.2008.08.020

22. Starr CJ, Cha S. Meningioma mimics: five key imaging features to differentiate them from meningiomas. *Clin Radiol*. 2017;72(9):722-728. doi:10.1016/j.crad.2017.05.002

23. Watts J, Box G, Galvin A, Brotchie P, Trost N, Sutherland T. Magnetic resonance

imaging of meningiomas: A pictorial review. *Insights Imaging*. 2014;5(1):113-122. doi:10.1007/s13244-013-0302-4

24. Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD, Lukas R V. An overview of meningiomas. *Futur Oncol*. 2018;14(21):2161-2177. doi:10.2217/fon-2018-0006

330 **Figure 1.** Flow diagram of eligible breast cancer patients included in the analytic cohort.

331 **Figure 2.** Trend of the standardized incidence ratio of subsequent meningioma in

332 breast cancer patients over time.

Abbreviations List:

BC-M: Breast Cancer and Meningioma

BC: Breast Cancer

CI: Confidence Interval

ER: Estrogen Receptor

ICD-O-3: International Classification of Diseases for Oncology, third edition

IQR: Interquartile Range

NH: Non-Hispanic

NOS: Not Otherwise Specified

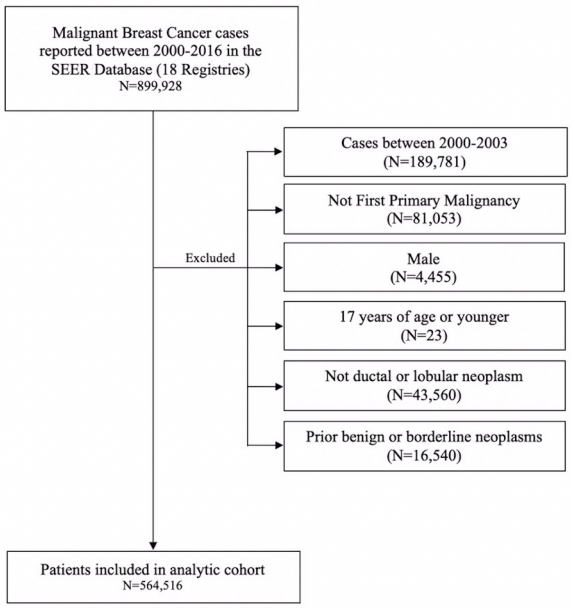
OR: Odds Ratio

PR: Progesterone Receptor

RT: Radiotherapy

SEER: Surveillance, Epidemiology and End Results

SIR: Standardized Incidence Ratio



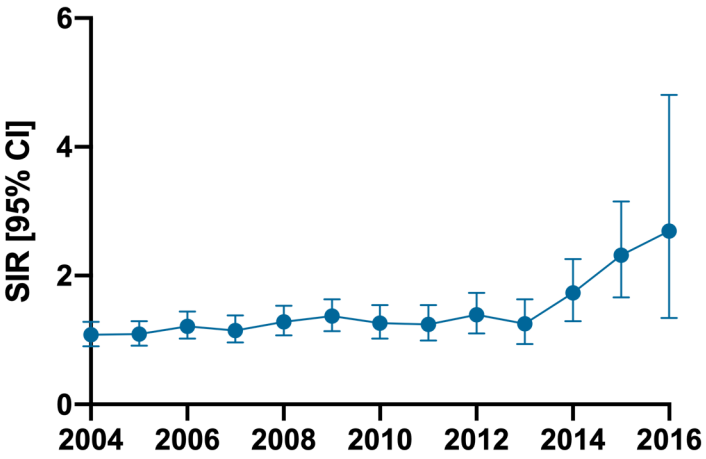


Table 1. Patient characteristics in analytic cohort by subsequent meningioma for breast cancer patients (N=564516).

Factor, N (%)	Breast CA without seq meningioma	Breast CA with seq meningioma	*P*
Total	563357	1159	
Socio-demographics			
Age at diagnosis, median (IQR)	60 (50, 70)	63 (54, 73)	<0.001
Age group at diagnosis			<0.001
18-49	135586 (24.1)	186 (16.0)	
50-59	143857 (25.5)	250 (21.6)	
60-69	141683 (25.1)	351 (30.3)	
70-79	91357 (16.2)	246 (21.2)	
80-	50874 (9.0)	126 (10.9)	
Year of diagnosis			<0.001
2004-2007	162169 (28.8)	505 (43.6)	
2008-2011	176114 (31.3)	424 (36.6)	
2012-2016	225074 (40.0)	230 (19.8)	
Race/ethnicity			<0.001
Hispanic (All Races)	61895 (11.0)	92 (7.9)	
NH American Indian/Alaska Native	2403 (0.4)	NA	
NH Asian or Pacific Islander	46237 (8.2)	85 (7.3)	
NH Black	60557 (10.7)	120 (10.4)	
NH Unknown	2895 (0.5)	NA	
Non-Hispanic White	389370 (69.1)	859 (74.1)	
Marital status at diagnosis			<0.001
Divorced	59557 (10.6)	152 (13.1)	
Married (including common law)	312597 (55.5)	588 (50.7)	
Separated	5961 (1.1)	NA	
Single (never married)	80779 (14.3)	142 (12.3)	
Unknown	27104 (4.8)	52 (4.5)	
Unmarried or Domestic Partner	1009 (0.2)	NA	
Widowed	76350 (13.6)	214 (18.5)	
Insurance			<0.001
Uninsured	7537 (1.3)	16 (1.4)	
Any Medicaid	51308 (9.1)	101 (8.7)	
Insured/insured, NOS	374669 (66.5)	641 (55.3)	
Unknown	129843 (23.0)	401 (34.6)	
Clinical treatments			
Surgery			<0.001
None/local tumor destruction	37328 (6.6)	59 (5.1)	
Partial/subcutaneous mastectomy	306355 (54.4)	634 (54.7)	
Total/simple/bilateral mastectomy	109059 (19.4)	194 (16.7)	
Radical mastectomy	107596 (19.1)	268 (23.1)	
Mastectomy/Surgery, NOS	1824 (0.3)	NA	
Unknown	1195 (0.2)	NA	
RT			0.490
None/Unknown	273987 (48.6)	552 (47.6)	
Yes	289370 (51.4)	607 (52.4)	
Chemotherapy			0.600
None/Unknown	319877 (56.8)	667 (57.5)	
Yes	243480 (43.2)	492 (42.5)	
Tumor features			
Tumor size, median (IQR)	18 (11, 30)	17 (11, 30)	0.280
Tumor size group			<0.001
0-9	103716 (18.4)	221 (19.1)	
10-20	200699 (35.6)	467 (40.3)	
21-50	164587 (29.2)	345 (29.8)	
51-	40945 (7.3)	80 (6.9)	
Unknown	53410 (9.5)	46 (4.0)	
Tumor stage			<0.001
I	238911 (42.4)	518 (44.7)	
IIA	124656 (22.1)	276 (23.8)	
IIB	58142 (10.3)	141 (12.2)	
IIIA	35909 (6.4)	79 (6.8)	
IIIB	11331 (2.0)	19 (1.6)	
IIIC	16802 (3.0)	37 (3.2)	
IIINOS	683 (0.1)	NA	
IV	21000 (3.7)	39 (3.4)	
Unknown	55923 (9.9)	47 (4.1)	
ER status			0.290
Negative	102034 (18.1)	190 (16.4)	
Positive	441138 (78.3)	929 (80.2)	
Unknown	20185 (3.6)	40 (3.5)	
PR status			0.730
Negative	159956 (28.4)	318 (27.4)	
Positive	380236 (67.5)	795 (68.6)	
Unknown	23165 (4.1)	46 (4.0)	
HER2 status			<0.001
Negative	246881 (43.8)	329 (28.4)	
Positive	54529 (9.7)	66 (5.7)	
Unknown	261947 (46.5)	764 (65.9)	
Histology			0.120
Infiltrating Duct Ca	441707 (78.4)	885 (76.4)	
Lobular Ca, NOS	51424 (9.1)	119 (10.3)	
Infiltrating duct mixed with other Ca	18651 (3.3)	46 (4.0)	
Infiltrating duct and lobular Ca	37022 (6.6)	87 (7.5)	
Unknown	14553 (2.6)	22 (1.9)	

NA= not available. Data from a total of 564,516 patients. Data were suppressed if less than a certain number according to the privacy policy of SEER.
The Mann-Whitney U test or Pearson's chi-squared test was performed.

Table 2. Patient characteristics with subsequent meningioma following breast cancer (N=1159).

Factor, N (%)	BC-M Cohort
Age group at diagnosis	107 (9)
18-49	224 (19)
50-59	326 (28)
60-69	279 (24)
70-79	223 (19)
80-	223 (19)
Race/ethnicity	
NH White	859 (74)
NH Black	120 (10)
Hispanic	92 (8)
NH Asian/Pacific Islander	85 (7)
NH American Indian/Alaska Native	NA
NH Unknown	-
Year of diagnosis	
2004-2007	100 (9)
2008-2011	320 (28)
2012-2016	739 (64)
Marital status	
Single	155 (13)
Married	535 (46)
Separated	127 (11)
Divorced	NA
Widowed	259 (22)
Partner	NA
Unknown	70
Insurance status	
Uninsured	14 (1)
Any Medicaid	895 (77)
Insured/insured, NOS	151 (13)
Unknown	44 (4)
Histology	
Meningioma, NOS	1015 (88)
Meningothelial meningioma	55 (5)
Atypical meningioma	27 (2)
Psammomatous meningioma	18 (2)
Fibrous meningioma	17 (1)
Transitional meningioma	14 (1)
Tumor size group (mm)	
0-9	106 (9)
10-20	343 (30)
21-50	314 (26)
51-	54 (5)
Unknown/uncertain	342 (30)
Multiple Tumors (Meningiomatosis)	23 (2)
Surgery	
None	810 (70)
Excision of tumor, lesion, or mass	223 (19)
Subtotal resection	45 (4)
Partial resection	51 (5)
Gross total resection	22 (3)
Surgery, NOS/Unknown	NA
RT	
None/Unknown	1062 (92)
Yes	97 (8)

NA= not available. Data from a total of 1,159 patients. Data were suppressed if less than a certain number according to the privacy policy of SEER.

Table 3. Standardized Incidence Ratio (SIR) of subsequent meningioma following initial diagnosis of breast cancer.

	3-11 months			12-59 months			60 months -			Total		
Factor	SIR	95%CI	*P*	SIR	95%CI	*P*	SIR	95%CI	*P*	SIR	95%CI	*P*
Total	1.99	1.74-2.26	<0.05	1.20	1.10-1.30	<0.05	1.10	0.99-1.21	NS	1.26	1.19-1.33	<0.05
Age group at diagnosis												
18-49	3.57	2.46-5.02	<0.05	2.00	1.53-2.57	<0.05	1.46	0.85-2.34	NS	2.16	1.78-2.61	<0.05
50-59	2.95	2.24-3.81	<0.05	1.39	1.14-1.68	<0.05	1.26	0.97-1.62	NS	1.56	1.36-1.77	<0.05
60-69	2.08	1.61-2.64	<0.05	1.26	1.07-1.47	<0.05	1.13	0.92-1.38	NS	1.32	1.18-1.47	<0.05
70-79	1.23	0.88-1.68	NS	1.02	0.85-1.20	NS	1.04	0.85-1.25	NS	1.05	0.93-1.18	NS
80-	1.44	0.99-2.03	NS	0.99	0.81-1.19	NS	1.00	0.08-1.22	NS	1.04	0.91-1.18	NS
Race/ethnicity												
NH White	1.91	1.63-2.23	<0.05	1.17	1.06-1.29	<0.05	1.12	0.99-1.25	NS	1.24	1.16-1.32	<0.05
NH Black	1.39	0.81-2.22	NS	1.39	1.07-1.77	<0.05	1.31	0.94-1.79	NS	1.36	1.13-1.63	<0.05
NH American Indian/Alaska	0.00	0-10.3	NS	0.00	0-2.60	NS	3.22	0.66-0.94	NS	1.11	0.23-3.24	NS
NH Asian/Pacific Islander	2.86	1.72-4.46	<0.05	1.65	1.20-2.21	<0.05	1.14	0.71 - 1.72	NS	1.62	1.29-2.00	<0.05
Hispanic	2.94	2.00-4.18	<0.05	1.00	0.72-1.35	NS	0.66	0.40-1.04	NS	1.13	0.91-1.39	NS
Marital status												
Single	2.54	1.76-3.55	<0.05	1.37	1.08-1.72	<0.05	0.98	0.69-1.35	NS	1.38	1.16-1.62	<0.05
Married	2.01	1.66-2.41	<0.05	1.10	0.97-1.24	NS	1.06	0.93-1.22	NS	1.19	1.10-1.29	<0.05
Separated	1.06	0.03-5.92	NS	1.06	0.29-2.72	NS	1.77	0.58-4.14	NS	1.33	0.64-2.44	NS
Divorced	2.00	1.28-2.97	<0.05	1.61	1.27-2.00	<0.05	1.39	1.03-1.83	<0.05	1.57	1.33-1.84	<0.05
Widowed	1.67	1.20-2.26	<0.05	1.18	0.97-1.41	NS	1.03	0.79-1.32	NS	1.20	1.04-1.37	<0.05
Partner	6.28	0.16-34.98	NS	0.00	0-9.38	NS	0.00	0.00-1.25	NS	1.75	0.04-9.76	NS
Insurance status												
Uninsured	3.78	1.03-9.69	<0.05	2.28	1.04-4.33	<0.05	2.05	0.42-5.99	NS	2.47	1.41-4.02	<0.05
Any Medicaid	3.57	2.44-5.04	<0.05	1.77	1.33-2.29	<0.05	1.17	0.62-2.00	NS	1.95	1.59-2.37	<0.05
Insured	1.94	1.62-2.31	<0.05	1.18	1.05-1.32	<0.05	1.14	0.95-1.37	NS	1.29	1.19-1.40	<0.05
Insured, NOS	1.55	0.97-2.35	NS	0.97	0.73-1.27	NS	1.24	0.82-1.80	NS	1.13	0.92-1.37	NS
Tumor stage												
I	1.56	1.24-1.93	<0.05	1.06	0.93-1.19	NS	1.00	0.86-1.15	NS	1.09	1.00-1.19	NS
IIA	1.87	1.38-2.48	<0.05	1.31	1.11-1.54	<0.05	1.17	0.81-1.26	NS	1.27	1.12-1.43	<0.05
IIB	2.72	1.83-3.88	<0.05	1.44	1.12-1.83	<0.05	1.49	1.10-1.98	<0.05	1.62	1.37-1.91	<0.05
IIIA	2.64	1.54-4.22	<0.05	1.44	1.03-1.97	<0.05	1.34	0.86-1.97	NS	1.55	1.23-1.93	<0.05
IIIB	1.63	0.44-4.18	NS	1.18	0.57-2.18	NS	1.08	0.35-2.51	NS	1.22	0.74-1.91	NS
IIIC	2.53	1.09-4.99	<0.05	1.77	1.09-2.70	<0.05	1.32	0.61-2.51	NS	1.74	1.23-2.39	<0.05
IV	5.37	3.32-8.20	<0.05	1.39	0.76-2.34	NS	1.80	0.59-4.21	NS	2.39	1.71-3.25	<0.05
ER status												
Negative	2.46	1.80-3.30	<0.05	1.26	1.02-1.54	<0.05	1.00	0.75-1.29	NS	1.31	1.13-1.50	<0.05
Positive	1.94	1.66-2.24	<0.05	1.20	1.10-1.32	<0.05	1.12	1.00-1.25	NS	1.26	1.19-1.35	<0.05
Borderline	0.00	0-33.39	NS	0.00	0-6.89	NS	1.69	0.04-9.39	NS	0.81	0.02-4.50	NS
PR status												
Negative	2.38	1.87-2.99	<0.05	1.21	1.03-1.42	<0.05	1.05	0.85-1.28	NS	1.30	1.16-1.44	<0.05
Positive	1.91	1.61-2.24	<0.05	1.21	1.10-1.34	<0.05	1.13	0.99-1.27	NS	1.27	1.18-1.36	<0.05

Borderline	0.00	0-9.03	NS	0.97	0.12-3.50	NS	1.33	0.28-3.90	NS	1.06	0.34-2.47	NS
HER2 status (2010+)												
Negative	1.89	1.53-2.29	<0.05	1.29	1.13-1.46	<0.05	-	-	-	1.41	1.26-1.57	<0.05
Positive	2.43	1.51-3.72	<0.05	1.42	1.02-1.94	<0.05	-	-	-	1.63	1.25-2.09	<0.05
Borderline	0.68	0.02-3.81	NS	1.04	0.34-2.42	NS	-	-	-	0.94	0.34-2.04	NS
HR/HER2 status (2010+)												
HR+/HER2+	2.31	1.26-3.88	<0.05	1.36	0.90-1.98	NS	-	-	-	1.55	1.12-2.11	<0.05
HR-/HER2+	2.74	1.10-5.65	<0.05	1.59	0.85-2.72	NS	-	-	-	1.83	1.12-2.83	<0.05
HR+/HER2-	1.81	1.45-2.24	<0.05	1.28	1.11-1.46	<0.05	-	-	-	1.38	1.23-1.55	<0.05
HR-/HER2-	2.47	1.38-4.07	<0.05	1.38	0.91-2.01	NS	-	-	-	1.65	1.19-2.22	<0.05
RT												
None/Unknown	2.05	1.70-2.45	<0.05	1.01	0.97-1.25	NS	1.20	1.04-1.39	<0.05	1.26	1.16-1.37	<0.05
Yes	1.92	1.58-2.32	<0.05	1.28	1.15-1.43	<0.05	1.01	0.87-1.17	NS	1.25	1.16-1.36	<0.05
Chemotherapy												
None/Unknown	1.57	1.31-1.88	<0.05	1.05	0.94-1.17	NS	1.03	0.90-1.17	NS	1.11	1.02-1.19	<0.05
Yes	2.85	2.33-3.44	<0.05	1.49	1.31- 1.69	<0.05	1.22	1.04- 1.43	<0.05	1.54	1.41-1.69	<0.05

*NS= Not significant.