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ORIGINAL ARTICLE – BREAST ONCOLOGY

Poorer Survival Outcomes for Male Breast Cancer Compared with Female Breast Cancer May Be Attributable to In-Stage Migration

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ABSTRACT

Background. Male breast cancer accounts for less than 1% of all breast cancers, yet males have a worse prognosis than females with breast cancer.

Methods. Using the 1988–2003 Surveillance, Epidemiology, and End Results Program data, we conducted a retrospective, population-based cohort study to investigate stage-specific differences in breast cancer-specific and all-cause mortality between males and females. We calculated adjusted hazard ratios (aHR) and 95% confidence intervals (CI) using Cox regression models to compare breast cancer-specific and all-cause mortality by stage between males and females, controlling for potential confounding variables.

Results. There were 246,059 patients with a first, single, primary breast cancer [1,541 (0.6%) male; 244,518 (99.4%) female]. Compared with females, males were more likely to be older, Black, married, diagnosed at more advanced stages, and treated with mastectomy (each $P < 0.001$). Males also were more likely to have lower grade and estrogen/progesterone receptor-positive tumors (each $P < 0.001$). After controlling for confounders, males were more likely to die from their breast cancer when compared with females, only if diagnosed with stage I disease (aHR 1.72, CI 1.15–2.61). For all-cause mortality, males were more likely than females to die at each stage of disease except stage IV.

Conclusions. Although all-cause mortality was higher for men than women at all stages of nonmetastatic breast cancer, higher male breast cancer-specific mortality was attributed to poorer survival in stage I disease. However, this statistical difference is unlikely to be clinically relevant and attributable to in-stage migration.

Male breast cancer is uncommon, accounting for slightly less than 1% of all breast cancers in the USA and less than 1% of all cancers in men.[1] The American Cancer Society estimates there will be 1,910 new cases of male breast cancer and 440 deaths attributed to this disease in 2009.[1] In contrast to the recent decline in incidence of female breast cancer, the incidence of male breast cancer has been steadily increasing over the past three decades.[2–4] The reason for this rise in incidence of male breast cancer is unknown, but it is likely due to several factors, including longer lifespan, increased public awareness, and rising levels of obesity in the general male population.[4] This increasing trend highlights the importance of understanding this cancer and whether it differs from female breast cancer.

There is a paucity of studies investigating either the tumor biology of male breast cancer or treatment strategies for this disease in men. The majority of retrospective studies have not included a male cohort, and there have been no prospective randomized controlled trials conducted for males with breast cancer to date.[5] A major

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limitation to both retrospective and prospective studies is the relative lack of males diagnosed with breast cancer and the amount of tumor tissue available to study. Another limitation is the inability to generalize results from clinical trials for female breast cancer to the treatment of male breast cancer.[5] As more data on the tumor biology of male breast cancer emerge, it is becoming clear that male breast cancer is a unique disease requiring its own trials and treatment guidelines.

In the past two decades, several retrospective studies have described the epidemiology of male breast cancer and its prognosis, with inconsistent results. Some studies showed that there was worse prognosis associated with male breast cancer compared with female breast cancer, and explained this worse prognosis in a variety of ways, including more advanced stage at diagnosis, older age at diagnosis, inappropriate staging, increased comorbidity, and more aggressive tumor biology in males with breast cancer.[6–11] Other studies observed no association between male breast cancer and survival and suggested that the sex of the patient did not influence mortality.[2,12–18] A few of these studies further suggested that the natural history of breast cancer development is the same in both sexes and thus the treatment of male breast cancer should and can follow the same treatment strategies applied to female breast cancer.[19,20] Finally, one study showed that, although overall survival was equivalent between the two sexes, disease-specific survival was significantly better in males with breast cancer.[21] Thus, there is no consensus on the relationship between the patient's sex and prognosis in breast cancer. To expand the knowledge in this area, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program data to investigate differences in breast cancer-specific mortality and all-cause mortality by stage at diagnosis for males and females diagnosed with a primary breast tumor.[22]

PATIENTS AND METHODS

We conducted a retrospective, population-based cohort study of males and females with a first primary diagnosis of breast cancer recorded in the SEER Program database between January 1, 1988 and December 31, 2003. Nine SEER registries were included: San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, and Metropolitan Atlanta. We only included patients with a single primary breast cancer (sequence number = 00 in the SEER public-use dataset). Patients with a second primary breast cancer, two or more primary cancers, or a primary tumor in another organ were excluded from the study. Patients younger than 18 years of age also were excluded.

Demographic information included age at diagnosis (<40, 40–49, 50–64, >65 years), race (Caucasian, Black, other), and marital status (married, unmarried, unknown). Tumor characteristics were classified by stage (in situ, I, II, III, IV, unstaged), grade (1, 2, 3, 4, unknown), estrogen receptor (ER) and progesterone receptor (PR) status (positive, negative, unknown), and laterality (right, left, unilateral/unspecified, bilateral). Though data on tumor size and nodal involvement are available in the SEER public-use data, we did not include them in our primary models as potential confounders, as this information is also captured in the assigned stage at diagnosis. However, frequencies for T1 subsets were calculated for males and females.

Treatment characteristics included receipt of surgery and radiation therapy. Two SEER variables, "site-specific surgery" (for 1983–1997 records) and "surgery of the primary site" (for 1998–2003 records), were recoded to form a single, dichotomous variable categorizing patients as receiving or not receiving any surgery on the primary site. Patients who received surgical resection were further divided into having either mastectomy or partial mastectomy (i.e., lumpectomy) of the primary breast tumor. Patients who did not receive any formal resection of their primary tumor or who only underwent breast biopsies for tissue diagnosis were categorized as not having surgery. Patients whose surgery status was not recorded were categorized as "unknown." In addition, patients were categorized as having received or not received radiation therapy (including external-beam radiation, radioactive implants, radioisotopes, or other radiation), or as "unknown," if radiation therapy was not recorded.

Breast cancer-specific mortality (dying of breast cancer specifically) and all-cause mortality (dying of any cause including breast cancer) were the two main outcomes of interest in this study. Vital status was recorded as "alive" or "dead" in the SEER dataset. Survival time (in months) was calculated for each patient using the "completed months of follow-up" variable in the SEER database. The "cause of death" recode variable was used to distinguish between deaths due to breast cancer or to other causes. All-cause mortality was determined by comparing males/females who had died with males/females who were alive at the end of the study period or who were alive at their last follow-up. Breast cancer-specific mortality was determined by comparing males/females whose cause of death was recorded as due to breast cancer with males/females who were alive at the end of the study period, had died due to other causes, or who were alive at their last follow-up.

Chi-square tests were used to compare the distribution of patient demographic, tumor- and treatment-related characteristics between males and females with breast cancer. Cox regression models were generated to describe

the relationship between being male and risk of death overall (across all stages) and within each stage at diagnosis. Since death during the study period was the event of interest, patients who were alive at the end of the study period or lost to follow-up before the end of the study period (December 31, 2003) were considered censored. Separate models were generated for the outcomes of all-cause mortality and breast cancer-specific mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for overall and stage-specific breast cancer mortality in males compared with females. Both crude (cHR) and adjusted hazard ratios (aHR) were calculated for each stage-specific comparison, the latter controlling for potential confounders of the relationship between being male and survival (adjusted for age at diagnosis, race, marital status at diagnosis, grade, estrogen receptor status, progesterone receptor status, surgical treatment received, and radiation treatment received). Two-tailed $P < 0.05$ was considered to be statistically significant. SPSS 16.0™ statistical software (SPSS, Inc., Chicago, IL, 2008) was used for all analyses.

RESULTS

A total of 279,181 males and females with breast cancer were diagnosed during the 1988–2003 study period; we excluded from the analysis 14 patients who were younger than 18 years of age and 33,108 patients who were diagnosed with two or more primary cancers. Of the remaining 246,059 patients diagnosed with a first, single, primary breast cancer, 1,541 (0.6%) were male and 244,518 (99.4%) were female.

Differences in patient demographics, tumor characteristics, treatments, and outcomes between the two groups are summarized in Table 1. Median age at diagnosis was 65 years (23–103 years) for males and 60 years (18–108 years) for females. Compared with females, males were more likely to be Black, married, and diagnosed at more advanced stages (each $P < 0.001$). Biological characteristics of the tumors also differed significantly between the sexes, with male breast tumors more likely to be lower grade, ER positive, and PR positive (each $P < 0.001$). Males also were more likely to have mastectomy and less likely to receive radiation compared with females (each $P < 0.001$).

Of the total 246,059 patient cohort, 36.9% of men and 25.0% of women died from any cause, while 15.8% of men and 12.9% of women died from breast cancer specifically. Overall, across all stages of disease, males were more likely to die due to all causes (cHR 1.78, CI 1.64–1.94) and to breast cancer specifically (cHR 1.42, CI 1.25–1.61) when compared with females.

TABLE 1 Characteristics of persons with a single primary breast cancer occurrence, SEER 1988–2003

	Male (%) (n = 1,541)	Female (%) (n = 244,518)	Chi-square P value
Demographic characteristics			
Age (years)			<0.001
<50	15.2	26.0	
50–59	21.5	22.8	
60–69	25.7	21.2	
>70	37.6	30.0	
Race			<0.001
White	82.0	84.2	
Black	12.0	8.4	
Others	5.1	6.9	
Unknown	1.0	0.5	
Marital status			<0.001
Not married	30.0	40.0	
Married	65.3	55.2	
Unknown	4.7	4.8	
Tumor characteristics			
Stage			<0.001
In situ	10.8	15.3	
I	28.0	37.7	
II	40.2	31.6	
III	7.5	5.4	
IV	6.3	4.1	
Unstaged	7.2	5.9	
Grade			<0.001
1	9.9	12.4	
2	34.7	29.4	
3	26.2	26.8	
4	2.4	3.2	
Unknown	26.8	28.1	
ER status			<0.001
Positive	56.1	49.1	
Negative	5.6	15.1	
Unknown	38.4	35.9	
PR status			<0.001
Positive	48.2	41.8	
Negative	12.3	20.9	
Unknown	39.5	37.3	
Nodal involvement			<0.001
No	54.7	65.3	
Yes	34.6	26.0	
Unknown	10.7	8.8	
Laterality			0.012
Right	48.0	48.3	
Left	49.7	50.4	
Unilateral/unspecified	0.5	0.2	
Bilateral	1.8	1.1	

TABLE 1 continued

	Male (%) (n = 1,541)	Female (%) (n = 244,518)	Chi-square P value
Treatment characteristics			
Radiation			<0.001
No	74.6	56.3	
Yes	23.0	41.2	
Unknown	2.4	2.5	
Surgery			<0.001
None	5.5	5.6	
Lumpectomy	19.4	57.1	
Mastectomy	74.2	36.6	
Unknown	0.9	0.7	
Outcomes			
Vital status			<0.001
Alive	63.1	75.0	
Dead	36.9	25.0	
Cause of death			<0.001
None (alive)	63.1	75.0	
Breast cancer	15.8	12.9	
Other cause	19.4	11.2	
Unknown	1.7	0.8	

Percentages shown are for column totals

SEER Surveillance, Epidemiology, and End Results, *ER* estrogen receptor, *PR* progesterone receptor

The percentages of total deaths due to breast cancer, other causes, or unknown causes are presented for men and women by stage at diagnosis in Table 2. A lower percentage of males were alive at the end of the study compared with females (63.1% vs. 75.0%). Males were more likely to die from other causes (causes other than breast cancer) within each stage at diagnosis compared with females. The percentage of females dying from other causes was fairly stable across stages I–IV (range 11.4–11.8%), while the percentage of males dying from other causes appeared to increase by stage at diagnosis from stages 0 to III (range 15.1–20.7%), but not for stage IV disease. As expected for breast cancer-specific mortality, a lower percentage of both males and females with more advanced stages of disease were alive at the end of the study. Also, the proportion of patients who died from breast cancer increased for both males and females diagnosed at more advanced stages of disease.

Multivariate Cox regression models were generated to describe the association between sex and mortality by stage at diagnosis (Table 3). Separate models were estimated for breast cancer-specific mortality and for all-cause mortality by stage of diagnosis comparing males with females. Males were more likely than females to die from all causes at each stage of disease, except stage IV breast cancer. After controlling for potential confounders, males were more likely to die from their breast cancer compared with females only among patients with stage I disease (aHR 1.72, CI 1.15–2.61). However, the absolute percentage of stage I deaths included 5.3% males and 3.7% females, representing a difference of only 1.6 percentage points. For males with stage I breast cancer, 30 (7%) were T1a, 61 (14%) were T1b, and 340 (79%) were T1c. In contrast, of females with stage I breast cancer, 13,827 (15%) were T1a, 23,968 (26%) were T1b, and 54,388 (59%) were T1c ($P < 0.05$ compared with males).

DISCUSSION

Male breast cancer mortality has not significantly improved in the past three decades.[23] The current study, like previously published studies, showed poorer survival in males with breast cancer when compared with females.[6–11] Males were more likely to die overall during the 1988–2003 study period, with significantly higher all-cause mortality compared with females for all stages of disease except for stage IV breast cancer, where there was no survival disparity between the sexes. Our analysis also showed that males were more likely to die from their breast cancer overall compared with females, but this survival disparity was limited to patients diagnosed with stage I breast cancer. There were no significant sex differences in breast cancer-specific mortality for in situ and stage II–IV disease. The lack of stage-specific mortality assessments in many previously published studies may account for the inconsistent findings in the literature. However, the absolute percentage increase in male breast cancer-specific mortality for stage I disease was only 1.6 percentage points, which is unlikely to be of significance clinically. Because of the large sample sizes in the SEER dataset, many results are statistically significant even though the odds of a given outcome may be just a few percentage points higher or lower between comparisons.

In the current analysis, male breast cancers were more likely to be diagnosed at more advanced stages of disease (stages II–IV) compared with female breast cancers. The more advanced breast cancer stage at diagnosis for men has been attributed to delay in diagnosis.[2,7] Given that breast cancer is uncommon in men, there is not a high index of suspicion for the disease, and there are no routine screening guidelines for men as there are for women. There also is a lack of public awareness of this disease in men. Thus, the delay in diagnosis comes from both the general public not being cognizant of the disease and physicians not recognizing the signs and symptoms of this rare cancer.

Consistent with previous studies, males in this study tended to be older than females at time of diagnosis.[2,24]

TABLE 2 Vital status and cause of death outcomes for persons with a single primary breast cancer occurrence by stage at diagnosis, SEER 1988–2003

Stage	*N* (%)	Alive (%)[a]	Death due to breast cancer (%)[a]	Death due to other causes (%)[a]	Unknown cause of death (%)[a]
Men					
In situ	166 (10.8)	83.1	1.2	15.1	0.6
I	431 (28.0)	75.4	5.3	18.1	1.2
II	620 (40.2)	62.7	14.5	20.6	2.1
III	116 (7.5)	38.8	37.9	20.7	2.6
IV	97 (6.3)	26.8	56.7	14.5	2.1
Unstaged	111 (7.2)	45.0	26.1	27.0	1.8
Overall	1,541 (100.0)	63.1	15.8	19.4	1.7
Women					
In situ	37,313 (15.3)	93.2	0.5	5.9	0.4
I	92,125 (37.7)	83.8	3.7	11.8	0.7
II	77,347 (31.6)	71.8	15.7	11.6	1.0
III	13,266 (5.4)	48.4	38.9	11.5	1.1
IV	10,021 (4.1)	19.3	67.7	11.4	1.5
Unstaged	14,446 (5.9)	52.7	27.2	18.8	1.3
Overall	244,518 (100.0)	75.0	13.0	11.2	0.8

[a] Percentages shown are for row totals and are rounded

SEER surveillance, epidemiology, and end results

TABLE 3 Crude and adjusted hazard ratios for breast cancer-specific and all-cause mortality by stage at diagnosis comparing men with women

Stage	Breast cancer-specific mortality		All-cause mortality	
	cHR (95% CI)	aHR (95% CI)	cHR (95% CI)	aHR (95% CI)
In situ	2.87 (0.71–11.57)	3.09 (0.76–12.51)	2.77 (1.91–4.02)	2.96 (2.04–4.30)
I	1.77 (1.18–2.67)	1.72 (1.15–2.61)	1.93 (1.60–2.34)	1.79 (1.48–2.17)
II	1.11 (0.90–1.36)	1.20 (0.98–1.48)	1.60 (1.40–1.82)	1.47 (1.29–1.67)
III	1.19 (0.88–1.59)	1.19 (0.88–1.60)	1.45 (1.15–1.84)	1.35 (1.07–1.71)
IV	0.86 (0.66–1.12)	0.91 (0.70–1.19)	0.94 (0.74–1.18)	1.00 (0.79–1.26)
Unstaged	1.04 (0.72–1.50)	1.28 (0.89–1.85)	1.28 (1.00–1.65)	1.53 (1.19–1.98)

Reference group for each model was "women"

cHR crude hazard ratio, *CI* confidence interval, *aHR* adjusted hazard ratio (adjusted for age at diagnosis, race, marital status at diagnosis, grade, estrogen receptor status, progesterone receptor status, surgical treatment received, and radiation treatment received)

Older age at diagnosis is associated with higher prevalence of comorbidities, which likely explains the overall poorer survival among male compared with female breast cancer patients. Donegan et al. reported that a major contributor to the poor survival in male breast cancer patients was from the high rate of posttreatment mortality from comorbid disease.[8] Approximately one-third of posttreatment deaths were due to heart disease or other nonbreast cancers.[8] Only in stage IV disease was all-cause mortality similar between the sexes; one would expect that the risk of dying from metastatic breast cancer would be high regardless of other prognostic factors for both men and women.

There are other risk factors that are similar between the two sexes; genetic factors play an important role in both male and female breast cancers, with *BRCA2* mutations associated with a significant number of inherited male breast cancers.[25] Increased estrogen levels due to obesity, testicular disorders, Klinefelter's syndrome, and radiation exposure also seem to be consistently associated with male breast cancer.[25] Male breast tumors also tend to be characterized by lower grade, ER and PR positivity, and Bcl-2 overexpression when compared with female breast tumors.[23,24,26,27] Conflicting data regarding the prognostic effect of human epidermal growth factor receptor 2 (HER-2)/neu-positive tumors in males have been reported, with many studies showing lower expression or lack of prognostic significance compared with female tumors, and some studies showing overexpression.[23,28–31] The sex differences in epidemiologic risk factors and tumor biology indicate that prognosis and treatment, particularly endocrine and HER-2/neu therapies, may differ for male and female breast cancers.

Although it may be counterintuitive to think that male breast tumors may be more likely than female breast

tumors to be hormone receptor positive, data suggest that over 80% of male breast tumors are ER positive.[2,5,24,26] However, there are inconsistent findings regarding the benefits of treating male breast tumors with the same endocrine therapies used to treat female breast tumors (e.g., tamoxifen). Although two studies reported endocrine therapy was associated with improved survival in men, other studies suggested that male ER-positive tumors do not respond to tamoxifen therapy in the same manner as female ER-positive tumors do.[32,33] Consequently, hormone receptor positivity does not translate into better prognosis for male ER-positive breast cancers.[9,34,35] One study found that male patients who had hormone receptor-positive tumors had inferior survival compared with female patients despite using similar endocrine therapy.[24] In addition, a recent analysis of the SEER data from 1996 to 2005 suggested that there was a 42% decrease in breast cancer-specific mortality among women compared with only a 28% decrease among men, suggesting that the treatments being used in male breast cancer are not as effective as they are for female breast cancer.[36] Thus, male breast cancer, despite expression of similar biomarkers, may be different biologically in other, unmeasured ways.

While male breast cancers were more likely to be diagnosed at advanced stages of disease, our study is unique in that it demonstrated greater breast cancer-specific mortality for males than females in stage I disease only. There are some possible explanations for this finding. The molecular biology of the tumor and the response of the tumor to traditional management may be one contributing factor responsible for the survival disparities observed. This molecular variability would have the greatest impact in early-stage, lymph-node-negative disease, where curative-intent treatment results in >90% long-term survival for female breast cancer patients. Data suggest that certain breast cancers grow more rapidly/aggressively in specific microenvironments.[37] In turn, breast cancer-specific survival can vary widely depending on site of metastasis. The location of metastatic disease has been shown to correlate with survival: less than 6 months for visceral metastases, 18 months for nodal disease, and 3–4 years for bone-only metastases.[38] Perhaps male breast cancers progress and metastasize differently than female breast cancers. If this is true, based on our observations, the difference would be most pronounced for patients with stage I disease.

Although biological differences likely exist between female and male breast cancers, we acknowledge that our finding of a statistically significant difference in survival for males with stage I breast cancer is likely due to in-stage migration. This is supported by the finding that males with T1 tumors were more likely to have larger T1 tumors than their female counterparts. This is not unexpected given the fact that females are more likely to have a T1 breast cancer identified asymptomatically by screening mammography, whereas males are more likely to have a T1 breast cancer identified by a palpable mass on examination. Hill et al. demonstrated the impact of screening mammography in the female population compared with the male population over time.[11] Prior to 1980, there was no significant effect of gender on the proportion of advanced stage of disease at diagnosis. Since 1980, there has been a decreasing trend in the proportion of advanced-stage disease in women, corresponding to an increase in screening mammography, while the trend among men does not demonstrate a marked decrease in incidence at the advanced stages.[11] We believe that the lack of screening in males and the resultant in-stage migration observed in our T1 subgroup account for the small absolute difference in survival observed between males and females with stage I breast cancers.

There are several limitations to our study, which are inherent to any retrospective cohort study. One limitation of retrospective cohort studies is the inability to control for selection bias. Male patients in this study were more likely to be treated by mastectomy and less likely to receive radiation compared with females. The utility of breast-conserving surgery is just starting to be evaluated in men.[30,39–41] Perhaps, operative management was dictated by the smaller amount of breast tissue in males, central location of the tumor, more advanced disease stage, more nodal involvement, or even larger tumor size.[41] Male patients in this study tended to be older than female patients at diagnosis, which suggests that they also may have had more comorbidities, which plays a role in the treatment decision-making process as well as successful completion of their adjuvant therapy. The SEER database does not contain information about comorbidities, margin status after primary tumor resection, location of and surgery on metastatic disease sites, or receipt and completion of systemic treatments, including chemotherapy and endocrine therapy, which could potentially affect survival in both men and women. Socioeconomic status and access to health care, both of which could affect treatment options, also are not available in the SEER Program data. Finally, genetic risk factors (e.g., *BRCA1* and *BRCA2* mutations), family history of breast cancer, and behavioral risk factors (physical activity, alcohol consumption, and use of hormone-replacement therapy) also are unavailable.

The SEER database, while limited in the types of variables that are included, is a high-quality, national, population-based database that is widely used in epidemiological studies, despite its inherent limitations.[42] After controlling for potential confounders of survival in multivariate analyses, our study demonstrated a significantly greater breast cancer-specific mortality in stage I disease for males compared with females. However, this difference is small and is likely a statistical observation attributable to

in-stage migration, rather than a significant clinical finding. Despite the lack of a significant breast cancer-specific survival difference between males and females, the pathologic features of male breast cancer and potential lack of response to conventional treatment do warrant further investigation. Future translational studies should focus on the tumor biology and treatment efficacy of male breast cancers to determine whether optimum treatment parallels that of female breast cancers.

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