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Research Paper

Second primary breast cancer after diagnosis of breast cancer among male patients: An examination of population characteristics and overall survival

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ABSTRACT

Background: Male patients with breast cancer (BrC) have increased risk of developing 2nd-primary BrC (2nd-BrC). Given the relative rarity of male BrC, population-based registries are needed to analyze overall survival (OS) outcomes for these patients.
Methods: Using the Surveillance, Epidemiology and End Results registry of patients diagnosed from 1975 to 2016, a cohort study of men whose only malignancy was BrC (BrC—O; n = 6,475), and men who developed 2nd-BrC after initial BrC diagnosis (BrC-2; n = 85) was performed. The standardized incidence ratio (SIR) of 2nd-BrC, Kaplan-Meier OS and multivariable Cox regression modelling were performed.
Findings: The SIR for 2nd-BrC was 32.95 (95%CI:[23.85−44.38],$p < 0.05$). The majority (88%) of 2nd-BrC for BrC-2 were contralateral from 1st-BrC; suggesting the unlikeliness of miscoding local recurrences as 2nd-BrC for most patients. There was no statistically significant difference between rates of hormone (reported in 44%) or HER-2 (reported in 33%) receptor status between BrC-O and BrC-2, albeit with limited data. The 2nd-BrC for BrC-2 was significantly more likely to be localized or distant stage (rather than regional) than BrC-O. Median OS was 103 months (95% CI: [99, 108]) for BrC-O and 62 months (95% CI [49, 128] after 2nd-BrC. When sub-grouped by BrC stage, and when analyzed by Cox regression, there was no significant difference in OS between BrC-O and BrC-2.
Interpretation: Patients with male BrC are at significantly increased risk of 2nd BrC, but they can expect similar post-BrC prognosis (versus those without 2nd-BrC), after adjusting for patient demographics and tumor characteristics known to affect OS.
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1. Introduction

Male patients with breast cancer (BrC) are at increased risk of developing a second primary BrC relative to males without a history of BrC [1]. Understanding risk of second malignancies after male BrC, and survival outcomes after such malignancies is helpful in determining post-treatment screening guidelines for patients with primary BrC, and for guiding treatment for those patients diagnosed with second malignancy.

Males who are survivors of primary BrC are at increased risk of a variety of second malignancies including breast, rectal, pancreatic, skin, and prostate cancers, as well as hematologic malignancies [2,3]. Estimates of the rate of observed to expected cases (O/E ratio) or standardized incidence ratio (SIR) of second BrC among male patients have ranged from 30 to 110 in the literature [1]. Reasons for these increased risks are likely multifactorial, including receipt of chemotherapy and/or radiotherapy, in addition to general underlying risk factors for cancer and other predisposing factors that can include testicular disease, benign breast disease, treatment with exogenous hormones, and alcohol consumption [4]. Underlying germline genetic and genomic susceptibility are likely significant contributors to risk (including gene mutations such as BRCA2 [5,6]) as well.

For women treated with radiotherapy, radiation exposure of the contralateral breast may impact risk of second BrC [7]. While a study published in 1992, using the Surveillance, Epidemiology and End Results (SEER) database did not show an increased risk of second primary breast cancer with radiation to the contralateral breast [8], a

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Research in context

Evidence before this study

For many malignancies, having a history of prior malignancy may decrease overall survival. It is now known that male patients who develop a second primary breast cancer after a first primary breast cancer are at increased risk of death relative to male patients with only one (single) primary breast cancer.

Added value of this study

This population-based cohort study includes 6,475 males with primary breast cancer and no subsequent breast cancer, and 85 males with a second primary breast cancer that developed after an initial breast cancer. Males with second primary breast cancer are not at a significantly increased risk of death, after adjusting for factors known to affect overall survival.

Implications of all the available evidence

Male patients who develop a 2nd primary breast cancer share a similar prognosis, and should therefore be treated with similar treatment intent (curative or palliative), to male patients with a single primary breast cancer.

2008 case control study, taking into account dosimetric information, demonstrated that radiation dose is at least partly predictive of risk of second malignancy [7]. Among female patients treated for BrC, those receiving a dose of > 1 Gy to the contralateral breast had a clinically and statistically higher risk of second primary BrC than patients whose contralateral breast did not receive that dose [7]. However, overall, rates of receipt of radiation among male patients with BrC are low, both because of high rates of mastectomy, and also low rates of adjuvant radiation even in patients receiving lumpectomy [9].

To date, no studies have compared survival outcomes for patients with second primary BrC after a first primary BrC with single primary BrC in male patients. For many malignancies, having a history of prior malignancy may decrease overall survival. For instance, female patients with a history of Hodgkin lymphoma who later develop BrC have, on average, poorer overall survival than female patients whose first primary is BrC relative to female BrC patients without a history of Hodgkin lymphoma after adjusting for other factors known to affect overall survival [10] This increased risk may be due to competing causes of mortality, including cardiac causes and subsequent malignancies (e.g., third malignancies). Given the relative rarity of the disease, a population-based registry is needed to analyze a sufficient number of patients to make reliable inferences. We hypothesized that men with second primary BrC would have an increased risk of mortality (as among survivors of many other cancers who develop second malignancies), after adjusting for patient- and tumor-related characteristics known to affect survival. In addition to our primary goal of analyzing overall survival and population characteristics among men with second primary male BrC, we also aimed to compute an updated estimate of the risk of second primary male BrC, which has not been published from recent SEER data.

2. Methods

Using the Surveillance, Epidemiology and End Results (SEER) registry [11,12] data from 1975 to 2016, we identified male patients whose only malignancy was BrC (BrC-O), and male patients who developed second primary BrC after initial diagnosis of BrC (BrC-2). The standardized incidence (observed/expected) ratio (SIR) of 2nd-BrC was calculated using data from the SEER 9 database (which is the database in SEER recommended for computing SIR). For the rest of the analyses the SEER 18 database was used. SEER 18 draws its data from the regions of Alaska (Native Tumor Registry), Connecticut, Detroit, Georgia, California, Hawaii, Iowa, Kentucky, Louisiana, New Mexico, New Jersey, Seattle-Puget Sound, and Utah within the United States. SEER 9 consists of the same regions, except does not include the Alaska Native Tumor Registry, Rural Georgia, parts of California, Kentucky, Louisiana, and New Jersey. Data were collected by state registries in coordination with SEER staff. The process for following up patients to measure survival is described here: https://training.seer.cancer.gov/followup/process/ [13]. A minimum 2-month latency between first and second primaries was used for both analyses to eliminate synchronous primaries from all our analyses. Our sample of patients consisted of all patients who met the inclusion criteria above.

2.1. Statistical analyses

Summary statistics were computed for the following variables: age at first BrC diagnosis (years), year of first BrC diagnosis, histology, grade, stage of BrC, radiation for 1st BrC, chemotherapy for 1st BrC, latency between BrC-1 and BrC-2 (years), estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). A comparison of laterality of 1st and 2nd primaries for BrC-2 was tabulated. For BrC-1 and the second primary of BrC-2, stage, age at BrC diagnosis (years), year of diagnosis, percent of county with less than high school education in 2000, cancer-directed surgery, radiation, chemotherapy, histology, grade, ER, PR, and HER2.

For univariable analysis of categorical variables, Pearson chi-squared (for cases where expected counts >5 for all cells) and Fisher's Exact tests (for cases when expected counts <5) were used. Two-sided statistical tests, type I error rate of 0.05, and 95% confidence intervals (CI) were used throughout the study. Statistical analysis was performed using SAS 9.4 software, with the exception of the univariable analysis of categorical variables, which was performed using R 3.5.2 software.

Univariable Kaplan-Meier survival outcomes [14] and multivariable Cox proportional hazards model [15] were used to assess potential factors affecting survival for BrC-O and BrC-2 cohorts. The median and interquartile range (IQR) were computed for overall survival (both overall and separated by stage). Throughout the paper, the IQR is expressed as the Q3 (upper quartile) - Q1 (lower quartile). The primary outcome for the study was the adjusted hazard ratio for the Cox model for presence or absence of history of BrC. The following were adjusted for in the multivariable Cox proportional hazards model: patient age, patient race, year of BrC diagnosis, BrC stage, BrC grade, radiotherapy for BrC, chemotherapy for BrC, surgery for BrC, and percent of people with high school diploma or more within the patient's county of residence. Percent of people with high school diploma or more within the patient's county of residence in the year 2000 was used as SEER does not provide individual educational data due to the need to anonymize the data. Multiple imputation using fully conditional specification under the missing-at-random (MAR) assumption [16] was used for the analysis for the Cox proportional hazard model [17]. PROC MI in SAS was used to implement the multiple imputation algorithm, and all covariates were used in the imputation models. For situations where >40% of the date were missing, variables were excluded from the primary analysis. However, additional analyses using multiple imputation also under the MAR assumption were employed including these variables. ER, PR, and HER2 status fell into this category and were included in these analyses (and thus excluded from the primary analysis). The two sensitivity analyses were as follows: firstly, a multivariable Cox regression model identical, but also including ER and HER2 (PR was excluded as it is highly collinear with ER). Secondly, a reanalysis was performed using the same model as above (including adjustment for ER and HER2), except excluding all patients before 1992 (that is, patients

Table 1
Characteristics at first primary breast cancer (BrC) diagnosis among male patients who developed second primary breast cancer.

Total	85
Age at first BrC diagnosis (years)	
<40	0 (0%)
40–59	32 (38%)
>59	53 (62%)
Year of First BrC diagnosis	
1973–1979	3 (4%)
1980–1989	5 (6%)
1990–1999	22 (26%)
2000–2016	55 (65%)
Histology	
Ductal and Lobular	71 (84%)
Neoplasms	
Epithelial Neoplasms, NOS	5 (6%)
All others	
Grade	
I, Well differentiated	9 (11%)
II, Moderately	12 (14%)
differentiated	35 (41%)
III, Poorly differentiated	22 (26%)
IV, Undifferentiated	1 (1%)
Unknown	15 (18%)
Stage of BrC	
Localized	42 (49%)
Regional	34 (40%)
Distant	6 (7%)
Unknown	3 (4%)
Radiation for BrC	
Yes	24 (28%)
No/Unknown	61 (72%)
Chemotherapy	
Yes	35 (41%)
No/Unknown	50 (59%)
Latency between BrC-1 and BrC-2 (years)	
<1	9 (10%)
≥1 and <5	30 (35%)
≥5 and <10	33 (39%)
≥10 and <15	9 (11%)
≥15	4 (5%)
ER	
Positive	33 (39%)
Negative	1 (1%)
Unknown	51 (60%)
PR	
Positive	30 (35%)
Negative	4 (5%)
Unknown	51 (60%)
HER2	
Positive	1 (1%)
Negative	12 (14%)
Unknown	73 (86%)

BrC = breast cancer. ER = estrogen receptor, PR = progesterone receptor HER2= human epidermal growth factor receptor 2.

Table 2
Laterality and ER/PR/HER2 Status of BrC-2 patients, for their first vs second primaries.

	First Left	First Right	Total
Second Left	3 (4%)	37 (43%)	40
Second Right	36 (42%)	7 (8%)	43
Total	39	44	83[a]

[a] 2 patients had missing data for either first or second primary.
b BrC = breast cancer, ER = estrogen receptor, PR = progesterone receptor HER2= human epidermal growth factor receptor 2.

with BrC-O diagnosed 1992 or later or for BrC-2, their second malignancy was diagnosed in 1992 or later), when estrogen receptor status was routinely included in SEER.

2.2. Role of the funding source

This research was done without funding.

3. Results

3.1. Risk of second primary male BrC and population characteristics

The SIR for second primary BrC after initial BrC diagnosis was 32.95 (95% CI: [23.85, 44.38], $p < 0.05$). 6475 BrC-O patients and 85 BrC-2 patients were identified using the SEER 18 database. The latency between BrC diagnoses ranged from 2 months - 34 years, 11 months with a median of 5 years, 3 months (IQR: 7 years, 6 months - 2 years 5 months). 46 (54%) patients had a latency > 5 years. Table 1 outlines the patient- and tumor-specific characteristics of the patient who developed a 2nd primary cancer. Notably, all were >40 years in age, and most (89%) had initial localized or regional stage BrC.

The vast majority (88%) of 2nd-BrC were contralateral from the first cancer (Table 2) suggesting that miscoding a local recurrence as a second cancer is unlikely for most patients. Table 3 shows the patient- and tumor-related characteristics for the BrC-2 and BrC-O groups, including results of statistical tests. BrC-2 patients were more likely to be diagnosed with localized (BrC-O: n = 2692 [42%, 95% CI: {40%, 43%}, BrC-2: n = 45 [53%, 95% CI: {42%, 64%}]) or distant (BrC-O: n = 676 [10%, 95% CI: {10%, 11%}], BrC-2: n = 14 [16%, 95% CI: {9%, 26%}]) rather than regional stage disease (BrC-O: n = 2842 [44%, 95% CI: {43%, 45%}], BrC-2: n = 20 [24%, 95% CI: {15%, 34%}]), p = 0.001. Significantly more BrC-O patients had cancer-directed surgery compared with BrC-2 patients for their 2nd-BrC (BrC-O: n = 5695 [88%, 95% CI: {86%, 89%}], BrC-2: n = 69 [81%, 95% CI: {71%, 89%}], p = 0.027). Significantly more BrC-O patients were coded as having received chemotherapy compared with BrC-2 patients for their 2nd-BrC (BrC-O: n = 2233 [34%, 95% CI: {33%, 36%}], BrC-2: n = 18 [21%, 95% CI: {13, 31}]). Among patients with reported ER (44% reported, BrC-O: 96% [95% CI: {95%, 96%}, BrC-2: 96% [95% CI: {87%, 100%} positive), PR (44% reported, BrC-O: 87% [95% CI: {86%, 89%}, BrC-2: 87% [95% CI: {76%, 95%} positive), and HER2 receptor (33% reported, BrC-O: 14% [95% CI: {12%, 15%}, BrC-2: 13% [95% CI: {4%, 28%} positive) status, there was no statistically or clinically significant difference between the rates of receptor status between BrC-O and BrC-2.

3.2. Overall survival in BrC-O vs. BrC-2 cohorts: univariable and multivariable analyses

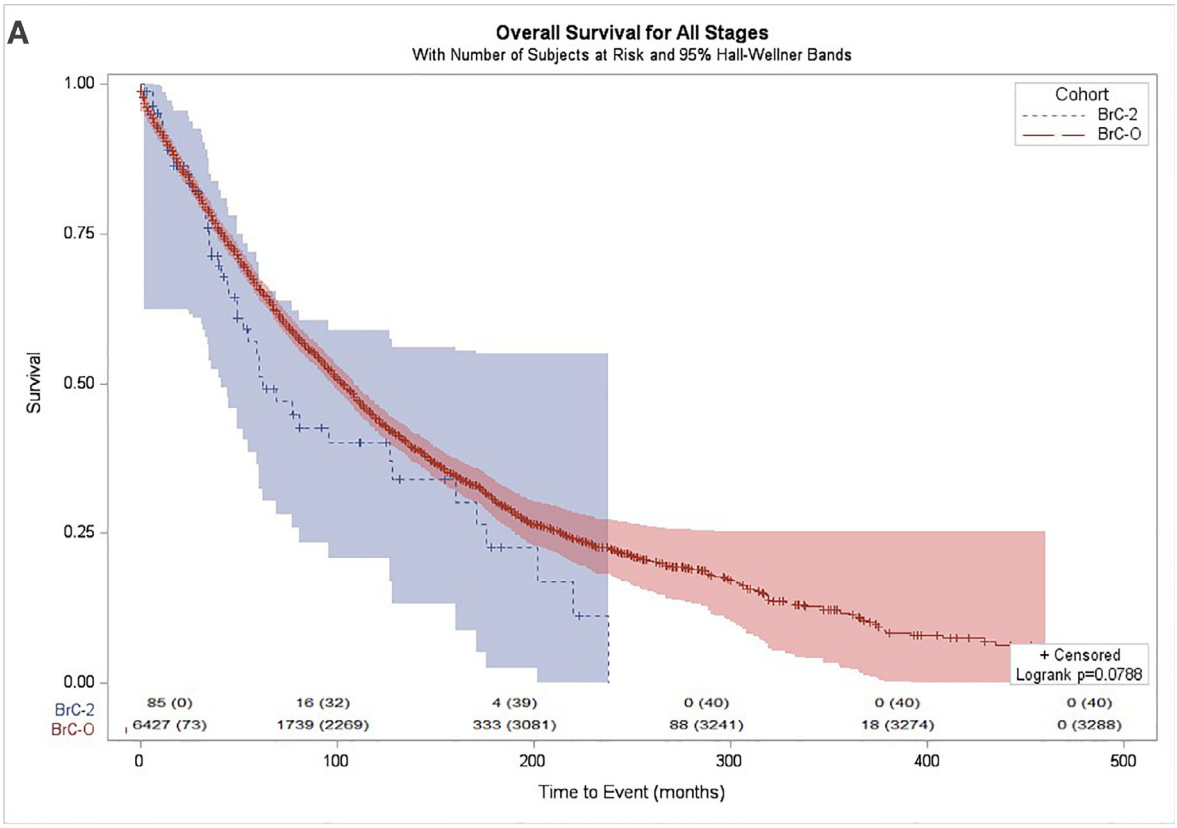
Kaplan–Meier plots are presented in Fig. 1. The median OS after BrC diagnosis was 103 months (95% CI: [99, 108], IQR: 215–42) for BrC-O and 62 months (95% CI [49, 128], IQR: 176–35) for BrC-2 after the 2nd-BrC (p = 0.0788). Median survivals (in months) for localized stage disease was 155 (95% CI: [145, 169], IQR: 308–72) months for BrC-O and 96 (95% CI [60, 176], IQR: 176–55) months for BrC-2 (log-rank p-value = 0.0578). Median survivals for regional stage disease was 95 (95% CI: [90, 100], IQR: 184–43) months for BrC-O and 171 (95% CI: [31, 238], IQR: 238–36) months for BrC-2 (p-value = 0.6579). Median survivals for distant stage disease was 26 (95% CI: [21, 29], IQR: 54–6) months for BrC-O and 35 (95% CI: [6, 60], IQR: 60–13) months for BrC-2 (logrank p-value = 0.4421). Crude cause-of-death data are presented in Table 4.

Second primary male BrC (HR: 1.11, 95% CI: [0.82, 1.49], two-sided p-value = 0.49) was not significantly associated with worse survival in a multivariable Cox proportional hazards model, adjusting for patient age, patient race, year of BrC diagnosis, BrC stage, BrC grade, radiotherapy for BrC, surgery for BrC, and percent of county with less than high school education in 2000 (Table 5). Missingness

Table 3
Comparison among patients with second primary breast cancer (BrC) diagnosis at time of second breast cancer diagnosis compared with patients with only single primary breast cancer.

	BrC-2 (for Second Primary) †	Single Primary BrC	*P*-value
Total	85	6475	
SEER Stage			
Localized	45 (53%)	2692 (42%)	0.001 (ChiSq)
Regional	20 (24%%)	2842 (44%)	
Distant	14 (16%)	676 (10%)	
Unstaged/unknown	6 (7%)	265 (4%)	
Age at BrC diagnosis (years)			
			0.067 (Fisher)
15–39	0 (0%)	166 (3%)	
40–59	19 (22%)	1995 (31%)	
>60	66 (78%)	4314 (66%)	
Year of Diagnosis			
1973–1980	2 (2%)	223 (3%)	0.056 (Fisher)
1980–1989	1 (1%)	525 (8%)	
1990–1999	10 (12%)	862 (13%)	
2000–2016	72 (85%%)	4865 (85%)	
Percent of County with less than high school education in 2000			0.026 (ChiSq)
Quartile 1 (<14.72%)	16 (19%)	1592 (25%)	
Quartile 2 (14.73–17.41%)	21 (25%)	1530 (24%)	
Quartile 3 (17.42–24.33%)	30 (35%)	1731 (27%)	
Quartile 4 (at least 24.34%)	18 (21%)	1622 (25%)	
Cancer-directed surgery			
Yes	69 (81%)	5695 (88%)	0.027 (ChiSq)
No	15 (18%)	631 (10%)	
Unknown	1 (1%)	149 (2%)	
Radiation Therapy			
Yes	14 (16%)	1648 (25%)	0.077 (ChiSq)
No/Unknown	71 (84%)	4827 (75%)	
Chemotherapy			
Yes	18 (21%)	2233 (34%)	0.014 (ChiSq)
No/Unknown	67 (79%)	4242 (66%)	
Histology			
Ductal and Lobular Neoplasms	75 (88%)	5665 (87%)	0.569 (Fisher)
Adenomas and adenocarcinomas	4 (5%)	431 (7%)	
Epithelial Neoplasms, NOS	4 (5%)	174 (3%)	
All others	2 (2%)	205 (3%)	
Grade			
I, Well differentiated	13 (15%)	597 (9%)	0.048 (Fisher)
II, Moderately differentiated	38 (45%)	2608 (40%)	
III, Poorly differentiated	16 (19%)	1936 (30%)	
IV, Undifferentiated	0 (0%)	74 (1%)	
Unknown	18 (21%)	1260 (19%)	
Radiation and Surgery			
Radiation and surgery	12 (14%)	1495 (23%)	0.039 (Fisher)
Surgery alone (or unknown radiation)	57 (67%)	4200 (65%)	
Radiation alone	2 (2%)	140 (2%)	
Neither surgery nor radiation (or unknown radiation)	13 (15%)	528 (8%)	
Surgery status unknown	1 (1%)	112 (2%)	
ER			
Positive	53 (62%)	3477 (54%)	*P* = 1.000 (Fisher)
Negative	2 (2%)	152 (2%)	
Unknown	30 (35%)	2846 (44%)	
PR			
Positive	48 (56%)	3128 (48%)	*P* = 1.000 (ChiSq)
Negative	7 (8%)	449 (7%)	
Unknown	30 (35%)	2898 (45%)	
HER2			
Positive	5 (6%)	294 (5%)	*P* = 1.000 (ChiSq)
Negative	33 (39%)	1832 (28%)	
Unknown	47 (55%)	4349 (67%)	

BrC = breast cancer, NOS = not otherwise specified, ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2, ChiSq = Pearson chi-squared test, Fisher = Fisher's exact test.



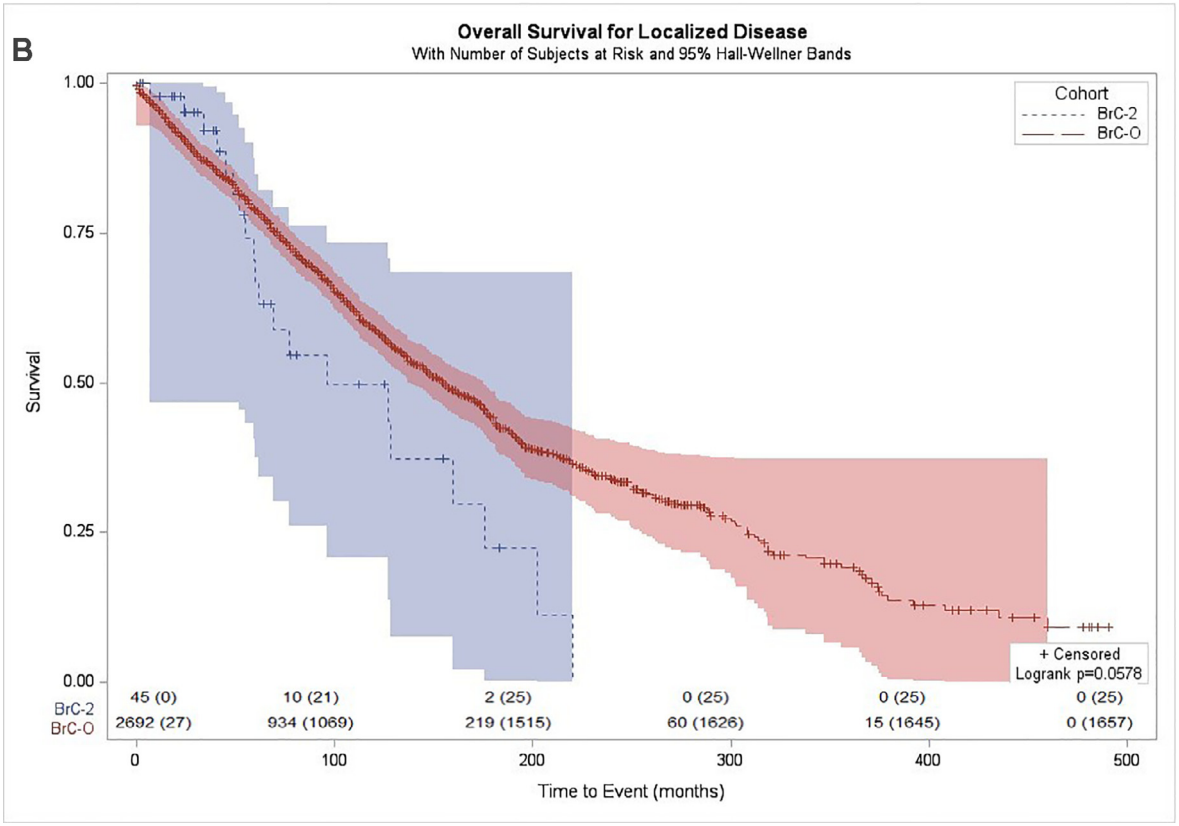


Fig. 1. Kaplan–Meier plots of overall survival for the (A) entire cohort, (B) localized, (C) regional, and (D) distant stage patients. Number at risk is shown at bottom of graph, with number censored in parentheses.

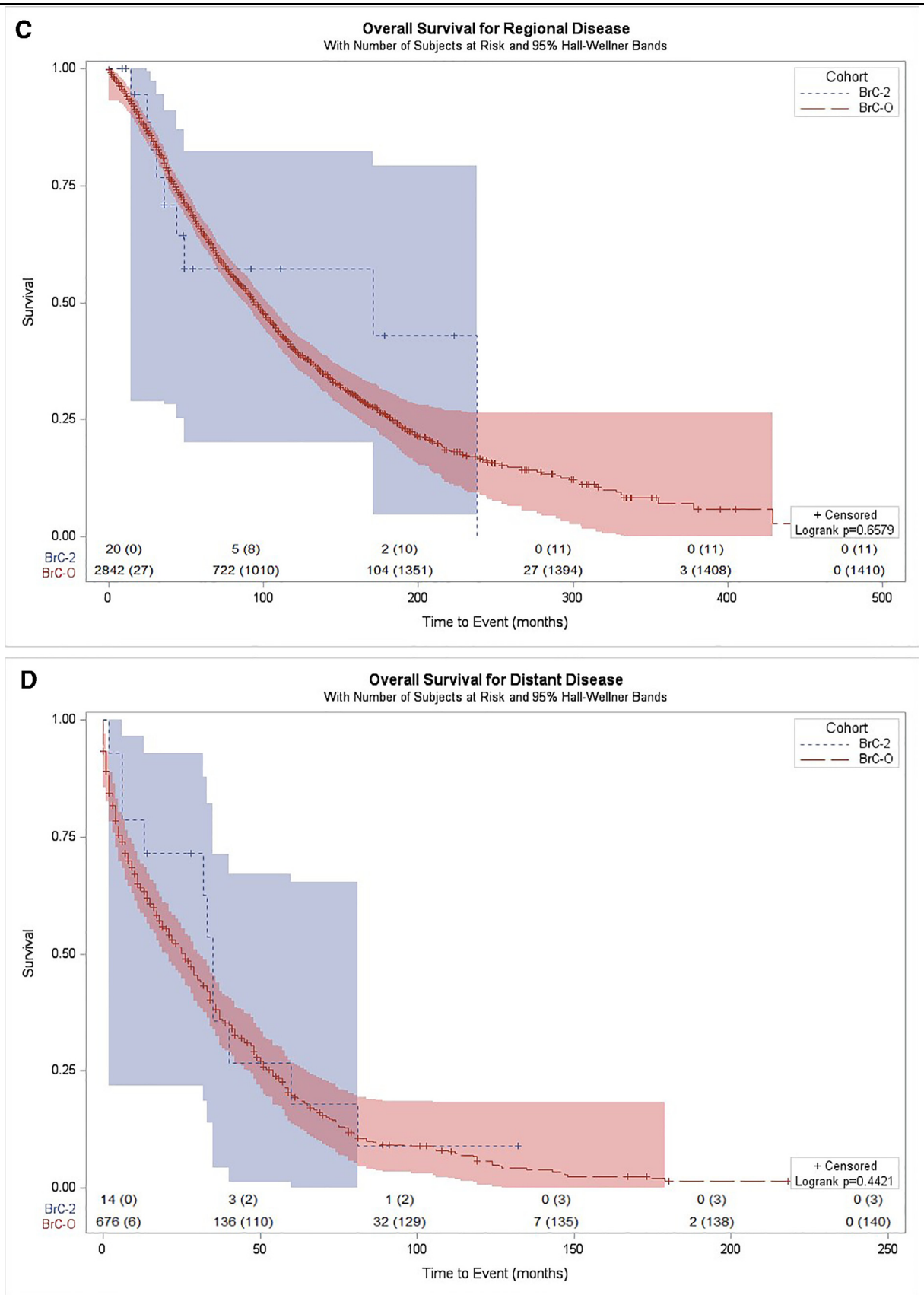


Fig. 1 Continued.

Table 4
Cause of death among male patients with second primary breast cancer (BrC) vs. male patients with single primary BrC.

	BrC-O	BrC-2
Breast Cancer Total	6475	85
Cause of Death		
Alive at last follow-up	3288 (51%)	40 (47%)
Deceased	3187 (49%)	45 (53%)
Cancer deaths[a]	1575 (49%)	29 (64%)
Breast Cancer[b]	1400 (89%)	23 (79%)
Other cancer[b]	175 (11%)	6 (21%)
Other causes [a]	1536 (48%)	14 (31%)
Missing cause [a]	76 (2%)	2 (4%)

[a] percentage of deaths.
[b] percentage of cancer deaths
BrC = breast cancer.

Table 5
Multivariable Cox proportional hazards model for overall survival using multiple imputation to account for missing covariates.

	Hazard Ratio	95% Confidence Limits		*P*-value
Second Primary [a]	1.11	0.82	1.49	0.4900
Age (per year)	1.05	1.04	1.05	<0.0001
Race (White vs. Other)	0.87	0.79	0.96	0.0046
Radiation (Yes vs. No/ Unknown)	1.02	0.93	1.11	0.6851
Surgery (Yes vs. No)	0.46	0.41	0.53	<0.0001
Chemotherapy (Yes vs. No/ Unknown)	1.02	0.94	1.12	0.5957
Year of Diagnosis (per year)	0.98	0.98	0.98	<0.0001
Education [b]	1.01	1.00	1.01	0.0012
Distant vs. Local Stage	4.03	3.51	4.63	<0.0001
Regional vs. Local Stage	1.61	1.48	1.76	<0.0001
Moderately Differentiated (II) vs. Well Differentiated (I) Grade	1.14	0.98	1.32	0.0793
Poorly Differentiated (III) vs. Well Differentiated (I) Grade	1.39	1.19	1.63	<0.0001
Undifferentiated (IV) vs. Well Differentiated (I) Grade	1.79	1.27	2.53	0.0011

[a] Primary outcome. Though all patients are being used for estimation of all hazard ratios, given that the vast majority of these patients have single primary breast cancer (>6000 patients), their information is predominantly being used to generate the model, with the patients in the second primary group being used to estimate the hazard ratio for first vs. second primary cancer.
[b] Hazard ratio is for each 1% increase in percent of individuals age >25 with a high school education in the county of residence of the patient (as SEER only provides county-level data for educational status).
BrC = breast cancer.

information for covariates is presented in Table 6. The additional analyses included models including ER, PR, and HER2 (ER and PR were included in separate models due to multicollinearity), which did not change the statistical or clinical conclusion (Supplementary Tables 1–3). Results of PR analysis not shown as they were nearly identical to ER results.

4. Discussion

Most importantly, based on the upper and lower bounds of the confidence intervals from multivariable regression, with a new diagnosis of male BrC, a history of prior BrC is unlikely to be a clinically significant adverse prognostic risk factor for OS sufficient to change goals of care. Furthermore, we showed that tumor characteristics are overall similar between male patients with single and second primary BrC. Other important findings include a significant increase in risk of second primary BrC among male patients with a history of BrC and the finding that most of these patients had contralateral second primaries, and this supports that these are truly second primaries rather than local recurrences. While the second primary cohort had a greater proportion of patients with local stage disease than the single primary cohort, it also included a greater proportion of patients with distant metastases. The tumors were significantly more likely to be found at a localized stage than single primaries, which suggest an increase in detection at an earlier point in time. This may be because most male patients do not undergo routine screening, but male patients with history of primary BrC may be screened for future malignancies. That said, these patients are less likely to have cancer directed surgery than male patients with single primary BrC. Understanding population characteristics and survival of men with BrC can inform screening and diagnosis guidelines. Moreover, understanding the population characteristics and prognosis for these patients will help guide physicians when caring for these patients with second primary BrC.

There is an increasing rate of screening men at increased risk for BrC. One recent study of 1869 men [18] found that screening is increasing in men at increased risk for BrC (relative to the screening rates for women). They also found that after 4 years of screening, a cancer detection rate of 18 per 1000 examinations (95% CI: [7,41]) among male patients screened for BrC (all had family/personal history of BrC or genetic mutations).

While the National Comprehensive Cancer Institute (NCCN) [19] does not routinely require mammography after treatment for early stage BrC in men, recent American Society of Clinical Oncology (ASCO) guidelines [20] recommends imaging for male patients with BrC. We are in agreement with the ASCO guidelines, which state that "Contralateral annual mammogram may be offered to men with a history of BrC and a genetic predisposing mutation (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate)." Although this study did not include information about germline mutations, it is informative about the average risk in these patients. As the relative risk of second primary BrC is high as demonstrated by the SIR, and given fact that more of these patients are diagnosed at a distant stage than among the patients with first/only BrC supports the role for screening of these patients, our results support this recommendation.

As this study looked at second primary malignancies as opposed to local recurrence, it did not address the question of the role for ipsilateral mammograms. We agree that ipsilateral mammogram be offered to "men with a history of BrC treated with lumpectomy, if technically feasible, regardless of genetic predisposition." Also, in agreement with the ASCO guidelines, more research is needed before breast MRI could be routinely recommended in this population.

We next consider the impact of these findings on how male patients with second primary BrC are treated. Given the similar prognosis of male patients with second primary BrC as compared with single primary BrC, particularly those with contralateral malignancy, should generally be treated with similar treatment intent (curative or palliative) to male patients with single primary BrC. For localized ipsilateral cancers, we would favor mastectomy over lumpectomy with post-lumpectomy radiation for most patients, although breast-conserving therapy remains an option. There are data for lumpectomy followed by reirradiation, primarily with brachytherapy (with the caveat that most patients studied have been female) [21].

We note that our data are observational; therefore, we do not claim to infer causality from our study, including the similar survival outcomes between our 2 study groups (BrC-2 and BrC-O). We therefore cannot determine the optimal, evidence-based, treatment course for male patients with 2nd-BrC. However, given what is known about the natural history of male BrC, and the overall survival data from this study, we believe that the best approach is to treat BrC-2 patients similarly to male patients with first primary BrC.

While our results are derived from SEER populations that are selected to be representative of the United States population, they

Table 6
Missingness patterns in covariates from Cox regression model from primary analysis. A "." denotes that the information is missing, and an X denotes that the information is present.

Group	Second Primary	Age	Race	Radiation	Surgery	Chemotherapy	Year of Diagnosis	Education	Stage	Grade	Frequency	Percent
1	X	X	X	X	X	X	X	X	X	X	5175	78.89
2	X	X	X	X	X	X	X	X	X	.	1037	15.81
3	X	X	X	X	X	X	X	X	.	X	52	0.79
4	X	X	X	X	X	X	X	X	.	.	138	2.1
5	X	X	X	X	X	X	X	.	X	X	1	0.02
6	X	X	X	X	X	X	X	.	X	.	1	0.02
7	X	X	X	X	.	X	X	X	X	X	27	0.41
8	X	X	X	X	.	X	X	X	X	.	17	0.26
9	X	X	X	X	.	X	X	X	.	X	3	0.05
10	X	X	X	X	.	X	X	X	.	.	63	0.96
11	X	X	X	X	.	X	X	.	X	X	1	0.02
12	X	X	.	X	X	X	X	X	X	X	20	0.3
13	X	X	.	X	X	X	X	X	X	.	9	0.14
14	X	X	.	X	X	X	X	X	.	X	1	0.02
15	X	X	.	X	X	X	X	X	.	.	12	0.18
16	X	X	.	X	X	X	X	.	X	X	1	0.02
17	X	X	.	X	.	X	X	X	.	X	1	0.02
18	X	X	.	X	.	X	X	X	.	.	1	0.02

may not be generalizable to other parts of the world, particularly countries with lower rates of BrC and/or less access to screening and cancer care.

As with any study that uses a national database, some information may be missing. BRCA and other germline genetic information is not available in SEER. Radiation and chemotherapy data in SEER are limited, and some patients categorized as not having received radiation or chemotherapy may have actually received the respective treatments. Moreover, the education data reflected the average county-level education, while educational levels may vary significantly within a county. Men with distant or regional stage BrC at initial diagnosis may have a prognosis that is more impacted by their original BrC than the second BrC. It should be noted that three of the patients in this study whose second primary was diagnosed at distant stage, were also diagnosed with distant disease at time of second malignancy diagnosis (which implies that these metastases could be from their first primary). However, many patients with even metastatic BrC, particularly oligometastatic BrC, have long duration of overall survival [22]. Only a subset of patients in our cohort had ER/PR/HER2 reported. Though we included ER/PR/HER2 in sensitivity analyses, it should be noted that as only about 1% of male BrC are triple negative and about 5% of male BrC are HER2 positive, therefore, our study has low power to detect statistically significant differences in outcome from tumor receptor status, particularly with such low rates of receptor status reporting in our cohort. These limitations suggest that there may be bias in our precise estimates of the impact of prior history of BrC on overall survival. However, that said, our estimates of Kaplan-Meier overall survival and our adjusted Cox proportional hazards model taken together suggest that survival is unlikely to be appreciably different in these patients to warrant changing goals of care based on history of prior BrC malignancy alone. In the absence of a prospective cohort study designed to answer this question, our study, despite its limitations and risk of bias, provides the most data to date on the question of the prognosis of male patients with second primary cancer after first primary male BrC.

In summary, patients with male BrC are at significantly increased risk of second male BrC but can expect similar prognosis (vs those without 2nd primary BrC), after adjusting for patient demographics and tumor characteristics known to affect overall survival.

Data sharing statement

Data may be obtained by requesting access on the SEER website (https://seer.cancer.gov/).

Author contributions

A.K.C., D.N.C., and M.T.M conceived of the study. A.K.C. organized data and performed statistical analyses. A.K.C., D.N.C., M.S., and M.T.M. participated in interpreting the results and writing the manuscript.

Declaration of Competing Interest

M.T.M. receives royalties from Wolters Kluwer (UpToDate) and Galera Therapeutics. All other authors have nothing to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100551.

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